Is modelling complexity always needed?

Insights from modelling PrEP introduction in South Africa

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Abstract

Background: Mathematical models can be powerful policymaking tools. Simple, static models are user-friendly for policymakers. More complex, dynamic models account for time-dependent changes, but are complicated to understand and produce. Under which conditions are static models adequate? We compare static and dynamic model predictions of whether behavioural disinhibition could undermine the impact of HIV pre-exposure prophylaxis (PrEP) provision to female sex workers in South Africa.

Methods: A static model of HIV risk was developed and adapted into a dynamic model. Both models were used to estimate the possible reduction in condom use, following PrEP introduction, without increasing HIV risk. The results were compared over a 20-year time-horizon, in two contexts: at epidemic equilibrium and during an increasing epidemic.

Results: Over time-horizons of up to five years, the models are consistent. Over longer timeframes, the static model overstates the tolerated reduction in condom use where initial condom use is reasonably high ($\geq$50%) and/or PrEP effectiveness is low ($\leq$45%), especially during an increasing epidemic.

Conclusions: Static models can provide useful deductions to guide policymaking around the introduction of a new HIV intervention over short-medium time-horizons of up to five years. Over longer timeframes, static models may not sufficiently emphasize situations of programmatic importance, especially where underlying epidemics are still increasing.

Background

Mathematical models play an important role in policy making for public health.[1–3] They can be used to assess the impact of different policy options, which may be impractical to test in implementation settings or over longer time horizons.[1] Nonetheless, there is often hesitation among policy makers to rely on models, perceived to be an intimidating 'black box' process of uncertain applicability to real-world settings.[4,5] This may be owing to complexity in model structure, uncertainty around model assumptions or challenges in model communication.[6] As a consequence, potentially useful models may be underemployed or in some cases inappropriately used to inform decision making.[4]

Simple models have a comparative appeal for use in policy making. They can be used to deduce broad principles to guide decision-making through an approach that is easier for policy makers to understand and critique.[7,4] For this reason, we previously used a simple, static model of HIV risk to assess the potential effect of behavioural disinhibition (in this case: reductions in the use of condoms) following the introduction of pre-exposure prophylaxis (PrEP) among female sex workers (FSW) in South Africa.[8] Simple models have been used to obtain insights into a number of other pertinent HIV policy questions – from resource prioritization across low and middle income countries[9] to the scale up of microbicides[10,11], the cost-effectiveness of male circumcision in sub-Saharan Africa[12,13], declining HIV test positivity[14] and projecting HIV diagnoses among children and adolescents in New York State[15].

To date there has been limited assessment of the conditions under which models of simple structural form are sufficient to guide policy making in HIV.[16–20] A key element of modelling complexity is the extent to which model conclusions account for time-dependent changes. Static models take a snap-shot approach and cannot capture the downstream effects of population interaction. They are typically structurally more straightforward, and less data- and time-intensive to develop.[21,22] By comparison, dynamic models account for changes over time owing to population interactions and evolving contextual factors. Dynamic models are typically represented by a system of differential or difference equations, evaluated numerically using programming tools with increased data requirements. [21,23] As a result, they are more time-intensive and expensive to devise and calibrate, and often require critical assumptions to be made about current and future trends.[20,21]

Other key considerations in the design of models to inform policy making include the extent to which models can be devised, computed and appropriately interpreted by policy makers themselves, or whether external technical support is required.[1,20,24] Simpler models, such as those calculated in Microsoft Excel, that can be developed and owned by policy makers themselves, may improve their uptake to inform decision making. However, accessibility needs to be balanced against the risk of inaccuracies through model over-simplification, leading to misleading model outcomes or interpretation, and the derivation of incorrect policy conclusions.[2]

Modelling studies[16,20,25,26] have proposed broad frameworks to guide the development of models for policy making, noting that models should adopt only the minimum level of complexity needed to appropriately represent the policy question at hand, in view of the availability of data, the importance of accounting for interactions between population groups, the time horizon of assessment and epidemiological context. However, none have given specific guidance around the characteristics or contexts in which simpler models suffice. Given that simple, static models form the basic building blocks for more complex models,[22] it is important to determine conditions under which they can reliably provide an accessible approach to guide policy making.

In 2009 Foss et al[11] incorporated dynamic features into a static model of HIV risk[10] to explore the impact of microbicide STI-efficacy. In 2014 Mishra et al[17,27] assessed the static UNAIDS Modes of

Transmission model,[9] used by many countries to prioritise HIV prevention interventions between groups at population-level. These studies[11,17,27] concluded that by not capturing dynamic effects of partner interaction, the static model underestimates the contribution of epidemic drivers to HIV transmission over time. Other studies have used static and dynamic models to explore different aspects of a policy question but have not compared model outcomes.[13,28] To the best of our knowledge, no study has examined the extent to which the conclusions of static models remain robust to the incorporation of dynamic effects over multiple time-horizons, when assessing the introduction of a new HIV intervention to a population group.

