Agent-Based Models for Causal Inference

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AGENT-BASED MODELS FOR CAUSAL INFERENCE

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A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

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Abstract

Sound clinical decision making requires evidence-based estimates of the impact of different treatment strategies. In the absence of randomized trials, two potential approaches are agent-based models (ABMs) and the parametric g-formula. Although these methods are mathematically similar, they have generally been considered in isolation. In this dissertation, we bridge the gap between ABMs and the parametric g-formula, in order to improve the use of ABMs for causal inference.

In Chapter 1, we describe bias that can occur when ABM inputs or estimates are extrapolated to new populations, and demonstrate the impact of this bias by comparison with the parametric g-formula. We describe the assumptions that are required for extrapolation of an ABM and show that violations of these assumptions produce biased estimates of the risk and causal effect.

In Chapter 2, we describe an approach to provide calibration targets for ABMs, and to identify the set of parameters of the ABM that interfere with transportability of the model results to a particular population. We illustrate this approach by comparing the estimates from an existing ABM, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, to estimates from the parametric g-formula applied to a prospective clinical data of HIV-positive individuals under different treatment initiation strategies.

In Chapter 3, we focus on the core problem of causal inference from ABMs: how to define and estimate the parameters described in Chapter 2 in light of the bias described in Chapter 1. To illustrate this problem, we consider CEPAC input parameters for opportunistic diseases. We formally define the effect of interest, describe the conditions under which this effect is or is not identifiable, and describe the assumptions required for transportability of this effect. Finally, we show that the estimation of these parameters via a naïve regression analysis approach provides implausible estimates.
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Eleanor J. Murray
Introduction

Sound clinical decision making requires estimating the outcome distribution under different treatment strategies. In the absence of randomized trials, two possible approaches are agent-based models (ABM) and the parametric g-formula. Though mathematically similar, these methods have generally been considered in isolation. In this dissertation, we bridge the gap between ABMs and the parametric g-formula, and provide recommendations to use ABMs for causal inference.

In Chapter 1, we describe a previously unrecognized bias that can occur when extrapolating ABM estimates to a population different from the one that was used to construct the model. The bias will occur when the outcome and time-varying confounders of the treatment-outcome relationship share causes, and the conditional association between treatment and outcome is endowed with an unwarranted causal interpretation. We demonstrate the impact of this bias by comparing estimates from the parametric g-formula and several versions of an ABM in simulated data. We discuss the conditions required for unbiased results.

In Chapter 2, we describe an approach to provide calibration targets for ABMs, and to identify the set of parameters of the ABM that interfere with transportability of the model results to a particular population. We illustrate this approach by comparing the 7-year mortality estimated by an existing ABM, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, to estimates from the parametric g-formula applied to a prospective clinical data from 60178 HIV-positive individuals under different treatment initiation strategies. The CEPAC estimates were most sensitive to associational parameters interpreted causally as the effect of treatment on opportunistic infections and chronic AIDS-related mortality. Changes to these parameters eliminated the discrepancies between CEPAC and g-formula estimates, but the question remains about how to interpret and estimate these parameters.
In Chapter 3, we focus on the core problem of causal inference from ABMs: how to define and estimate the parameters described in Chapter 2 in light of the bias described in Chapter 1. To illustrate this problem, we consider CEPAC input parameters for opportunistic diseases—namely, the 1-month probabilities of each opportunistic disease, conditional on current CD4 count and the multiplier of these probabilities under treatment. We formally define the effect of interest for these inputs and describe the conditions under which this effect is or is not identifiable. We then describe the assumptions required to allow transportability of this effect between populations. Finally, we show that the estimation of these parameters via a naïve regression analysis approach provides implausible estimates.
Chapter 1 A comparison of agent-based models and the parametric g-formula for causal inference

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ABSTRACT

Medical decision making requires choosing from treatment strategies on the basis of correctly estimated outcome distributions. In the absence of randomized trials, two possible approaches are agent-based models (ABMs) and the parametric g-formula. Validity of the g-formula requires strong assumptions, and is limited to the population from which data were collected. ABMs are used to estimate effects across populations, but rely on assumptions that are generally even stronger; substantial bias can arise when these are incorrect. We describe potential biases when using ABMs for causal inference. We estimated 12-month mortality, using an ABM and the parametric g-formula, in three simulated populations differing only in the prevalence of an unknown common cause of mortality and a known time-varying confounder. The g-formula and ABM correctly estimated mortality when all inputs came directly from the population of interest. The ABM was biased when any inputs came from another population. Both methods can afford to ignore unmeasured determinants of the outcome when causal inference is restricted to a population with sufficient data on confounders, treatment, and outcome. However, the use of ABMs for causal inferences on another population may be biased even if the causal network linking all variables is identical in both populations.
INTRODUCTION

Medical decision making requires choices among treatment strategies. For these decisions to be sound, researchers need to correctly estimate the distribution of the outcome—survival, cost-effectiveness, or another utility function—under each of the candidate strategies. When a randomized controlled trial of these strategies is not feasible, two possible approaches for estimating the impact of candidate treatment strategies are agent-based, or individual-level, models (ABMs)\(^1,^2\), and the parametric g-formula\(^3,^4\).

ABMs and the parametric g-formula use a similar mathematical approach: construction of a sequential model which is the basis of a Monte Carlo simulation of a (counterfactual) population under each treatment strategy of interest. However, despite the shared approach and goals, ABMs and the parametric g-formula have generally been considered in isolation and there is typically little overlap in the population of researchers familiar with each method\(^5,^6\).

To construct the sequential model, ABMs typically combine data from multiple sources, whereas applications of the parametric g-formula use data from a single prospective study. As a result, inferences from the parametric g-formula tend to be restricted to populations similar to the study population and to the time horizon and treatment strategies that are observed in the data. In contrast, ABMs are generally seen as a tool to address questions that are not constrained by the population characteristics, time horizon, and treatment strategies observed in any particular study\(^7\).

The greater flexibility of ABMs comes at a price: for the extrapolations to be correct, the model needs to make implicit or explicit assumptions about variables that remain unmeasured in most human studies. In contrast, the parametric g-formula is agnostic about the distribution of those unmeasured variables that do not confound the effect of interest given the measured variables. In practice, this often
implies that the input parameters of ABMs are implicitly endowed with a causal interpretation whereas
the input parameters of the parametric g-formula quantify statistical associations that may or may not
have a causal interpretation. In other words, ABMs use causal models to yield causal estimates that can
be extrapolated to many populations, whereas the parametric g-formula uses non-causal models to
yield causal estimates in a single population.3,4.

In this paper we explore the practical consequences of this divergent interpretation of the
model parameters between ABMs and the parametric g-formula. We start with the description of a
simplified decision analysis example; the goal is to determine whether we can improve the 12-month
survival of HIV-positive individuals by offering them antiretroviral therapy.

A SIMPLIFIED DECISION ANALYSIS EXAMPLE

Let $A_k$ be an indicator for initiation of antiretroviral treatment in month $k$, $L_k$ an indicator for high
CD4 cell count (defined as ≥350 cells/μl) measured at the beginning of month $k$, and $Y_{k+1}$ an indicator for
death by the beginning of month $k+1$. We use overbars to represent history. For example, an individual
with a high CD4 cell count in months 1 and 2, and low in month 3, has CD4 count history $L_3=(1,1,0)$.

As shown in the decision tree depicted in Figure 1.1, a decision to start treatment is more
likely when previous CD4 cell counts are low, which indicates a worse prognosis. Therefore an
individual’s probability of initiating treatment at $k$, $Pr(A_k = 1|L_k, A_{k-1} = 0, Y_k = 0)$, depends on her
CD4 cell count history and possibly her treatment history. Once initiated, treatment is maintained until
death. The probabilities of having a low CD4 cell count, $Pr(L_k = 1|L_{k-1}, A_{k-1}, Y_k = 0)$, and of
dying, $Pr(Y_{k+1} = 1|L_k, A_k, Y_k = 0)$, for an individual alive in month $k$, depend on her CD4 cell count and
treatment histories.
Figure 1.1: Simplified decision process for the use of treatment among HIV-positive individuals at each month $k$. Square black nodes represent decision points where intervention is possible, white circles represent nodes where an individual’s path depends on the conditional probability distribution specified, triangles represent terminal nodes.

Suppose we are interested in the effect of treatment on 1-year mortality risk. We might specify treatment strategies, such as ‘always treat’ and ‘never treat’. We can then create an ABM where treatment at each time point is assigned based on one of these strategies and compare the (counterfactual) 1-year mortality risk under each. Similarly, we can use the parametric g-formula to estimate these mortality risks.

Agent-based model

The model is defined by non-overlapping, mutually exclusive states based on $L_k$ (i.e., low and high CD4 cell count) and $Y_k$ (i.e., dead and alive) specified by the investigators. The transition
probabilities \( \Pr(L_k = 1|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{Y}_k = 0) \) and \( \Pr(Y_{k+1} = 1|\overline{L}_k, \overline{A}_k, \overline{Y}_k = 0) \) govern movement between states conditional on prior history. These probabilities are obtained from published sources, including randomized trials and observational studies. The dependence of these probabilities on prior history is often achieved through modeling. For example, a model for the monthly conditional probability of mortality may be \( \logit \Pr(Y_{k+1} = 1|\overline{L}_k, \overline{A}_k, \overline{Y}_k = 0) = \beta_0 + \beta_1 h(t) + \beta_2 L_k + \beta_3 L_{k-1} + \beta_4 A_k + \beta_5 A_{k-1} + \beta_6 (L_k \times A_k) \), where \( h(t) \) is a flexible function (e.g., restricted cubic splines) of time \( k \), and the vector of parameters \( \beta \) is replaced by estimates from a similar model fit to observational data in the literature. Similarly, a model for the monthly conditional probability of high CD4 cell count may be \( \logit \Pr(L_k = 1|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{Y}_k = 0) = \gamma_0 + \gamma_1 h(t) + \gamma_2 L_{k-1} + \gamma_3 L_{k-2} + \gamma_4 A_{k-1} + \gamma_5 A_{k-2} \), where the vector of estimated parameters is also obtained from one or more observational studies or randomized trials.

Investigators then use these models to simulate individuals’ trajectories under a strategy of interest. For example, if interested in comparing the 1-year mortality risk under the strategies “always treat” and “never treat,” we would set the conditional probability for initiating treatment \( \Pr(A_k = 1|\overline{L}_k, \overline{A}_{k-1}, \overline{Y}_k = 0) = 1 \) for the first time point and conduct a Monte Carlo simulation with 1,000,000 individuals, and, separately, set the conditional probabilities \( \Pr(A_k = 1|\overline{L}_k, \overline{A}_{k-1}, \overline{Y}_k = 0) = 0 \) for all \( k \) and conduct another Monte Carlo simulation. The 1-year mortality risks estimated from these simulations would then be compared.

**The parametric g-formula**

The implementation of the parametric g-formula has the same two steps as that of ABMs: specification of parametric models for \( \Pr(L_k = 1|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{Y}_k = 0) \) and \( \Pr(Y_{k+1} = 1|\overline{L}_k, \overline{A}_k, \overline{Y}_k = 0) \), followed by Monte Carlo simulation under the treatment strategies of interest. The parameters of these models are estimated from a single study, e.g., a follow-up study of HIV-positive individuals with
monthly measurements of CD4 cell count, treatment, and mortality. As long as data are available on all variables in the model, the parametric g-formula could be based on exactly the same parametric models that define the ABM.

Because of the dependence on observed data, parametric g-formula users tend to restrict their inferences to settings, populations, and time frames similar to those of the study population. In contrast, ABM users routinely make inferences across settings, populations, and time frames. This extrapolation generally requires that the model parameters are interpreted as causal effects. This causal interpretation, which is not necessary for the more modest aims of the parametric-g-formula, is problematic when treatment-confounder feedback exists, as we explain in the next section.

**TREATMENT-CONFOUNDER FEEDBACK**

The causal diagram in Figure 1.2 represents two time points for the setting described in the previous sections. We say that there is treatment-confounder feedback because, at each time point $k$, confounder CD4 cell count $L_k$ affects subsequent treatment $A_k$ and is affected by prior treatment $A_{k-1}$. The causal diagram also includes an unmeasured prognostic factor $U$ which independently affects both the confounder CD4 cell count and the mortality outcome. Unmeasured common causes of confounders and outcome are likely to exist in most settings. For example, in our example $U$ could be some other marker of underlying immunological status.
Figure 1.2: Causal directed acyclic graph depicting two arbitrary time points from a setting with time-varying treatment $A$, outcome $Y$, and confounder $L$. Conventional adjustment for $L$ is expected to introduce bias because $L$ is affected by prior treatment and shares a cause ($U$) with the outcome.

The simultaneous presence of treatment-confounder feedback and the unmeasured $U$ is the main reason why conventional outcome regression cannot be generally used to estimate the counterfactual probability under the treatment strategies of interest. Since an outcome regression model needs to include $L_k$ as a covariate to adjust for confounding for the effect of $A_k$ on $Y_k$, the method estimates the probability of the outcome $Y_k$ conditional on $L_k$. However, because $L_k$ is a collider (a common effect of two variables) on the path from $A_{k-1}$ to $Y_k$ and conditioning on a collider will generally induce an association between its causes $12$, conditioning on $L_k$ would create an association between $A_{k-1}$ and $U$, and therefore between $A_{k-1}$ and $Y_k$ (because $U$ is associated with $Y_k$).

As an example, consider the outcome regression model for $\text{logit} \Pr(Y_{k+1} = 1|L_k, \bar{A}_K, \bar{Y}_k = 0)$ described in the previous section. The parameter $\beta_5$ for past treatment quantifies the conditional association between $A_{k-1}$ and $Y_k$. Part of this association may be due to the direct causal effect on $A_{k-1}$ on $Y_k$ that is not mediated through $L_k$ and the other variables in the model, and another part of this association may be due to bias because of conditioning on $L_k$. That is, the parameter $\beta_5$ is expected to be non-zero even if treatment $A_{k-1}$ had no effect on any individual’s outcome $Y_k$, and therefore cannot be
interpreted causally as the direct effect of past treatment that is not mediated through the other variables in the model.

The impossibility to endow the parameter $\beta_5$ with a causal interpretation is not a problem for the parametric g-formula, which simply uses the models for $\Pr(L_k = 1|\tilde{L}_{k-1}, \tilde{A}_{k-1}, \tilde{Y}_k = 0)$ and $\Pr(Y_{k+1} = 1|\tilde{L}_k, \tilde{A}_k, \tilde{Y}_k = 0)$ as an intermediate step to estimate the counterfactual probability of death in the study population $^3_4$. ABMs, on the other hand, endow individual model parameters with a causal interpretation to allow for extrapolation. Thus the parameter $\beta_5$ in the outcome model of the ABM is interpreted as the direct effect of $A_{k-1}$ on $Y_k$. Unfortunately, such an effect cannot be estimated without bias in the presence of an unmeasured common cause $U$.

In the next sections, we summarize the sources of bias (including treatment-confounder feedback) for ABMs constructed using data from certain populations when making inferences for other populations.

**BIAS EVEN IF THE ABM IS BASED ON DATA FROM A PERFECT RANDOMIZED TRIAL**

ABM estimates may be biased even if the model is parametrized using data from a perfect randomized trial. To show this, we further simplify our example to treatment decisions ($A_0, A_1$) at two times only.

Suppose we have data on $A_0, A_1, L_1$ and $Y$ from a perfect randomized trial with four arms: ($A_0 = 0, A_1 = 0$), ($A_0 = 0, A_1 = 1$), ($A_0 = 1, A_1 = 0$), and ($A_0 = 1, A_1 = 1$). Suppose that Figure 1.3(a) depicts the true but unknown causal graph. Because the distribution of $Y$ does not depend on $A_0$ and $A_1$, a regression of $Y$ on $A_0$ and $A_1$ that ignores data on $L_1$ (as well as a g-formula analysis that uses data on $L_1$) will correctly estimate the null causal effects of $A_0$ and $A_1$ on $Y$. Similarly, a regression of $L_1$ on $A_0$ will correctly estimate the non-null effect of $A_0$ on $L_1$. However, a regression of $Y$ on $L_1$ only will yield a non-null
association, which is a biased estimate of the null causal effect of L1 on Y because of unmeasured confounding by the path L1 ← U1 U2 → Y, and a regression of Y on A0, A1, L1 will yield a non-null A0 - Y association, which is a biased estimate of the null causal effect of A0 on Y because L1 is a collider on the path from A0 to Y.

---

Figure 1.3: Causal directed acyclic graphs depicting four scenarios for an ideal randomized trial to estimate the effect of treatment A0 on L1 and the joint effect of treatments A0 and A1 on Y. U1 and U2 are unmeasured variables.

Now consider an ABM researcher who wants to use trial estimates and then transport them to a new population in which distribution of U1 is the same as in the trial, but the conditional distributions of U2 given U1 and Y given U2 are not. He believes that he can use regressions from the trial to estimate the effects of A0 on L1, of A0, A1 on L1, and of L1 on Y. Suppose that the researcher finds that the A0 - L1 association in the new population (he does not have data on Y) is equal to that in the trial. Now, he is
even more certain the trial can be used to parametrize his ABM. However, as we have discussed, an ABM using parameters estimated from the perfect trial will falsely find a causal effect of \( A_0 \) on \( Y \).

Now suppose that Figure 1.3(b) depicts the true causal graph, in which there is no arrow from \( U_1 \) to \( U_2 \). Because now there is no \( L_1 \)-\( Y \) confounding and no \( A_0 \)-\( Y \) association conditional on \( L_1 \), the regression of \( Y \) on \( A_0, A_1, \) and \( L_1 \) in the trial data will correctly estimate the null causal effects of \( A_0, A_1, \) and \( L_1 \) on \( Y \). In this case, the ABM will correctly show no effect of \( A_0 \) and \( A_1 \) on \( Y \). However, because the marginal distribution of \( U_2 \) and the conditional distribution of \( Y \) given \( U_2 \) differ between the trial population and the new population, the marginal distribution of \( Y \) from the new population data and that computed under any strategy using the ABM will be different. That is, the marginal distribution of \( Y \) is non-transportable from the trial to the new population, as can be seen from the graphical results of Bareinboim and Pearl\textsuperscript{13,14} or directly from the g-formula (Appendix 1).

Suppose, we still have the \( U_1 \) to \( U_2 \) arrow missing but now the marginal distribution of \( U_2 \) and the conditional distribution of \( Y \) given \( U_2 \) are the same between the trial and the new population, but the marginal distribution of \( U_1 \) and the conditional distribution of \( L_1 \) given \( A_0 \) and \( U_1 \) are different between these populations. Then, the law of \( L_1 \) given \( A_0 \) (and thus the causal effect of \( A_0 \) on \( L_1 \)) will now differ between the trial and the new population, but the ABM will correctly show no effect of \( A_0 \) and \( A_1 \) on \( Y \) in the new population, and the marginal distribution of \( Y \) will be transportable from the trial to the new population.

Next suppose that the true causal graph has an arrow from \( L_1 \) to \( Y \) (Figure 1.3(c)) or from \( A_0 \) to \( Y \) (Figure 1.3(d)) so that \( A_0 \) has an effect on \( Y \). Then, even in the absence of confounding (i.e., no \( U_1 \) to \( U_2 \) arrow), the magnitude of the causal effects of \( A_0 \) and \( A_1 \) on \( Y \) in the new population will differ from that in the trial on any scale. Furthermore, the causal effects in both populations will differ from the now
biased estimate given by the ABM of the effect in the new population. This again follows from the graphical results of Bareinboim and Pearl\textsuperscript{13,14} or directly from the g-formula (Appendix 1).

The next section describes a simulation study that quantifies these biases in our example with multiple treatment decisions over time.

**SIMULATIONS UNDER A NULL TREATMENT EFFECT**

*Simulation scenarios*

We simulated three scenarios: a base scenario with approximately 10% mortality at 12 months, a high-risk scenario with approximately 50% mortality, and a low-risk scenario with approximately 1% mortality. For each scenario, we simulated a cohort of \(10^6\) HIV-positive individuals followed for 12 months under the data generating mechanism depicted in Figure 1.2. We simulated the monthly CD4 count, treatment, and death status, with no missing data, for each individual. Treatment had a null effect on mortality, which could represent the comparison of two active treatments of equal effectiveness, or the comparison of an ineffective treatment with no treatment.

In each scenario, we estimate the counterfactual 12-month mortality risk under the two treatment strategies “always treat” and “never treat”. We first estimated these risks using the parametric g-formula applied to the simulated data. We then estimated these risks using ABMs with the same model specification as the parametric g-formula.