To contribute to wider understanding of the role of simple, static models in decision making, we modify our previous model of HIV risk for female sex workers (FSW) in Hillbrow, South Africa[8] to incorporate the dynamics of partner interaction over time. We assess the consistency of policy conclusions derived between the static and dynamic model formulations. We make this comparison over different time-horizons, as well as by HIV epidemic stage, to determine whether the underlying maturity of population epidemics affects the time-dependency of results. The introduction of PrEP for FSW in South Africa is a pertinent case study, in view of growing concerns around sub-optimal drug adherence[29,30] and behavioural disinhibition,[30,31] highlighting the need to understand trade-offs associated with PrEP outside of trial settings.[32]

Methods

Model structures and parameterisation

The static model was developed using the Bernoulli formulation of HIV risk,[8] where the probability of HIV being transmitted through each sexual contact is an independent risk event. The sexual partners of FSW are assumed to come from a single population in which the proportion HIV infected is p. To assess the effect of changes in condom consistency following the introduction of PrEP, condoms were assumed to be used with consistency γ_0 prior to PrEP introduction and γ_1 after its introduction. As the relationship between PrEP adherence and effectiveness is yet to be defined for women,[33] the model assumes an achieved level of PrEP use-effectiveness, b_α, corresponding to a level of PrEP adherence, α. The term 'use-effectiveness' is used to describe the HIV risk-reduction achieved through a level of use of an efficacious HIV prevention intervention (e.g. PrEP or condoms).

A dynamic version of the static model was developed using difference equations, taking the Bernoulli risk formulation as the force of infection on FSW per timestep, and an equivalent formulation for male partner population. The dynamic model system allows prevalence to change over time as the proportion of HIV infected individuals, I/N, where I is the number of HIV infected individuals and N the total population size.

The dynamic model was fitted to HIV prevalence data for both FSW and partner populations between 1980 and 2014 using Monte Carlo methods with Latin Hypercube Sampling (R FME package[34]), run on 50,000 parameter sets. This yielded at least 200 fits for each scenario explored. Both models were coded in R programming environment and were parameterised and evaluated using the same set of fitted parameters, allowing for the evaluation of uncertainty ranges. PrEP was introduced in 2015 in line with its introduction to FSW in Hillbrow under the TaPS demonstration project.[35]

Comparison between static and dynamic model outcomes

The static and dynamic models were used to calculate two outcomes of interest in relation to behavioural disinhibition on PrEP:

- *Model Outcome 1: Lowest level of condom consistency tolerated on PrEP*

  We used both models to explore the lowest level of condom use, γ_1^*, that FSW could drop to without increasing their HIV risk on PrEP. This lowest level of condom use is denoted: *lowest level of condom consistency tolerated.* For each model, the lowest level of condom consistency tolerated on PrEP was calculated using optimisation algorithms (dynamic model: R FME package[34]; static model: R rootSolve package[36]).

- *Model Outcome 2: Percentage reduction in condom consistency tolerated on PrEP*

  These estimates of the *lowest level of condom consistency tolerated* were then used to calculate the *percentage reduction in condom consistency* $(\gamma_0 - \gamma_1^*)/\gamma_0$ that can be tolerated on PrEP without FSW's HIV risk increasing. This measure allows policy makers to assess the relative change in condom use that can be tolerated by FSW taking PrEP, across scenarios.

To demonstrate how the two outcomes are related, consider a hypothetical case in which a FSW's initial condom consistency is 80% and the lowest level of condom consistency tolerated (outcome 1) is 40%. Then, outcome 2, the percentage reduction in condom consistency tolerated on PrEP would be 50%.

Accounting for different time horizons

To assess how well the outcomes of the static and dynamic models match over longer time horizons, γ_1^*, the lowest level of condom consistency tolerated on PrEP, was calculated using the dynamic model over time horizons of 3 months to 20 years. Three months was taken as the minimum time horizon in order to align with the 3-month period of evaluation of the static model (chosen to match the 3-monthly schedule of HIV tests required on PrEP to check for seroconversion[30]). Twenty years was taken as the maximum time horizon to be able to fully explore the differences between model outcomes over a longer period of time.

Accounting for behavioural heterogeneity: differences in initial condom consistencies and PrEP use-effectiveness

Given the importance of accounting for heterogeneity in FSW's initial condom consistencies,[8,10] the parameter sets were fitted individually for initial condom consistencies (prior to introduction of PrEP) of 10%, 30%, 50% and 70%, spanning the range reported by this population.[8]

As studies to date have been unable to relate the number of weekly doses of PrEP to levels of HIV risk reduction in women,[37] we chose to span a spectrum of potential levels of PrEP use-effectiveness: 25%, 45%, 65% and 85%. 85% was simulated as the highest level, as it equates to the maximum use-effectiveness of condoms as in Grant and colleagues.[8]

The lowest level of condom consistency tolerated on PrEP, without HIV risk increasing, was calculated across these levels of initial condom consistency and PrEP use-effectiveness.

Accounting for stage of HIV epidemic

To assess whether the results change by underlying stage of HIV epidemic, the analyses were repeated 20 years earlier, when the HIV epidemics in FSW and their partner populations were still increasing. Under this scenario, *Increasing Epidemic,* initial condom consistency, γ_0, was fixed in 1994 and PrEP hypothetically introduced in 1995. This is in comparison to the base case analysis, *Epidemic Equilibrium,* where initial condom consistency was fixed in 2014 and PrEP introduced in 2015 once the epidemics had started to stabilise.