In the high- and low-risk scenarios, we implemented four types of ABMs depending on the origin of the model parameters:

1. The scenario of interest (high- or low-risk). This ABM #1 is expected to provide an unbiased mortality estimate.
2. The base scenario. This ABM #2 is expected to provide a mortality estimate that is unbiased for the base scenario but biased for the high- and low-risk scenarios, because of non-transportability.

3. The parameter for prior treatment $\theta_5$ from the base scenario and all other parameters from the scenario of interest. This ABM #3 is expected to provide a biased mortality estimate because the magnitude of the association between prior treatment and the outcome conditional on a collider generally varies across populations with different outcome risk.

4. The parameter for prior treatment $\theta_5$ from the scenario of interest, and all other parameters from the base scenario. This ABM #4 is subject to the two sources of bias in 2. and 3. above.

The data were simulated following the algorithm described by Robins 15 and Young et al 16 (Appendix 2). SAS 9.4 was used for all analyses.

**Estimation via the parametric g-formula**

Let $g$ represent a treatment strategy for $k=0,\ldots,K$ months of follow-up, $Y_{k+1}^g$ the counterfactual value for an individual’s outcome if she had followed strategy $g$, and $\bar{a}_k^g$ a treatment history up to month $k$ that is consistent with the strategy $g$. For example, for the strategy “always treat”, $\bar{a}_k^g = (a_0 = 1, a_1 = 1, \ldots, a_k = 1)$. Our goal is to estimate the counterfactual mortality risk under a strategy $g$ by time $k+1$, that is, $\Pr(Y_{k+1}^g=1)$. Under the decision process in Figure 1.1 (equivalent to the data generation mechanism in Figure 1.2), this counterfactual risk is equal to the g-formula 17:

$$
= \sum_{l_k} \sum_{j=0}^{k} \Pr[Y_{j+1} = 1|L_j = \bar{l}_j, A_j = \bar{a}_j^g, Y_j = 0] \\
\times \prod_{s=0}^{j} \left( \Pr[Y_s = 0|L_{s-1} = \bar{l}_{s-1}, A_{s-1} = \bar{a}_{s-1}^g, Y_{s-1} = 0] \times f(l_s|\bar{l}_{s-1}, \bar{a}_{s-1}^g, \bar{Y}_{s-1} = 0) \right)
$$
We estimated the factors of the g-formula via the parametric logit $\Pr(L_k = 1 | \bar{L}_{k-1} = \bar{L}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{Y}_k = 0) = \gamma_0 + \gamma_1 t + \gamma_2 h_1(t) + \gamma_3 h_2(t) + \gamma_4 h_3(t) + \gamma_5 L_{k-2} + \gamma_6 L_{k-1} + \gamma_7 A_{k-2} + \gamma_8 A_{k-1}$, and logit $\Pr(Y_{k+1} = 1 | \bar{L}_k, \bar{A}_k, \bar{Y}_k = 0) = \beta_0 + \beta_1 t + \beta_2 h_1(t) + \beta_3 h_2(t) + \beta_4 h_3(t) + \beta_5 A_{k-1} + \beta_6 A_k + \beta_7 L_{k-1} + \beta_8 L_k + \beta_9 (L_k A_k)$, where, $h_j(t)$ represents restricted cubic splines with knots at 3, 6, 9 and 12 months (Technical Appendix Table 1.6). We approximated the sum through a Monte-Carlo simulation of $10^6$ individuals under the strategy $g$ of interest (the value of $A_k$ at every month was assigned as 1 or 0 for the interventions ‘always treat’ and ‘never treat’, respectively). 95% confidence intervals were obtained via 500 bootstrap samples.

We used a SAS macro to get the parametric g-formula estimates. The macro is available at http://www.hsph.harvard.edu/causal/software/

**Estimation via the ABM**

The algorithm for estimating the ABM is similar to that for the g-formula, except for the source of parameters for the conditional distributions of $Y$ and $L$. The parameters estimated for each simulated population are given in Technical Appendix Table 1.6. The inputs to the ABMs were chosen from these estimates, based on the appropriate source for each ABM type and scenario. The conditional probability models used for the ABMs were identical to those specified above for the parametric g-formula. For all scenarios, the baseline confounder distribution was estimated from the corresponding empirical distribution. To reduce the impact of stochastic noise, we used the same set of random seeds to initialize the Monte-Carlo simulations for each method implemented within the same scenario.
**Simulation results**

The first row of Table 1.1 shows the 12-month mortality risk in the 3 simulated scenarios.

The next two rows show estimates under ‘always treat’ and ‘never treat’ for the parametric g-formula and ABM #1. As expected, both methods estimated identical risks. Table 1.1 shows the 95% confidence intervals around the g-formula estimates. See Appendix 4 for uncertainty intervals around the ABM estimates 19. Although the uncertainty intervals obtained from these sensitivity analyses are not interpretable as confidence intervals, they can provide some insight into the range of possible outcome distributions consistent with variations of the model 20.

The next rows of Table 1.1 show estimates for ABMs #2, #3, and #4 for the high- and low-risk scenarios. ABM #2 predictably replicates the g-formula estimates from the base scenario and the risk estimates are therefore biased for the high- and low-risk scenarios. However, since the effect is null in all populations, the causal effect estimate from ABM #2 is correct for the high- and low-risk scenarios. ABM #3 and ABM #4 yield biased estimates of the risk and causal effect for both scenarios.
Table 1.1: Null treatment effect simulation: 12 month risk of death (%) estimated under two interventions in different scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Base</th>
<th>High-Risk</th>
<th>Low-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated data</td>
<td>10.6</td>
<td>47.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Estimation method</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parametric g-formula*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Always treat</td>
<td>10.5 (10.5, 10.6)</td>
<td>47.8 (47.7, 47.9)</td>
<td>1.2 (1.1, 1.2)</td>
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<tr>
<td>Never Treat</td>
<td>10.4 (10.3, 10.5)</td>
<td>48.0 (47.9, 48.0)</td>
<td>1.1 (1.1, 1.1)</td>
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<td>-0.1 (-0.3, 0.02)</td>
<td>0.1 (-0.01, 0.1)</td>
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</tr>
<tr>
<td>scenario of interest</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>10.5</td>
<td>47.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Never Treat</td>
<td>10.4</td>
<td>48.0</td>
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<tr>
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<tr>
<td>treatment from base</td>
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<td>scenario, all others</td>
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<tr>
<td>from scenario of interest</td>
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<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>---</td>
<td>24.0</td>
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<td>Risk difference</td>
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<tr>
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<tr>
<td>Risk difference</td>
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<td>-3.6</td>
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</table>

*Numbers in parentheses are 95% confidence limits
SIMULATIONS UNDER A NON-NULL TREATMENT EFFECT

Simulation scenarios

We conducted two additional sets of simulations that were identical to the one described above except that the treatment effects were non-null. In one, treatment was designed to have a harmful effect on survival, with treated individuals expected to have a mortality rate approximately twice as high as untreated individuals. In the second, treatment was designed to have a beneficial effect on survival, such that individuals who were treated were expected to have a mortality rate approximately half that of individuals who were untreated.

Simulation results

When the treatment was harmful, 12-month mortality increased in all scenarios (Table 1.2). As expected, ABM #2 replicated the base scenario 12-month mortality. However, since the treatment effect was no longer null, the causal effect estimates from ABM #2 were no longer unbiased for the populations of interest. ABMs #3 and #4 were biased for both the high- and low-risk scenarios. The direction and magnitude of the bias varied between simulations.

When the treatment was protective, 12-month mortality decreased in all scenarios (Table 1.3). Again, ABM #2 replicated the base-case scenario, although less closely than with a null treatment effect, and the causal effect estimate was biased for both the high- and low-risk populations. ABM #3 and ABM #4 were also severely biased – in two cases across the null, suggesting a harmful treatment effect.
Table 1.2: Harmful treatment effect simulation: 12-month risk of death (%) estimated under two interventions in different scenarios.

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<th>Low-risk</th>
</tr>
</thead>
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<td>Estimation method</td>
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<td></td>
</tr>
<tr>
<td>Parametric g-formula*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>23.7 (23.6, 23.8)</td>
<td>65.1 (65.0, 65.1)</td>
<td>3.0 (2.9, 3.0)</td>
</tr>
<tr>
<td>Never Treat</td>
<td>11.0 (10.9, 11.1)</td>
<td>46.3 (46.2, 46.4)</td>
<td>1.2 (1.2, 1.3)</td>
</tr>
<tr>
<td>Risk difference</td>
<td>12.7 (12.6, 12.9)</td>
<td>18.8 (18.7, 18.9)</td>
<td>1.8 (1.7, 1.8)</td>
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<tr>
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<td>scenario of interest</td>
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<tr>
<td>Always treat</td>
<td>23.7</td>
<td>65.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Never Treat</td>
<td>11.0</td>
<td>46.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Risk difference</td>
<td>12.7</td>
<td>18.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Agent-based model 2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all parameters from</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>base scenario</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>---</td>
<td>24.0</td>
<td>23.7</td>
</tr>
<tr>
<td>Never Treat</td>
<td>---</td>
<td>12.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Risk difference</td>
<td>---</td>
<td>11.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Agent-based model 3:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parameter for past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment from base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scenario, all others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from scenario of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>---</td>
<td>53.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Never Treat</td>
<td>---</td>
<td>46.3</td>
<td>1.2</td>
</tr>
<tr>
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<td>7.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Agent-based model 4:</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment from</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scenario of interest,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all others from base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scenario</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>---</td>
<td>32.4</td>
<td>21.8</td>
</tr>
<tr>
<td>Never Treat</td>
<td>---</td>
<td>12.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Risk difference</td>
<td>---</td>
<td>20.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are 95% confidence limits
Table 1.3: Beneficial treatment effect simulation: 12-month risk of death (%) estimated under two interventions in different scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Base</th>
<th>High-Risk</th>
<th>Low-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated data</td>
<td>7.2</td>
<td>39.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Estimation method</td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parametric g-formula*</td>
<td>4.7 (4.6, 4.7)</td>
<td>29.3 (29.2, 29.4)</td>
<td>0.5 (0.5, 0.5)</td>
</tr>
<tr>
<td>Always treat</td>
<td>Never Treat</td>
<td>Risk difference</td>
<td>-5.3</td>
</tr>
<tr>
<td>Agent-based model 1: all parameters from scenario of interest</td>
<td>4.7</td>
<td>29.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Always treat</td>
<td>Never Treat</td>
<td>Risk difference</td>
<td>-5.3</td>
</tr>
<tr>
<td>Agent-based model 2: all parameters from base scenario</td>
<td>6.7</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>Never Treat</td>
<td>Risk difference</td>
<td>---</td>
</tr>
<tr>
<td>Agent-based model 3: parameter for past treatment from base scenario, all others from scenario of interest</td>
<td>11.8</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>Never Treat</td>
<td>Risk difference</td>
<td>---</td>
</tr>
<tr>
<td>Agent-based model 4: parameter for past treatment from scenario of interest, all others from base scenario</td>
<td>27.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Always treat</td>
<td>Never Treat</td>
<td>Risk difference</td>
<td>---</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are 95% confidence limits
DISCUSSION

In our simplified example, mortality risk was always correctly estimated when model parameters were estimated from the same population to which the model was applied, regardless of whether we used the parametric g-formula or an ABM. In our example, the ABM and the parametric g-formula are mathematically identical when the parameters of both are estimated from the population of interest. However, mortality risks were biased when parameters of ABMs were obtained from populations other than the target population. Bias arose even if the causal structure and magnitude of treatment effects were constant across populations. The bias has two distinct sources: 1) differences in distributions of unmeasured risk factors between populations and 2) use of models that require knowledge about the conditional association between treatment and outcome conditional on colliders.

The first source of bias was demonstrated by ABM #2, which was parameterized using parameters from the base-case scenario and therefore did not provide accurate mortality estimates in the high- and low-risk scenarios. This bias reflects the expected lack of transportability\(^\text{13,14}\). The second source of bias was demonstrated by ABM #3, in which the only parameter not estimated in the target population was the association between past treatment and the outcome conditional on confounders for subsequent treatment that were affected by both past treatment and unmeasured determinants of the outcome. This bias is expected, even under the null, because of collider stratification. If the true effect of treatment is non-null, bias can arise even when \(U\) is associated with only one of \(L_k\) or \(Y_k\) (see Appendix Section 1 for details). Our ABM #4 combined both sources of bias.

To avoid these biases, modelers might consider one of the following three strategies when constructing ABMS.
First, the ABM can be parameterized based on studies in which confounding by common causes of variables affected by treatment and of the outcome has been appropriately adjusted for. In our example, this strategy requires that some studies have unbiasedly estimated the effects of treatment and CD4 count on death, and the effects of past treatment on CD4 count and of CD4 count on treatment. Unfortunately, unbiased estimation of the effects of past treatment and CD4 count requires adjustment for confounding by common causes like the variable \(U\), which are generally unavailable to analysts.

Second, the ABM can incorporate all (measured and unmeasured) determinants of the outcome in the ABM. In our example, the ABM would need to include the unmeasured variable \(U\). Unfortunately, many of these determinants will be either unknown or unmeasured due to technical or resource limitations. Even if they were measured, it would be challenging to find parameter estimates from all components of a model that is now conditioned on generally unavailable variables.

Third, the ABM can be parameterized using parameter estimates from populations where the distribution of risk factors, including these common causes, is known to be identical to that in the population of interest. Unfortunately, this would severely limit the applicability of the model.

Given the difficulty of implementing the above strategies, a more realistic course of action may be design of sensitivity analyses on parameters that measure the association between treatment and outcome conditional on variables affected by treatment.

In summary, both the parametric g-formula and ABMs can afford to ignore unmeasured determinants of the outcome when causal inference is restricted to a population with sufficient data on confounders, treatment, and outcome. However, the use of ABMs for causal inferences on another population may be biased even if the causal network linking all variables is identical in both populations.
ACKNOWLEDGEMENTS

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TECHNICAL APPENDIX

1. Formalizing the expected biases in ABMs under null and non-null treatment effects

In this section, we provide an explanation of the expected biases in the ABMs. For simplicity, we consider only a single time point of treatment from our original data generating mechanism. In this simplified example, conditioning on CD4 count was not actually necessary, but is used to demonstrate the biases that can be introduced with multiple time points. In these examples, only the distribution of $U$ differs between populations. Table 1.4 presents a summary of the potential for bias in ABMs.

Table 1.4: Summary of potential for non-transportability and collider bias in risk and causal effect estimates obtained by ABMs, when only the distribution of $U$ differs between populations.

<table>
<thead>
<tr>
<th>$A$ causes $Y$, directly or through $L$?</th>
<th>$U$ causes $L$?</th>
<th>$U$ causes $Y$?</th>
<th>Bias in risk estimate (risk difference or ratio)</th>
<th>Bias in effect estimate (risk difference or ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>None†</td>
<td>None</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>ABM #2, ABM #3, ABM #4</td>
<td>None</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>None†</td>
<td>None</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>ABM #2, ABM #3, ABM #4</td>
<td>ABM #3, ABM #4</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>None†</td>
<td>None†</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>ABM #2, ABM #3, ABM #4</td>
<td>ABM #2, ABM #3, ABM #4</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ABM #2, ABM #3, ABM #4</td>
<td>ABM #2, ABM #3, ABM #4</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ABM #2, ABM #3, ABM #4*</td>
<td>ABM #2, ABM #3, ABM #4*</td>
</tr>
</tbody>
</table>

†When $U$ is not a cause of either $L$ or $Y$, and when the only difference between populations is in the (marginal) distribution of $U$, then there will be no bias in the risk or effect estimates. However, if the populations differ in the distribution of $A$ or in other causes of $Y$, then there may be bias.

*For the non-null case, bias is ensured when $U$ causes both $L$ and $Y$, because bias occurs when $U$ causes either $L$ or $Y$. 
**Scenario 1: True treatment effect is null in all populations**

Consider the DAG in Figure 1.4. Treatment (A) affects CD4 cell count (L). However, neither treatment nor CD4 cell count has any effect on mortality (Y). The table provides examples for two populations of 10000 individuals whose covariate distributions are described by the DAG above, and which only differ in the prevalence of U=1 (45% in the base-case and 15% in the low-risk population). Without knowledge of U, the g-formula for the low-risk population in Figure 1.4 can be estimated using equation 1, and correctly estimates the null effect and the probability of death in this population under each treatment value (21.0%).

\[
f[Y|A = a] = \sum_L f[Y|L, A = a]f[L|A = a]
\]  

(1)

**Figure 1.4:** Causal graph depicting a single time point with treatment A, outcome Y, covariate L, and an unknown variable U. The true causal effect of treatment on the outcome is null, and U is a cause of L and Y. The tables provide possible data for 10,000 individuals in two populations: base case and low risk.

When U is considered, both the function of Y and the function of L are dependent on U. The g-formula for the low-risk population in Figure 1.4 could be re-written using equation 2 to explicitly
account for the presence of $U$, and will still return the correct probability of mortality in the low-risk population for each treatment value ($f[Y]$) and risk difference.

$$f[Y|A = a] =$$ 

$$= \sum_L \sum_U f[Y|U, L, A = a] f[L|U, A = a] f[U]$$

$$= \sum_U f[Y|U] f[U] \sum_L f[L|U, A = a] = f[Y]$$

Thus, the estimates from the parametric g-formula in a single dataset are expected to produce unbiased estimates of the risk of the outcome and of the causal effect of treatment on the outcome for that dataset despite the exclusion of information on $U$ from the models, assuming the identifiability assumptions for causal inference hold – namely, conditional exchangeability of the treated and untreated given patient histories (no unmeasured common causes of treatment and the outcome), positivity for treatment strategies, consistency of treatment definition, and no misspecification of the models for the conditional probability distributions of the confounder and the outcome.

Now, let $f_1$ represent a function estimated in the base case population and let $f_2$ represent a function estimated in the low-risk population. Using this new notation, the model suggested by ABM #1, where all input probabilities are estimated in the cohort of interest, can be written as in equation 3. Regardless of whether we have information on $U$, ABM #1 gives us unbiased estimates of both the risk and the causal effect in the cohort of interest, under the same identifiability assumptions as the g-formula.

$$f_2[Y|A = a] = \sum_L f_2[Y|L, A = a] f_2[L|A = a] = f_2[Y]$$
In ABM #2 all input probabilities are estimated from the base-case cohort (as shown by the index $f_1$), rather than the population of interest (equation 4). Unless all distributions are the same in both populations, equation 4 will be biased.

$$f_2[Y|A = a] \neq \sum_L f_1[Y|L, A = a] f_1[L|A = a] = f_1[Y]$$  \hspace{1cm} (4)

For the example in Figure 1.4, the ABM #2 estimate of the mortality risk in the treated and untreated in the low-risk population is 33%, not 21%. This is the risk in the base-case population, but is incorrect for the low-risk population. The difference in the distribution of $U$ between the two populations created a lack of transportability in the risk estimates. However, since the null is true in both populations, the causal effect estimate obtained from ABM #2 will be correct.

Now consider ABM #3, where the input probabilities are selected from both the cohort of interest and the base-case cohort. Here, the probability of death $Y$ given treatment $A$ is estimated from the base-case and is used to estimate the risk in the other cohort. Thus, the distribution of $Y$ used for the ABM should be denoted with $f_1$, but the distribution of $L$ used in this ABM comes from the cohort of interest and is denoted with $f_2$, as in equation (5).

$$f_2[Y|A = a] \neq \sum_L f_1[Y|L, A = a] f_2[L|A = a]$$  \hspace{1cm} (5)

It is clear that unless $f_1[Y|L, A = a] = f_2[Y|L, A = a]$, the risk estimate will be biased. In addition, we can no longer expect the causal effect estimate to be unbiased, even when the null is true in both populations. In the Figure 1.4 example, the risk difference estimate using ABM #3 is 2.5 percentage points. The bias in ABM #3 is a result of conditioning on the collider at $L$, which induces an association between $A$ and $Y$ through $U$, and is not an issue of transportability. Similar logic holds for
ABM #4, where the distribution of Y is taken from the population of interest, \( f_2[Y|L, A = a] \), and the distribution of L is taken from the base case, \( f_1[L|A = a] \).

In Figure 1.5, \( U \) is only a cause of \( L \) and not of \( Y \). Here, \( Y \) has no parents at all, and the marginal distribution of \( Y \) is the best estimate of the risk in both populations. If the only difference between populations is the prevalence of \( U \), then the risk and the causal effect are transportable between all populations and there is no bias; all of ABMs #1-#4 will provide unbiased estimates of the risk and causal effect.

![Causal graph]

In Figure 1.6, \( U \) is only a cause of \( Y \) and not of \( L \). Here, the conditional distribution of \( Y \) will differ between populations whenever the distribution of \( U \) differs. Therefore, we expect non-transportability of the risk estimates from ABM #2, but not the causal effect if the null is true. There will be bias in this scenario for the risk estimate from ABMs #3 and #4 because \( f_1[Y] \) is not equal to \( f_2[Y] \). However, the causal effect will not be biased in this scenario because the null is true.