Additional analyses

To assess whether the inclusion of antiretroviral treatment (ART), circumcision and sexually transmitted infections (STIs) in the models affected our conclusions, we conducted a model structural sensitivity analysis, removing all related parameters from the models and rerunning the analyses. To assess whether our conclusions were sensitive to PrEP being introduced when the

epidemics are fully endemic in the populations (*Fully Endemic* scenario), we repeated the analysis with PrEP introduced in 2030.

Comparison of qualitative policy conclusions between static and dynamic models

In order to explore the contexts in which the qualitative conclusions made on the basis of static models may be appropriate to guide HIV policy making, we assessed the robustness of the policy conclusions derived from the static model compared to those derived from the dynamic model. The qualitative policy conclusions derived from the static model were outlined in our previous study, however they were deduced using a static model only, and not substantiated using a dynamic model formulation.[8]

Supplementary Materials contains further information on the model structure, parameterization and calibration.

Results

The lowest levels of condom consistency that can be tolerated by FSW on PrEP (without their HIV risk increasing) at *Epidemic Equilibrium* and in the context of an *Increasing Epidemic*, are shown in Figure 1 and Figure 2 respectively.

In Figure 1 and Figure **2**, the three rows, from top to bottom, represent FSW initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70% respectively. The three columns represent, from left to right, PrEP use-effectiveness of 25%, 45% and 65% respectively. For each combination of initial condom consistency and PrEP use-effectiveness, boxplot graphs depict the lowest level of condom consistency tolerated on PrEP (vertical-axis). The far-left boxplot on the horizontal-axis of each of the graphs is the lowest level of condom consistency estimated using the static model. The boxplots to the right of it are the lowest level of condom consistencies estimated using the dynamic model, at time points of 3 months, 1 year, 2 years, 5 years, 10 years and 20 years, from left to right. The boxplots depict uncertainty in the estimated lowest level of condom consistency tolerated, with the black line representing the median value, the coloured section the interquartile range (25-75% of the values) and the whiskers the maximum and minimum values. The differences between the static and dynamic model outcomes can be understood by comparing how similar the lowest level of condom consistency estimated by the static model is to the lowest level of condom consistency estimated by the dynamic model over time.

Whilst Figure 1 and Figure **2** depict the key trends in model differences for each scenario, more detailed plots including FSW initial condom consistency of 10% and PrEP use-effectiveness of 85% are shown in *Supplementary Materials, Figures S5 and S7* for the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios respectively. The *Supplementary Materials* also contain the equivalent boxplot graphs for the second model outcome: percentage reduction in condom consistency tolerated on PrEP (*Supplementary Materials Figures S6 and S8*), the model fits to HIV prevalence (*Supplementary Materials Figures S1-S4)*, as well as all underlying data (*Supplementary Materials Tables S2-S10)*.

Comparison of static and dynamic model outcomes

Under the scenario that PrEP is introduced at *Epidemic Equilibrium*, the percentage reductions in condom consistency estimated by the static and dynamic models are very similar up to a time-horizon of one year. By five years, the model predictions remain consistent to within 25% relative difference between medians (<35% between credible intervals (CrIs)), and by 20 years to within 35% between medians (≤100% between CrIs) (*Supplementary Materials Table S2a).* The differences between the percentage reductions in condom consistency predicted by the static and dynamic models are less consistent over time where initial condom consistency is higher (≥50%) and PrEP use-effectiveness is lower (≤45%). This is consistent with our previous work based on the static model, which indicated that reductions in condom consistency should be of greatest concern for FSW with high initial condom consistencies achieving low levels of PrEP use-effectiveness[8]. However, the results suggest that the magnitude of concern predicted by the static model was understated over the long-term.

Under the *Increasing Epidemic* scenario, the differences between the percentage reductions in condom consistency predicted by the models are more pronounced over time. By five years the relative difference between model medians is less than 10% (<25% between CrIs) at high levels of PrEP use-effectiveness (85%) but up to 100% (100% between CrIs) at low levels of PrEP use-

effectiveness (25%). By 20 years, the differences between the models start to decrease in response to the natural plateau of the underlying epidemics (*Supplementary Materials Table S2b)*.

For both epidemic scenarios, removing ART, circumcision and STIs from the models under the structural sensitivity analysis led to bigger differences between model outcomes in situations where PrEP use-effectiveness is low (≤45%) and initial condom consistency is at least 30% (<45% relative difference between CrIs by 5 years, and <50% relative difference by 20 years) (*Supplementary Materials Tables S3a and Sb, Figures S9-S12)*. Introducing PrEP in 2030 under the *Fully Endemic* rather than in 2015 in the *Epidemic Equilibrium* scenario led to differences under the same situations, although the magnitude of differences was smaller (<25% relative difference between CrIs by 5 years, and <35% between by 20 years) (*Supplementary Materials Table S4, Figures S13 and S14)*. Additional analysis comparing the model outcomes by scenario is set out in *Supplementary Materials, Additional Assessment of Results* section.

Comparison of policy conclusions between static and dynamic models

To explore the contexts in which the qualitative conclusions made on the basis of static models may be appropriate to guide HIV policy making, we list three policy conclusions derived based on the static model[8], and assess their validity under dynamic model formulation.