**Figure 1.5:** Causal graph depicting a single time point with treatment \( A \), outcome \( Y \), covariate \( L \), and an unknown variable \( U \). The true causal effect of treatment on the outcome is null, and \( U \) is a cause of \( L \) but not \( Y \). The tables provide possible data for 10,000 individuals in two populations: base case and low risk.

In Figure 1.6, \( U \) is only a cause of \( Y \) and not of \( L \). Here, the conditional distribution of \( Y \) will differ between populations whenever the distribution of \( U \) differs. Therefore, we expect non-transportability of the risk estimates from ABM #2, but not the causal effect if the null is true. There will be bias in this scenario for the risk estimate from ABMs #3 and #4 because \( f_1[Y] \) is not equal to \( f_2[Y] \). However, the causal effect will not be biased in this scenario because the null is true.
Figure 1.6: Causal graph depicting a single time point with treatment A, outcome Y, covariate L, and an unknown variable U. The true causal effect of treatment on the outcome is null, and U is a cause of Y but not L. The tables provide possible data for 10,000 individuals in two populations: base case and low-risk.

Scenario 2: Treatment effect is non-null

Finally, consider Figure 1.7, where the treatment effect is non-null. Assuming the identifiability criteria described above are true, the g-formula and ABM #1 will still give unbiased estimates of the risk and the causal effect in the cohort of interest for all scenarios in Figure 1.7. However, ABM #2, ABM #3, and ABM #4 will all return biased estimates of the risk and the causal effect. This will happen even when U is a cause only of L (Figure 1.7(b)) or when U is a cause only of Y (Figure 1.7(c)).
Figure 1.7: Causal graphs depicting a single time point with treatment $A$, outcome $Y$, covariate $L$, and an unknown variable $U$. The true causal effect of treatment is non-null. (a) $A$ is a cause of $Y$ through $L$ only, and $U$ is a cause of both $L$ and $Y$; (b) $A$ is a cause of $Y$ through $L$ only, and $U$ is a cause of $L$ but not $Y$; (c) $A$ is a cause of $Y$ through $L$ only, and $U$ is a cause of $Y$ but not $L$; (d) $A$ is a cause of $Y$ directly and through $L$, and $U$ is a cause of $L$ and $Y$.

2. Simulation procedure

The data were simulated following the algorithm described by Robins\textsuperscript{15} and Young et al\textsuperscript{16}.

Briefly, for each of $10^6$ simulated individuals:

**Step 1:** Simulate the counterfactual failure time in the absence of treatment $T_0$ under an exponential distribution with hazard $\lambda_0(t)$, and set $U = T_0$.

Then for each $k \in [0,12]$ implement steps 2, 3, and 4:

**Step 2:** Simulate $L_k$ using the probability model: $\Pr(L_k = 1| \bar{A}_{k-1}, U, Y_k = 0) = (1 - \gamma_2) * \exp[\gamma_1 + \kappa * \ln(U + \tau)]/[1 + \exp(\gamma_1 + \kappa * \ln(U + \tau))] + \gamma_2 A_{k-1}$, where $0 < \tau < 1$. Note: $L_k$ is simulated from $k = -2$. By definition, $A_k = 0$ for $k < 0$. 


**Step 3:** Simulate $A_k$ for previously untreated individuals using the logistic regression model:

$$\text{logit} \Pr(A_k = 1|L_k, \bar{A}_{k-1}, Y_k = 0) = \alpha_0 + \alpha_1 L_k + \alpha_2 L_{k-1} + \alpha_3 L_{k-2}.$$ Set $A_k=1$ if $A_{k-1}=1$.

**Step 4:** Generate the failure time as the solution to: $T_0 = \int_0^T \exp[\gamma(t, \bar{A}_t, L_t, \psi)] dt$,

where $\gamma(t, \bar{A}_t, L_t, \psi) = -\psi A_k$. If $T=k+1$ set $Y_{k+1}=1$ and go to Step 1 for a new subject. Otherwise set $Y_{k+1}=0$ go to Step 2 for $k+1$. $\psi$ is set to 0 for a null treatment effect, to -1 for a protective effect, and to 1 for a harmful effect. By definition, everybody has $Y_0=0$.

Parameter values for $\lambda_0(t)$ were varied to simulate data from populations with differences in the distribution of $U$, and therefore different background mortality levels. Parameter values for the models in step 2 and 3 are given in Table 1.5.

**Table 1.5:** Input parameters used to simulated outcome distribution and conditional probability distributions of treatment and CD4 cell count when creating the simulated population data.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exponential Parameter for $T_0$ ($\lambda_0(t)$):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base case</td>
<td>0.010</td>
<td>--</td>
</tr>
<tr>
<td>High-risk population</td>
<td>0.100</td>
<td>--</td>
</tr>
<tr>
<td>Low-risk population</td>
<td>0.001</td>
<td>--</td>
</tr>
<tr>
<td><strong>Conditional probability distribution for $L_k$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{k-1}$</td>
<td>0.675</td>
<td>--</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>25</td>
<td>--</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>-11.2</td>
<td>--</td>
</tr>
<tr>
<td>$\tau$</td>
<td>0.38</td>
<td>--</td>
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<tr>
<td><strong>Conditional probability distribution for $A_k$, logistic regression model parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.1</td>
<td>--</td>
</tr>
<tr>
<td>$L_k$</td>
<td>-0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>$L_{k-1}$</td>
<td>-0.25</td>
<td>0.8</td>
</tr>
<tr>
<td>$L_{k-2}$</td>
<td>-0.10</td>
<td>0.9</td>
</tr>
</tbody>
</table>
3. Simulation procedure: ABMs and parametric g-formula

The simulation procedure for the parametric g-formula and the ABMs is provided in the main text. The estimated input parameters used for the microsimulation portion of these methods are given in Table 1.6. The parametric g-formula used the estimated parameters from the population of interest, while the ABMs used parameters from one or more source populations as specified in the methods section.
Table 1.6: Output parameter estimates for logistic regression models for treatment, CD4 cell count, and mortality, by population for the null effect scenario. Parameters for CD4 cell count and mortality models used as inputs for parametric g-formula and for the ABMs.

<table>
<thead>
<tr>
<th>Model / parameter</th>
<th>Base population</th>
<th>High-risk population</th>
<th>Low-risk population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Logistic regression model for L_k</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intercept</td>
<td>-3.49</td>
<td>-1.85</td>
<td>-5.72</td>
</tr>
<tr>
<td>t</td>
<td>0.03</td>
<td>0.03</td>
<td>0.004</td>
</tr>
<tr>
<td>h_1(t)</td>
<td>-0.23</td>
<td>-0.28</td>
<td>-0.03</td>
</tr>
<tr>
<td>h_2(t)</td>
<td>0.45</td>
<td>0.57</td>
<td>0.05</td>
</tr>
<tr>
<td>h_3(t)</td>
<td>-0.32</td>
<td>-0.43</td>
<td>-0.04</td>
</tr>
<tr>
<td>L_k-2</td>
<td>0.26</td>
<td>0.73</td>
<td>0.03</td>
</tr>
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<td>0.30</td>
<td>0.88</td>
<td>0.03</td>
</tr>
<tr>
<td>A_k-2</td>
<td>-0.34</td>
<td>-1.04</td>
<td>-0.04</td>
</tr>
<tr>
<td>A_k-1</td>
<td>4.28</td>
<td>3.43</td>
<td>6.46</td>
</tr>
<tr>
<td><strong>Logistic regression model for A_k</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.55</td>
<td>-1.55</td>
<td>-1.55</td>
</tr>
<tr>
<td>t</td>
<td>0.002</td>
<td>0.001</td>
<td>0.00</td>
</tr>
<tr>
<td>h_1(t)</td>
<td>-0.003</td>
<td>-0.01</td>
<td>-0.004</td>
</tr>
<tr>
<td>h_2(t)</td>
<td>0.001</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>h_3(t)</td>
<td>0.01</td>
<td>-0.03</td>
<td>-0.01</td>
</tr>
<tr>
<td>L_k-2</td>
<td>-0.10</td>
<td>-0.10</td>
<td>-0.09</td>
</tr>
<tr>
<td>L_k-1</td>
<td>-0.25</td>
<td>-0.25</td>
<td>-0.27</td>
</tr>
<tr>
<td>L_k</td>
<td>-0.30</td>
<td>-0.29</td>
<td>-0.31</td>
</tr>
<tr>
<td>A_k-2</td>
<td>0.23</td>
<td>0.23</td>
<td>0.24</td>
</tr>
<tr>
<td>A_k-1</td>
<td>22.17</td>
<td>22.21</td>
<td>22.17</td>
</tr>
<tr>
<td><strong>Logistic regression model for Y_k</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-4.87</td>
<td>-2.55</td>
<td>-7.13</td>
</tr>
<tr>
<td>t</td>
<td>-0.01</td>
<td>-0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>h_1(t)</td>
<td>-0.14</td>
<td>-0.07</td>
<td>-0.11</td>
</tr>
<tr>
<td>h_2(t)</td>
<td>0.31</td>
<td>0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>h_3(t)</td>
<td>-0.25</td>
<td>-0.16</td>
<td>-0.01</td>
</tr>
<tr>
<td>L_k-1</td>
<td>1.13</td>
<td>0.34</td>
<td>1.53</td>
</tr>
<tr>
<td>A_k-1</td>
<td>-1.41</td>
<td>-0.28</td>
<td>-1.95</td>
</tr>
<tr>
<td>L_k</td>
<td>2.18</td>
<td>0.54</td>
<td>4.18</td>
</tr>
<tr>
<td>A_k</td>
<td>0.10</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>L_k*A_k</td>
<td>-1.23</td>
<td>-0.35</td>
<td>-3.02</td>
</tr>
</tbody>
</table>
4. Uncertainty intervals for ABMs

Although we cannot estimate confidence intervals for ABMs, it is common practice to perform some type of uncertainty analysis. We conducted a one-way sensitivity analysis for the effect of past treatment ($A_{k-1}$) using ABM #3 when the null hypothesis was true. We used 500 bootstrapped samples of the original simulated data to obtain estimates of the mean and variance of the parameter for past treatment and then randomly sampled the input for past treatment from a normal distribution based on this estimated mean and variance. We ran ABM #3 using each of the 500 past treatment inputs; all other inputs were estimated from the population of interest and remained the same throughout the 500 runs. In the base-case scenario, this was equivalent to a one-way sensitivity analysis of ABM #1, with the distribution for past treatment, and the estimated values of all other inputs obtained from the base-case. The median, and 2.5th and 97.5th percentiles of the resulting mortality and risk difference estimates are presented in Table 1.7.