1. Condom use can be reduced to zero without increasing HIV risk, if the level of HIV risk reduction achieved through PrEP is at least high as the maximum risk reduction possible through condom use

This conclusion holds under the dynamic model in the *Epidemic Equilibrium* scenario, as well as in the *Increasing Epidemic* scenario, other than at high levels of initial condom consistency (70%), where after five years the dynamic model predicts that a reduction in condom consistency to zero may start to lead to an increase in HIV risk (Figure 1 & Figure **2**; *Supplementary Materials Table S2a &S2b and Figures S6 & S8*).

2. Reductions in condom consistency are especially well tolerated where:

i. Higher levels of PrEP use-effectiveness are achieved (e.g. ≥65%)

Figure 3 shows the lowest levels of condom consistency tolerated calculated using the static and dynamic models for PrEP use-effectiveness levels of 65% and 85%. The lowest levels of condom consistency are shown for initial condom consistencies of 10% (in blue), 30% (in orange), 50% (in pink), and 70% (in green). The dotted lines represent median estimates and shaded areas represent the 95% CrIs. The top row depicts the *Epidemic Equilibrium* scenario, and bottom row the *Increasing Epidemic* scenario.

With PrEP use-effectiveness of at least 65%, the static model predicts that median reductions in condom use of at least 85% will be possible without increasing HIV risk. The dynamic model broadly supports this conclusion, with less than 25% relative difference between the model medians and CrIs after five years, and less than 35% relative difference after 20 years in the *Epidemic Equilibrium* scenario. Importantly, under the *Increasing Epidemic* scenario, these differences are much more pronounced, with up to 60% relative difference between medians and CrIs after five years, and up to 65% relative difference (85% between 95% CrIs) after 20 years.

For initial condom consistencies of up to 50%, the static model predicts that FSW on PrEP with use-effectiveness of at least 65% can stop using condoms completely without increasing HIV risk. This is consistent with the dynamic model conclusions under the *Epidemic Equilibrium* scenario. Under the *Increasing Epidemic* scenario, this only holds where PrEP use-effectiveness is at least 85% (rather than 65%) (Figure 3; *Supplementary Materials Table S2a & Sb*).

ii. Or where initial condom consistencies are low (e.g. <50%).

Figure 4 shows the lowest levels of condom consistency tolerated after PrEP introduction, calculated using the static and dynamic models for initial condom consistencies (before PrEP introduction) of 10% and 30%. The lowest levels of condom consistency tolerated are shown corresponding to PrEP use-effective of 25% (in green), 45% (in pink), 65% (in orange), and 85% (in blue). The dotted lines represent median estimates and shaded areas represent the 95% CrIs. The top row depicts the *Epidemic Equilibrium* scenario, and bottom row the *Increasing Epidemic* scenario.

Under the *Epidemic Equilibrium* scenario the dynamic model supports the outcomes of the static model especially well in the short term, with relative difference between medians of less than 5% after five years (<25% between the 95% CrIs), and less than 5% relative difference by 20 years (<70% between 95% CrIs). Under the *Increasing Epidemic* scenario, the model differences are large over time, e.g. estimates from the dynamic model of the lowest level of condom consistency tolerated are up to double the levels estimated by the static model after 5 years (Figure 4; *Supplementary Materials Table S2a & S2b*).

3. Even with the achievement of low levels of PrEP use-effectiveness (e.g. ≤45%), reductions in condom consistency are possible without increasing HIV risk.

As with the static model, under the *Epidemic Equilibrium* scenario the dynamic model predicts that some decreases in condom consistency on PrEP will always be possible without increasing HIV risk over the 20-year time horizon, even for lower levels of PrEP use-effectiveness of up to 45%. This holds true under the *Increasing Epidemic* scenario up to a five-year time horizon.

Discussion

Main findings of this study

This study demonstrates that there are contexts in which static models can provide useful deductions to guide policy making around the introduction of a new HIV intervention. Static models may have advantages to guide programming over short-medium time horizons in certain settings. However, over longer timeframes, static models may not sufficiently emphasize situations of programmatic importance, especially in contexts where underlying epidemics are not at equilibrium. PrEP is likely to be of benefit in reducing HIV risk in high-burden settings, even if moderate reductions in condom use occur.

What is already known on this topic

It is well established that dynamic models are more appropriate to address policy questions where it is important to account for the downstream effects of population interactions and evolving contextual factors over time.[4,5,25,26] Both static and dynamic models have been used to inform policy making in the field of HIV.[9,10,12,38,39] Existing studies have cautioned that static models may underestimate the contribution of epidemic drivers to HIV transmission over time.[17,27] However, to date, no study has assessed the epidemic contexts and timeframes over which simple static models may suffice to inform decision making in the field of HIV, especially in the context of the introduction of new prevention interventions.

What this study adds

This study compares the outcomes of a static model with the outcomes of a matched dynamic model, applied to different epidemic contexts across time horizons. Both models are used to assess the absolute and percentage reductions in condom consistency that can be tolerated, without HIV risk increasing, following introduction of PrEP for FSW. We found that over short-medium time-horizons of up to five years, the static model approximates the outcomes of the dynamic model fairly consistently. Over longer timeframes of up to 20 years, there are contexts in which the reductions in condom use predicted by the static model do not hold under the dynamic model formulation; particularly where initial condom consistency is reasonably high ($\geq$50%) and/or PrEP use-effectiveness is low ($\leq$45%). The differences between the two models are greater where the underlying HIV epidemic is increasing (Figure 1 & 2, *Supplementary Materials Tables S2a & S2b*). The structural sensitivity analysis (removing model parameters relating to ART, circumcision and STIs) showed bigger differences between model outcomes in situations where PrEP use-effectiveness is low ($\leq$45%) and initial condom consistency is at least 30%. Introducing PrEP where the underlying HIV epidemic is fully endemic in 2030 (rather than at equilibrium in 2015) led to differences under the same situations, although smaller in magnitude. The difference between the models' outcomes arise predominantly from the dynamic model's ability to capture changes in HIV prevalence over time, which is highlighted where PrEP use-effectiveness is insufficiently high enough to mask greater reductions in condom use.

Nonetheless, the broad-stroke policy conclusions predicted by the static model hold under the dynamic model formulation. Specifically, in high HIV burden contexts, PrEP for FSW is likely to be of benefit in reducing HIV risk even if reductions in condom use occur; that reductions in condom

consistency can be better tolerated by FSW achieving high levels of PrEP effectiveness or with low baseline condom consistencies; and efforts to promote condom use will be especially critical for FSW with high levels of baseline condom consistency but who are anticipated to adhere less well to PrEP.

Simple, static models have a structural advantage over dynamic models, as they can usually be more easily analytically manipulated to deduce conclusions to guide policy making. These take-aways are often additional to those that can be gleaned through numeric and graphic assessment of either model's outcomes. Noting that model results are usually discounted over longer time-horizons due to uncertainty in underlying assumptions or implementation contexts, there may be merits for using static models to guide the introduction of new HIV interventions over short-medium time horizons, especially where the underlying HIV epidemic is well-evolved. Static models may also be better suited to guide the roll out of interventions intended for short term-use, such as PrEP, which is intended to cover seasons of risk.[30]

In contexts with increasing epidemics, dynamic models may be more appropriate to guide the programming of interventions for long-term use. Building on the conclusions in Mishra and colleagues,[17] this study underscores that decision maker reliance on the magnitude of intervention effectiveness assessed through static models, such as the UNAIDS Modes of Transmission model,[9] should be cautioned in contexts where HIV prevalence is increasing, e.g. in the relevant sub-epidemics in Eastern Europe, South East Asia, the Middle East and South America, especially in relation to high burden (e.g. key) populations.

Future studies could extend this model comparison to other infectious diseases to understand the conditions under which static models are sufficient to inform policy making. This may be especially pertinent for diseases where there is limited understanding of key components required in dynamic model construction (e.g. transmission dynamics or their quantification), but comparably better understanding of the narrower information set needed to formulate static models.

Limitations of this study

There are several limitations to this study. The models used in this analysis are simplified formulations of static and dynamic models, to facilitate comparison. They do not account for different levels of PrEP coverage or population heterogeneity, relying instead on population averages. For the same reason, these two populations were explored in isolation without accounting for interactions with wider societal groups. Assessment of the effects of behavioural disinhibition are limited to FSW, not the downstream effects on partner populations.

The analysis does not explicitly explore potentially important correlations between risk factors and PrEP effectiveness. However, the impact of correlations between initial condom consistency and PrEP adherence can be easily deduced through the scenarios explored (*Figures 1 & 2).*

The data used to characterise the FSW and their partner population in Hillbrow, South Africa, is limited by age and in some cases reliance on self-reports of sexual behaviour, which are susceptible to under-reporting. Data uncertainty is addressed to some extent through the uncertainty analysis.