Table 1.7: Uncertainty intervals for ABM #3 obtained from 500 runs using 1-way sensitivity analysis of the effect of past treatment on the outcome, when the true effect is null.

<table>
<thead>
<tr>
<th>Cohort of interest (equivalent to ABM #1)</th>
<th>Intervention</th>
<th>% Mortality</th>
<th>Median Estimate from SA</th>
<th>Uncertainty Interval Range of SA Estimates: 2.5th, 97.5th percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base scenario</td>
<td>Always Treat</td>
<td>10.5</td>
<td>5.6</td>
<td>5.3, 10.9</td>
</tr>
<tr>
<td></td>
<td>Never Treat</td>
<td>10.4</td>
<td>5.6</td>
<td>5.6, 10.4</td>
</tr>
<tr>
<td></td>
<td>Risk difference</td>
<td>0.1</td>
<td>-0.02</td>
<td>-0.3, 0.4</td>
</tr>
<tr>
<td>High-risk scenario</td>
<td>Always Treat</td>
<td>24.0</td>
<td>9.0</td>
<td>8.4, 24.3</td>
</tr>
<tr>
<td></td>
<td>Never Treat</td>
<td>48.0</td>
<td>10.6</td>
<td>10.6, 48.0</td>
</tr>
<tr>
<td></td>
<td>Risk difference</td>
<td>-24.0</td>
<td>-2.0</td>
<td>-24.4, -1.5</td>
</tr>
<tr>
<td>Low-risk scenario</td>
<td>Always Treat</td>
<td>1.9</td>
<td>3.2</td>
<td>1.9, 3.4</td>
</tr>
<tr>
<td></td>
<td>Never Treat</td>
<td>1.1</td>
<td>2.9</td>
<td>1.1, 2.9</td>
</tr>
<tr>
<td></td>
<td>Risk difference</td>
<td>0.8</td>
<td>0.4</td>
<td>0.2, 0.8</td>
</tr>
</tbody>
</table>
5. Sensitivity analyses for simulation and model building

We performed several checks on our models and on our simulated data. First, we estimated the conditional probability distribution of treatment in the simulated populations and then used the parametric g-formula to estimate the outcome risk under no intervention using the following logistic regression model for treatment initiation: 

$$
\logit \Pr(A_k = 1 | \bar{L}_k = \bar{L}_k, \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{Y}_k = 0) = \alpha_0 + \alpha_1 t + \alpha_2 h_1(t) + \alpha_3 h_2(t) + \alpha_4 h_3(t) + \alpha_5 L_{k-2} + \alpha_6 L_{k-1} + \alpha_7 L_k + \alpha_8 A_{k-2} + \alpha_9 A_{k-1}.
$$

We then repeated the Monte-Carlo simulation assigning treatment at each time point according to this model, rather than setting treatment to 0 or 1 as above. The estimated probability of death over follow-up from this model should replicate the observed mortality if the model is correctly specified. Note that the model under intervention could be incorrectly specified even if the model under no intervention is correctly specified. Results of the g-formula analyses under no intervention are provided in Table 1.8.

Table 1.8: Checking for model misspecification: estimated mortality risk over follow-up using the g-formula under no intervention for each population (% 95% confidence intervals).

<table>
<thead>
<tr>
<th>True effect</th>
<th>Base case</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>10.4 (10.3, 10.4)</td>
<td>47.8 (47.8, 47.9)</td>
<td>1.1 (1.1, 1.2)</td>
</tr>
<tr>
<td>Harmful</td>
<td>18.7 (18.6, 18.8)</td>
<td>56.1 (56.1, 56.2)</td>
<td>2.3 (2.3, 2.3)</td>
</tr>
<tr>
<td>Beneficial</td>
<td>6.7 (6.7, 6.8)</td>
<td>38.5 (38.4, 38.5)</td>
<td>0.7 (0.7, 0.7)</td>
</tr>
</tbody>
</table>

Second, we assessed the amount of confounding by CD4 cell count in our simulated populations by running the g-formula macro without inclusion of CD4 cell count as a covariate. The estimated risk differences are presented in Table 1.9. For the null scenario, the 95% confidence intervals, obtained via 500 bootstraps samples, for the confounded estimates predictably do not include the null.
Table 1.9: Checking for confounding in the simulated data: estimated difference in mortality risk over follow-up comparing ‘always treat’ to ‘never treat’, without adjustment for the time-varying covariate CD4 cell count (% risk difference, 95% confidence intervals).

<table>
<thead>
<tr>
<th>True effect</th>
<th>Base case</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>-1.8 (-1.9, -1.7)</td>
<td>-1.7 (-1.8, -1.5)</td>
<td>-0.2 (-0.3, -0.2)</td>
</tr>
<tr>
<td>Harmful</td>
<td>9.9 (9.7, 10.0)</td>
<td>16.2 (16.0, 16.3)</td>
<td>1.3 (1.3, 1.4)</td>
</tr>
<tr>
<td>Beneficial</td>
<td>-6.5 (-6.6, -6.4)</td>
<td>-18.3 (-18.4, -18.1)</td>
<td>-0.8 (-0.8, -0.7)</td>
</tr>
</tbody>
</table>
Chapter 2 Using HIV Cohorts to Calibrate Agent-based Models

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ABSTRACT

Agent-based models are useful for comparing outcomes under different treatment strategies. However, calibrating model inputs is a challenge because up-to-date calibration targets may not exist for most strategies. Observational data can provide information on a wider range of calibration targets if appropriate analyses are conducted. We propose estimating calibration targets under a range of strategies using the parametric g-formula.

We estimated the 7-year risks of death and AIDS in the HIV-CAUSAL collaboration using the parametric g-formula in three time periods, under a range of treatment initiation strategies. We used these targets re-calibrate the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) agent-based model.

Both CEPAC and HIV-CAUSAL found earlier treatment was associated with lower 7-year mortality, and combined AIDS or mortality, risks. CEPAC estimates of 7-year mortality and combined AIDS or mortality risks initially over-estimated those from HIV-CAUSAL. CEPAC was most sensitive to the inputs governing the effect of treatment on OIs and on chronic AIDS-related mortality. The best fitting scenarios for calibration occurred when treatment reduced the probability of death and/or of OIs to values close to zero. No single parameter set was sufficient to provide a good fit between CEPAC and HIV-CAUSAL for all outcomes and treatment strategies.

CEPAC and HIV-CAUSAL yielded the same ranking of treatment initiation strategies, but CEPAC estimated a lower absolute benefit of treatment on reducing both mortality andOI incidence. By providing a range of calibration targets, under several treatment strategies, the parametric g-formula can be used for improving agent-based models.
INTRODUCTION

Agent-based models (ABMs) are used to estimate the public health impact of treatment guidelines or interventions. The goal is to answer causal questions of the form: What would the outcome distribution in a population be if everyone received a particular treatment strategy? ABMs use a microsimulation approach to estimate these outcome distributions based on pre-specified probabilities of treatment and important time-dependent covariates (transition probabilities). These inputs, which define the relationships between covariates, treatments, and outcomes,\textsuperscript{1,2} are typically chosen from a range of sources including published studies and expert knowledge.

A key challenge for ABMs is that these input parameters typically cannot be directly estimated from the population of interest. If such data did exist, the counterfactual outcome distribution could be directly estimated from those data using standard causal inference tools rather than modeled with an ABM. Instead, ABM parameters often need to be selected from a variety of sources and thus some calibration is required to assess the model’s assumptions.\textsuperscript{3-6}

Calibration has two steps. First, investigators must identify appropriate benchmarks, or calibration targets—that is unbiased estimates of the outcome distribution estimated from a population of interest. Second, they must ensure that the ABM reproduces these targets when matched to the baseline characteristics of that population.\textsuperscript{4} A large literature is devoted to the second step, including methods for searching the input parameter space and determining goodness of fit.\textsuperscript{7-10} Here, we focus on the first step, for which two broad types of calibration targets may be of interest.

One possible benchmark is the observed outcome distribution—for example, the mean, risk, or prevalence—in the population of interest, which can be estimated from population statistics, observational studies, or randomized trials.\textsuperscript{6} However, replicating the observed outcome distribution
using an ABM requires knowing the distribution of treatment strategies present in the population so that they can be input to the model. This information may be difficult to obtain from population statistics or other observational data sources, and the outcome distribution under the typically better characterized treatment strategies of randomized trials is only available for the highly selected populations that participate in the trials.

Another possible benchmark is the outcome distribution under a single treatment strategy that investigators select from among the treatment strategies present in the population. The process can be repeated if investigators are interested in calibrating their ABMs under a range of realistic treatment strategies. The outcome distributions under these treatment strategies can be validly estimated from observational data under the assumption that all time-fixed and time-varying confounders are measured and appropriately adjusted for. In the presence of treatment-confounder feedback, causal inference techniques, such as the parametric g-formula, can be used to validly estimate these counterfactual outcome distributions.

Here we propose a marriage of ABMs and the parametric g-formula. Our aim is to demonstrate the use of the parametric g-formula to calibrate an ABM using complex longitudinal data in the presence of treatment-confounder feedback.

**METHODS**

*Study Population*

The HIV-CAUSAL Collaboration combines data from prospective studies of HIV-positive individuals in nine countries: Brazil, Canada, France, Greece, Netherlands, Spain, Switzerland, UK, and USA. All studies are based on clinical data collected within universal health care systems. We excluded data from Brazil from our analyses because a separate parameterization of the CEPAC model exists for
Brazil. The analyses presented here are based on data pooled in September 2013, which did not include Canada.

Our analyses included individuals 18 or older, who were antiretroviral naïve, did not have AIDS, were not pregnant, and had had a CD4 cell count and HIV viral load measurement within 3 months. The start of follow-up for each individual was defined as the first month in which all eligibility criteria were met. We defined three cohorts of individuals according to the start of follow-up: an early period with baseline between Jan 1 1996 and Dec 31 1999; an intermediate period with baseline between Jan 1, 2000 and Dec 31 2002; and a late period with baseline from Jan 1 2003 onwards. In each cohort, each individual was followed until the earliest of death; censoring, defined as 12 months after the last recorded CD4 cell count and HIV viral load measurements or pregnancy (if known); or the study-specific administrative end of follow-up between February 2010 and March 2013. Unlike in a previous application of the parametric g-formula, we did not require that baseline occur within 6 months of HIV diagnosis because date of diagnosis is not used in CEPAC.

**Treatment Strategies**

We consider three treatment strategies: (1) immediate universal initiation of antiretroviral therapy (ART) at diagnosis; (2) ART initiation immediately after the first time CD4 count falls below 500 cells/mm³; and (3) ART initiation when CD4 count falls below 350 cells/mm³. ART was defined as a regimen of antiretroviral drugs including at least two nucleoside reverse transcriptase inhibitors (NRTIs) and either one or more protease inhibitors, one non-nucleoside reverse transcriptase inhibitor (NNRTI), one entry or fusion inhibitor, or one integrase inhibitor.
Outcomes

The primary outcomes of interest were all-cause mortality and a combined AIDS diagnosis or death outcome. AIDS diagnosis was defined as first diagnosis of an AIDS-defining opportunistic disease. For each outcome, we estimated the 7-year risk, the survival curve, and the restricted mean survival time. We also estimated the mean CD4 cell count and the mean HIV RNA over time.

Parametric g-formula

We adjusted for baseline and time-dependent confounders using the parametric g-formula, which is a generalization of standardization to settings with time-varying treatment and confounders. Briefly, the components of the g-formula are estimated via parametric models fit to the observational data (see Appendix for details), and the estimates are combined in a weighted integral that is approximated via Monte-Carlo microsimulation.

We included baseline CD4 count per μL (<50, 50-99, 100-199, 200-349, 350-499, ≥500), HIV viral load log copies per mL (<4, 4-5, >5), sex, race, geographical origin (Europe and the USA, sub-Saharan Africa, rest of the world, unknown), transmission group (heterosexual, men who have sex with men (MSM) or men who have sex with men and women (MSMW), injection drug user, and other/unknown), age in years (<35, 35-50, >50), calendar year (2000-04, 2005-10, 2011-13), and cohort. We fit logistic regression models for time-varying indicators for death, AIDS diagnosis, and treatment initiation, and linear regression models for the natural logarithms of HIV viral load and CD4 cell count. All models included the two most recent values of the time-varying covariates, as well as time since last CD4 count and HIV viral load measurements, and all baseline covariates. Models for CD4 count and HIV viral load also included product terms for the number of months since ART initiation. To assess the goodness of fit of the g-formula, we also fit a logistic regression model for treatment initiation. We then estimated the
distribution of each outcome under no intervention, and compared the estimated and observed risks, as
well as the distributions of treatment and the time-varying covariates. See Appendix for details.

We used non-parametric bootstraps with 500 samples to obtain 95% confidence intervals. The
analyses were done using the GFORMULA macro in SAS 9.4.

**CEPAC microsimulation model**

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model to
simulate 3 populations of 10^5 individuals matched to each of the three HIV-CAUSAL subsets on baseline
distributions of CD4 count (mean and standard deviation), HIV viral load strata (% within strata), age
(mean and standard deviation), gender (% male), and transmission risk group (heterosexual,
homosexual or bisexual, injection drug use, other/unknown) (Table 2.1).
Table 2.1: Baseline characteristics of eligible individuals in the HIV-CAUSAL Collaboration by period for variables used in CEPAC.

<table>
<thead>
<tr>
<th></th>
<th>Early period: Jan 1996 to Dec 31 1999</th>
<th>Intermediate period: Jan 1 2000 to Dec 31 2002</th>
<th>Late period: on or after Jan 1 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 24,710</td>
<td>N = 16,689</td>
<td>N = 60,178</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>CD4 cell count, cells/mm³</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1,523 (6.2)</td>
<td>1,276 (7.6)</td>
<td>3,134 (5.2)</td>
</tr>
<tr>
<td>50-100</td>
<td>1,138 (4.6)</td>
<td>933 (5.6)</td>
<td>2,615 (4.3)</td>
</tr>
<tr>
<td>100-200</td>
<td>2,741 (11.1)</td>
<td>2,159 (12.9)</td>
<td>6,606 (11.0)</td>
</tr>
<tr>
<td>200-350</td>
<td>5,593 (22.6)</td>
<td>4,013 (24.0)</td>
<td>14,391 (23.9)</td>
</tr>
<tr>
<td>350-500</td>
<td>5,780 (23.4)</td>
<td>3,606 (21.6)</td>
<td>14,351 (23.8)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>7,935 (32.1)</td>
<td>4,702 (28.2)</td>
<td>19,081 (31.7)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>410.1 (1.7)</td>
<td>381.5 (2.0)</td>
<td>409.5 (1.0)</td>
</tr>
<tr>
<td><strong>HIV-RNA, copies/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>6,157 (24.9)</td>
<td>5,022 (30.1)</td>
<td>17,422 (29.0)</td>
</tr>
<tr>
<td>30,000-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000</td>
<td>5,374 (21.7)</td>
<td>4,170 (25)</td>
<td>15,384 (25.6)</td>
</tr>
<tr>
<td>10,000-30,000</td>
<td>4,665 (18.9)</td>
<td>3,010 (18)</td>
<td>11,542 (19.2)</td>
</tr>
<tr>
<td>3,000-10,000</td>
<td>3,710 (15)</td>
<td>2,200 (13.2)</td>
<td>8,331 (13.8)</td>
</tr>
<tr>
<td>500-3,000</td>
<td>3,094 (12.5)</td>
<td>1,725 (10.3)</td>
<td>5,901 (9.8)</td>
</tr>
<tr>
<td>20-500</td>
<td>1,696 (6.9)</td>
<td>550 (3.3)</td>
<td>1,559 (2.6)</td>
</tr>
<tr>
<td>0-20</td>
<td>14 (0.1)</td>
<td>12 (0.1)</td>
<td>39 (0.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19,156 (77.5)</td>
<td>12,332 (73.9)</td>
<td>47,565 (79.0)</td>
</tr>
<tr>
<td>Women</td>
<td>5,554 (22.5)</td>
<td>4,357 (26.1)</td>
<td>12,613 (21.0)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>Mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>37.6 (0.06)</td>
<td>---</td>
<td>38.1 (0.04)</td>
</tr>
<tr>
<td><strong>Transmission group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>6,738 (27.3)</td>
<td>6,131 (36.7)</td>
<td>19,530 (32.5)</td>
</tr>
<tr>
<td>MSM or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSMW*</td>
<td>7,701 (31.2)</td>
<td>5,241 (31.4)</td>
<td>28,548 (47.4)</td>
</tr>
<tr>
<td>Injection drug user</td>
<td>4,071 (16.5)</td>
<td>1,429 (8.6)</td>
<td>2,196 (3.6)</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>6,200 (25.1)</td>
<td>3,888 (23.3)</td>
<td>9,904 (16.5)</td>
</tr>
</tbody>
</table>

*MSM: men who have sex with men; MSMW: men who have sex with men and women
CEPAC is an ABM described by three types of health states—chronic infection, acute health events, and death—and time-varying covariates which govern transitions between states. We obtained HIV natural history inputs from a previous CEPAC assessment of the impact of testing and treatment strategies on HIV prevalence in Washington, DC (Table 2.2). We briefly describe these inputs and their sources.
Table 2.2: Input parameters for HIV natural history, CEPAC, all time periods.

<table>
<thead>
<tr>
<th>Mean 1-month CD4 count decrease (cells/mm³), by HIV RNA stratum, copies/mL</th>
<th>CD4 &gt; 500 cells/mm³</th>
<th>CD4: 350 – 499 cells/mm³</th>
<th>CD4: 200 – 299 cells/mm³</th>
<th>CD4: 100 – 199 cells/mm³</th>
<th>CD4: 50 – 99 cells/mm³</th>
<th>CD4 &lt; 50 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100,000</td>
<td>9.54</td>
<td>7.94</td>
<td>6.34</td>
<td>4.66</td>
<td>3.30</td>
<td>1.37</td>
</tr>
<tr>
<td>30,000-100,000</td>
<td>9.54</td>
<td>7.94</td>
<td>6.34</td>
<td>4.66</td>
<td>3.30</td>
<td>1.37</td>
</tr>
<tr>
<td>10,000-30,000</td>
<td>6.85</td>
<td>5.70</td>
<td>4.55</td>
<td>3.34</td>
<td>2.37</td>
<td>0.98</td>
</tr>
<tr>
<td>3,000-10,000</td>
<td>5.87</td>
<td>4.88</td>
<td>3.90</td>
<td>2.87</td>
<td>2.03</td>
<td>0.84</td>
</tr>
<tr>
<td>500-3,000</td>
<td>4.77</td>
<td>3.97</td>
<td>3.17</td>
<td>2.33</td>
<td>1.65</td>
<td>0.69</td>
</tr>
<tr>
<td>20-500</td>
<td>2.45</td>
<td>2.03</td>
<td>1.63</td>
<td>1.19</td>
<td>0.85</td>
<td>0.35</td>
</tr>
<tr>
<td>0-20</td>
<td>2.45</td>
<td>2.03</td>
<td>1.63</td>
<td>1.19</td>
<td>0.85</td>
<td>0.35</td>
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</table>

<table>
<thead>
<tr>
<th>Monthly risk of opportunistic infections (OIs), per 10,000</th>
<th>CD4 &gt; 500 cells/mm³</th>
<th>CD4: 350 – 499 cells/mm³</th>
<th>CD4: 200 – 299 cells/mm³</th>
<th>CD4: 100 – 199 cells/mm³</th>
<th>CD4: 50 – 99 cells/mm³</th>
<th>CD4 &lt; 50 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis pneumonia (PCP)</td>
<td>4.0</td>
<td>8.0</td>
<td>16.0</td>
<td>61.8</td>
<td>110.0</td>
<td>83.6</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>1.0</td>
<td>3.0</td>
<td>3.0</td>
<td>12.0</td>
<td>26.0</td>
<td>46.9</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>0.5</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>1.0</td>
<td>3.0</td>
<td>7.0</td>
<td>13.0</td>
<td>31.0</td>
<td>81.7</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>1.0</td>
<td>3.0</td>
<td>3.0</td>
<td>15.0</td>
<td>25.0</td>
<td>31.9</td>
</tr>
<tr>
<td>All other OIs</td>
<td>6.0</td>
<td>12.0</td>
<td>27.0</td>
<td>66.8</td>
<td>114.3</td>
<td>115.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monthly risk for HIV-related death, %</th>
<th>Pneumocystis pneumonia</th>
<th>Mycobacterium avium complex</th>
<th>Toxoplasmosis</th>
<th>Cytomegalovirus</th>
<th>Fungal infections</th>
<th>All other OIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5</td>
<td>4.5</td>
<td>18.2</td>
<td>4.8</td>
<td>3.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy of antiretroviral therapy</th>
<th>Suppression after 24 weeks, %</th>
<th>1-month risk of failure after suppression, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>
At baseline, CEPAC assigns each individual a propensity to respond to treatment, which was estimated from the distribution of treatment adherence in an US randomized trial comparing efavirenz (EVF)/ tenofovir (TDF) /emtricitabine (FTC) to elvitegravir (EVG)/cobicistat(COBI) /tenofovir /emtricitabine.24