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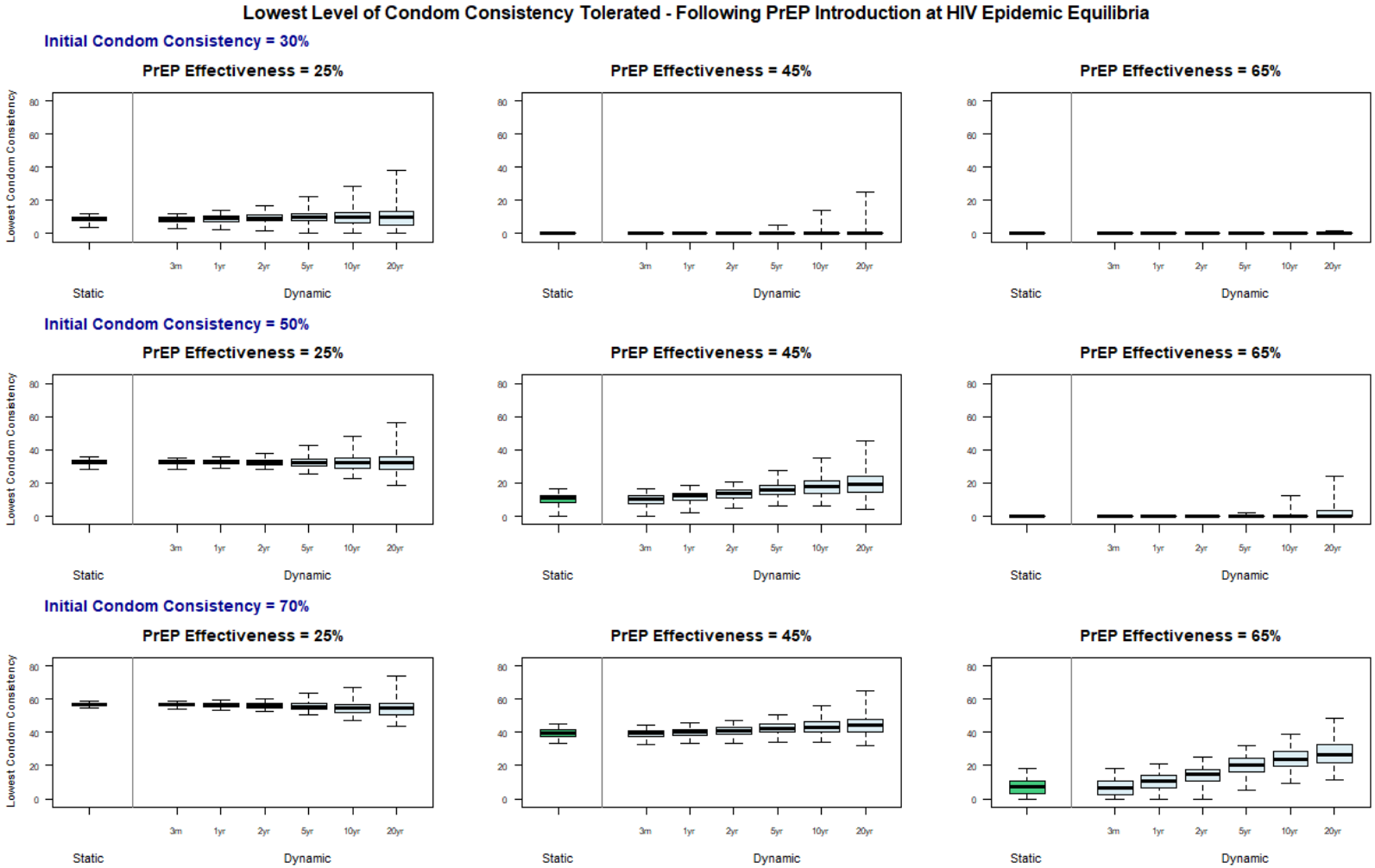

Figure 1: Boxplots showing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium. *The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45% and 65%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.*

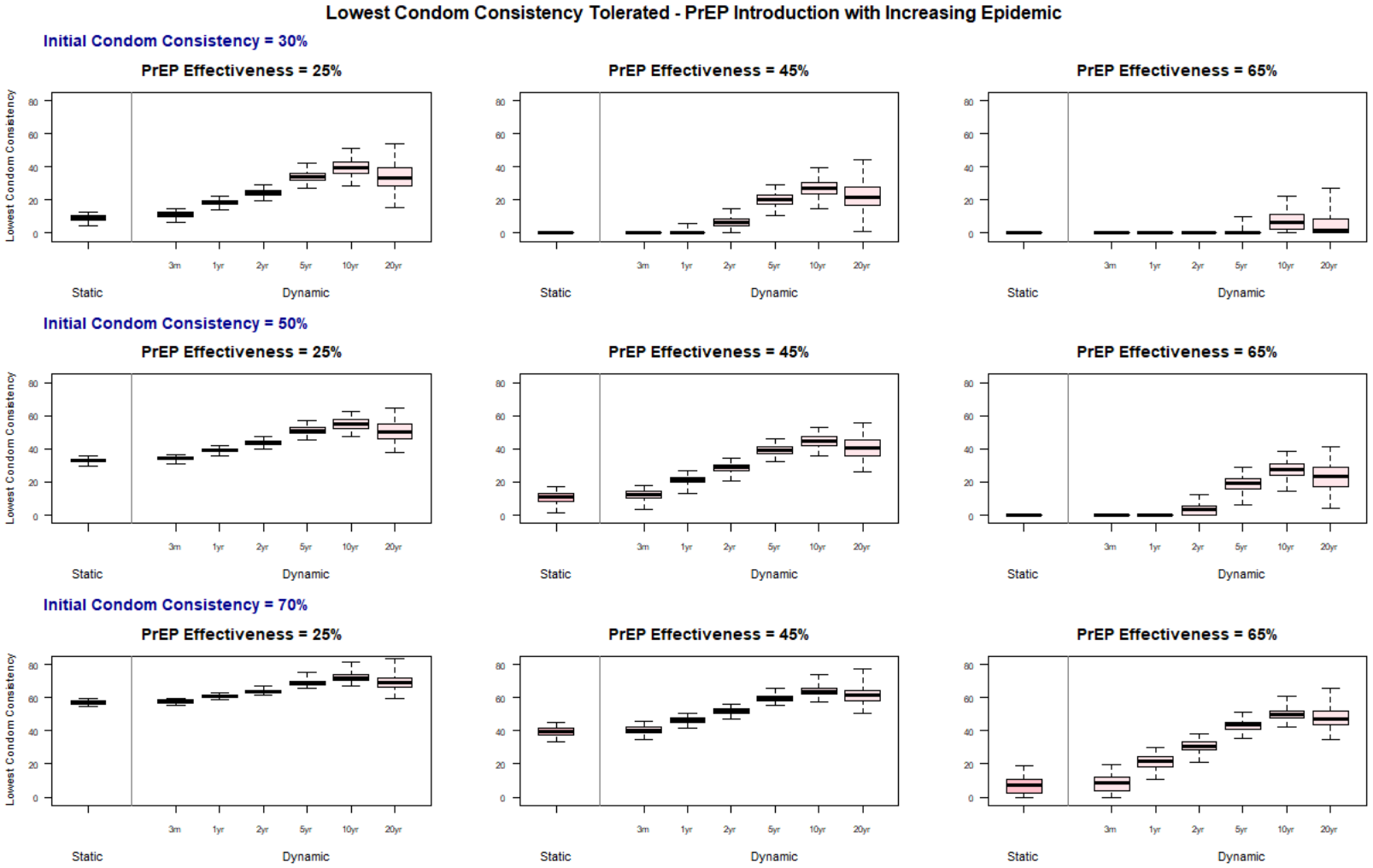

Figure 2: Boxplots showing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic. *The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45% and 65%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.*

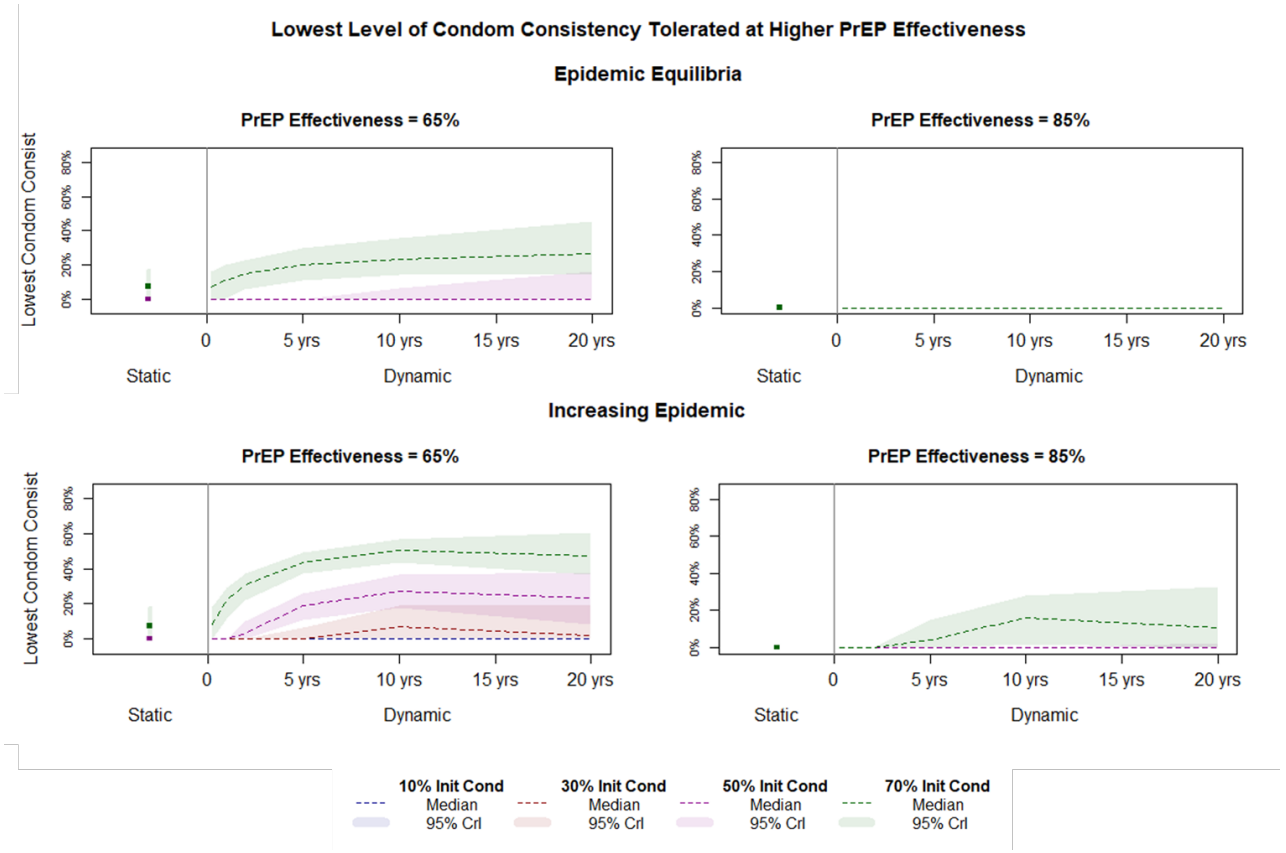

Figure 3: Lowest level of condom consistency tolerated at higher levels of PrEP use-effectiveness, for both scenarios Epidemic Equilibrium and Increasing Epidemic. *The lowest levels of condom consistency tolerated on PrEP are depicted for PrEP use-effectiveness levels of 65% (left) and 85% (right). Each graph shows the lowest level of condom consistency estimated by the static model, and by the dynamic model over a time horizon of 3 months to 20 years, corresponding to initial condom consistencies of 10%, 30%, 50% and 70%. The first row of graphs corresponds to the scenario Epidemic Equilibrium and the second row of graphs corresponds to the scenario Increasing Epidemic. The dotted lines are median estimates and shaded areas are 95% credible intervals (CrIs) (colour coding in legend). Where the median results corresponding to lower initial condom consistencies cannot be seen on the graph, it indicates that the estimated lowest level of condom consistency is 0%. Where the 95% CrI cannot be seen on the graph, it indicates that the 95% CrI is very close to or exactly the same as the median.*

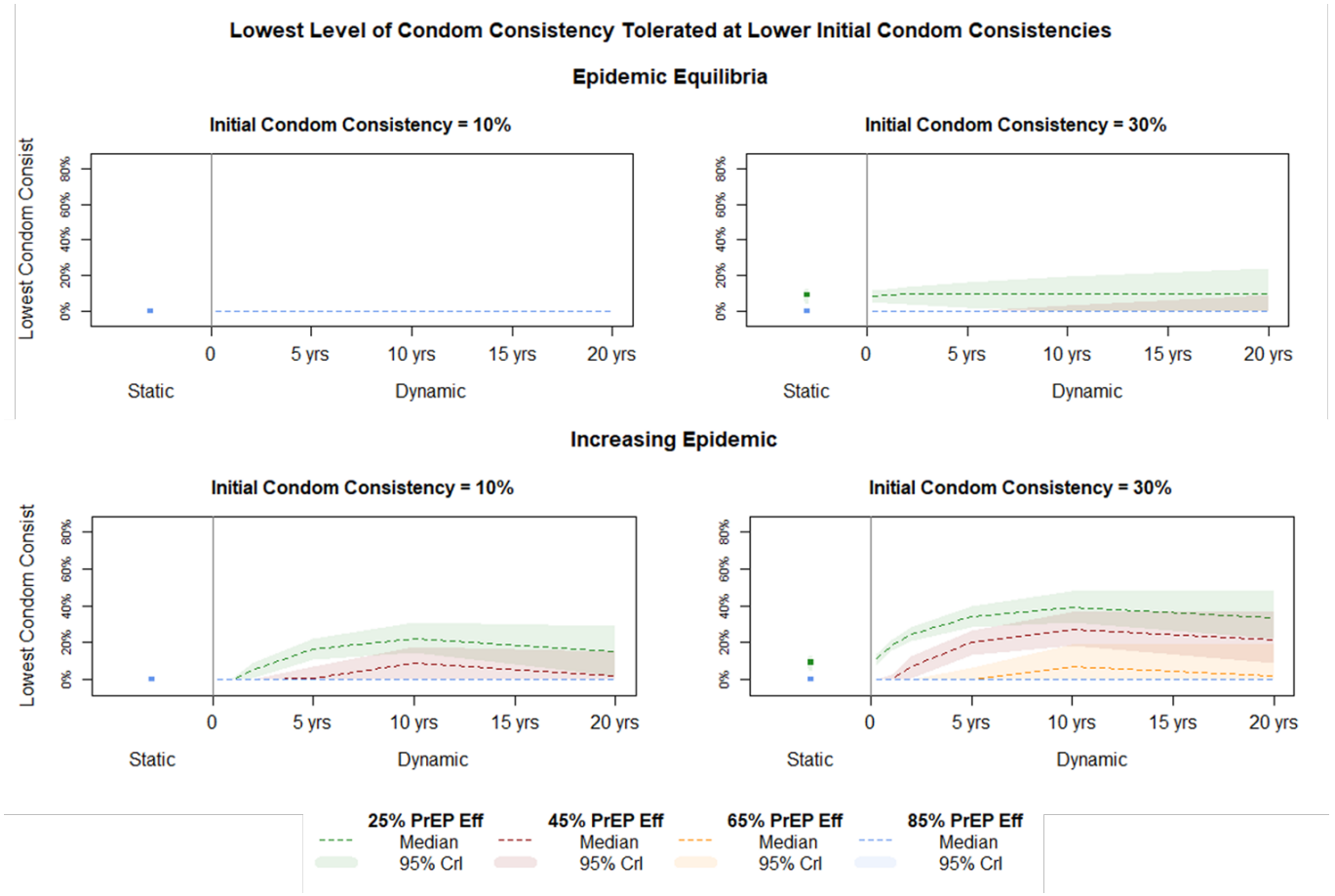

Figure 4: Lowest level of condom consistency tolerated at lower levels of initial condom consistency, for both scenarios Epidemic Equilibrium and Increasing Epidemic. *The lowest levels of condom consistency tolerated on PrEP are depicted for initial condom consistencies of 10% (left) and 30% (right). Each graph shows the lowest level of condom consistency estimated by the static model, and by the dynamic model over a time horizon of 3 months to 20 years, corresponding to PrEP use-effectiveness levels of 25%, 45%, 65% and 85%. The first row of graphs corresponds to the scenario Epidemic Equilibrium and the second row of graphs corresponds to the scenario Increasing Epidemic. The dotted lines are median estimates and shaded areas are 95% credible intervals (CrIs) (colour coding in legend). Where the median results corresponding to specific levels of PrEP effectiveness cannot be seen on the graph, it indicates that the lowest level of condom consistency tolerated is 0%. Where the 95% CrI cannot be seen on the graph, it indicates that the 95% CrI is very close to or exactly the same as the median.*