HIV RNA level is assigned to one of 7 strata at baseline (>100,000; 30,000-100,000; 10,000-30,000; 3,000-10,000; 500-3,000; 20-500; 0-20 copies/ml) and remains constant until the individual begins treatment, at which point it decreases based on the individual’s propensity to respond to treatment. Full responders, with propensity to respond above 0.95, are reduced to the lowest viral load stratum (RNA <20 copies/ml) in the month after treatment initiation. Partial responders, with propensity to respond between 0.65 and 0.95, experience a viral load decrease of 1 to 3 strata, but not below the detection threshold (500 copies/ml). The probability of suppression and the probability of treatment failure were obtained from the randomized trial of EVF/TDF/FTC and EVG/COBI/TDF/FTC24 and adjusted based on CD4 count declines stratified by medication adherence from the VOLTART study25 to account for propensity to respond.

CD4 cell count is assigned at baseline and declines at each month when not on treatment according to a conditional distribution specified by a mean cell count decline which varies by both CD4 count stratum and HIV RNA stratum, and a standard deviation which varies based on the individual’s propensity to respond to treatment. The values for mean CD4 count decline off treatment were originally obtained from observational data from 1984-2004 in the Research in Access to Care for the Homeless (REACH), San Francisco Men’s Health Study, and Multi-Center AIDS Cohort Study (MACS).22,23 When on treatment, CD4 count initially increases by a mean of 87.9 cells/mm³ in the first 2 months, and subsequently by a mean of 4.48 cells/mm³ in the following months, for all HIV RNA strata. These values were obtained from the randomized trial of EVF/TDF/FTC and EVG/COBI/TDF/FTC.24
The monthly probability of opportunistic infections (OIs), when not on treatment, varies based on CD4 cell count stratum and was obtained from the MACS cohort study.²

Three probabilities govern mortality when not on treatment: the probability of chronic AIDS-related mortality, the probability of acute OI-related mortality, and the probability of non-AIDS-related mortality. Sex-stratified lifetables for the probability of non-AIDS-related mortality for our calibration were obtained from the Eurostat website²⁶ for France, Greece, Netherlands, Spain, Switzerland, and the UK, combined. For the early period, we used lifetables for the period 1996-2013; for the intermediate period, we used 2000-2013; and for the late period, 2003-2013. The probabilities of chronic AIDS-related mortality and of acute OI-related mortality varied based on CD4 cell count and were obtained from the MACS cohort study.²

When on treatment, the probabilities of chronic AIDS-related mortality, acute OI-related mortality, and incidence of OIs are adjusted by multipliers (which can vary based on CD4 cell count). In the base case parameterization, we use a value of 1 for all multipliers. We then vary the multipliers for chronic AIDS-related mortality and OI incidence in our calibration, as described below.

Identification of key parameters

We compared the estimated mortality and combined AIDS or death risk at 7 years from CEPAC with the estimates from the parametric g-formula applied to HIV-CAUSAL in each of the three periods with the base case parameterization. We then varied a range of input parameters to identify those to which the CEPAC results were most sensitive. We varied the 1-month probabilities of OIs and of chronic AIDS-related mortality when not on treatment, the multipliers for the effect of treatment on OIs and chronic AIDS-related mortality, the highest CD4 count stratum at which OIs and/or chronic AIDS-related mortality could occur when on treatment, the probability of acute OI-related mortality (on and off...
treatment), the distribution of adherence types, and the probability of treatment failure after suppression. We also compared the model using independent or joint distributions for baseline CD4 count and HIV RNA stratum obtained from HIV-CAUSAL, and using transmission risk group distribution and non-AIDS-related mortality distributions from the US only \(^1\) rather than the updated HIV-CAUSAL distributions, to assess the importance of these baseline characteristics. CEPAC results were most strongly affected by changes to the probability of treatment failure, distribution of adherence types, and the multipliers for the effect of treatment on OIs and chronic AIDS-related mortality. We selected the latter two inputs for further calibration to demonstrate the benefits of the parametric g-formula for estimating calibration targets.

**Calibration of key parameters**

We identified the multipliers for the effect of treatment on OIs and chronic AIDS-related mortality as key inputs for further calibration. We varied these multipliers in combination between 1 and 0 by 0.2 units for a total of 36 calibration runs. We report survival and AIDS-free survival curves comparing all 36 runs where these parameters are varied to the HIV-CAUSAL estimates under each of the four treatment strategies. We also plot heat maps showing the estimated cumulative incidence of mortality and of AIDS or death combined by 7 years from these 36 calibration runs.

**RESULTS**

The HIV-CAUSAL Collaboration included 24,710 individuals who were eligible for our analysis in the early period, 16,689 in the intermediate period, and 60,178 in the late period. Their baseline characteristics are shown in Table 2.1. The median duration of follow-up was 62 months (IQR 26-144) in the early period, 64 months (IQR 27-144) in the intermediate period, and 33 months (17-58) in the late
period. Treatment initiation was similar in the three time periods—73% of participants initiated ART during follow-up in the early period, 75% in the intermediate period, and 69% in the late period.

In the early period, the estimated 7-year risk under immediate, universal ART initiation was 10.3% (95% CI: 9.7, 10.8) for mortality alone (Table 2.3) and 16.8% (95% CI: 16.1, 17.4) for combined AIDS or mortality (Table 2.4). The corresponding risks were 7.9% (95% CI: 7.4, 8.4) for mortality and 14.0% (95% CI: 13.3, 14.8) for mortality or AIDS in the intermediate period, and 4.4% (95% CI: 4.1, 4.8) for mortality and 8.9% (95% CI: 8.6, 9.3) for mortality or AIDS in the late period. Between the early and late periods, the mortality risk decreased by nearly 6 percentage points, and the combined AIDS or death risk decreased by approximately 8 percentage points. Earlier treatment initiation resulted in decreased mortality and improved restricted mean survival time for all time periods.
<table>
<thead>
<tr>
<th>Baseline period</th>
<th>ART initiation strategy (CD4/mm³)</th>
<th>Risk at 7 years, % (95% CI)</th>
<th>Risk ratio (95% CI)</th>
<th>Risk difference, % (95% CI)</th>
<th>Restricted mean survival time (days; 95% CI)</th>
<th>Difference in restricted mean survival time (days; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 1, 1996 - Dec 31, 1999</td>
<td>Immediate universal CD4 &lt;500</td>
<td>10.3 (9.7, 10.8)</td>
<td>--</td>
<td>--</td>
<td>79.3 (79.0, 79.5)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>10.6 (10.1, 11.1)</td>
<td>1.03 (1.02, 1.04)</td>
<td>0.3 (0.2, 0.4)</td>
<td>79.1 (78.8, 79.3)</td>
<td>-0.2 (-0.2, -0.2)</td>
</tr>
<tr>
<td></td>
<td>Jan 1, 2000 - Dec 31, 2002</td>
<td>Immediate universal CD4 &lt;500</td>
<td>7.9 (7.4, 8.4)</td>
<td>--</td>
<td>--</td>
<td>80.1 (79.9, 80.4)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>8.1 (7.5, 8.6)</td>
<td>1.02 (1.01, 1.02)</td>
<td>0.1 (0.1, 0.2)</td>
<td>80.0 (79.7, 80.3)</td>
<td>-0.1 (-0.1, -0.1)</td>
</tr>
<tr>
<td></td>
<td>Jan 1, 2003 onwards</td>
<td>Immediate universal CD4 &lt;500</td>
<td>4.4 (4.1, 4.8)</td>
<td>--</td>
<td>--</td>
<td>81.9 (81.8, 82.1)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>4.4 (4.2, 4.8)</td>
<td>1.02 (1.00, 1.03)</td>
<td>0.1 (0.02, 0.1)</td>
<td>81.9 (81.8, 82.0)</td>
<td>-0.1 (-0.1, -0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7 (4.4, 5.0)</td>
<td>1.1 (1.0, 1.1)</td>
<td>0.3 (0.1, 0.4)</td>
<td>81.8 (81.6, 81.9)</td>
<td>-0.2 (-0.2, -0.1)</td>
</tr>
</tbody>
</table>

*Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4 count, HIV-RNA and AIDS) and baseline characteristics (calendar period and age of HIV diagnosis, risk group, gender, geographical origin, ethnicity and cohort).
Table 2.4: Risk of AIDS or death in each baseline cohort by ART initiation strategy, HIV-CAUSAL Collaboration.

<table>
<thead>
<tr>
<th>Baseline period</th>
<th>ART initiation strategy (CD4/mm^3)</th>
<th>Risk at 7 years, % (95% CI)</th>
<th>Risk ratio (95% CI)</th>
<th>Risk difference, % (95% CI)</th>
<th>Restricted mean survival time (days; 95% CI)</th>
<th>Difference in restricted mean survival time (days; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 1, 1996 - Dec 31, 1999</td>
<td>Immediate universal CD4 &lt;500</td>
<td>16.8 (16.1, 17.4)</td>
<td>1.04 (1.03, 1.04)</td>
<td>0.6 (0.5, 0.7)</td>
<td>74.6 (74.3, 74.9)</td>
<td>-0.4 (-0.4, -0.3)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>18.7 (18.1, 19.4)</td>
<td>1.1 (1.1, 1.1)</td>
<td>1.9 (1.7, 2.2)</td>
<td>74.0 (73.7, 74.3)</td>
<td>-1.0 (-1.1, -0.9)</td>
</tr>
<tr>
<td>Jan 1, 2000 - Dec 31, 2002</td>
<td>Immediate universal CD4 &lt;500</td>
<td>14.0 (13.3, 14.8)</td>
<td>1.04 (1.03, 1.04)</td>
<td>0.5 (0.4, 0.6)</td>
<td>75.7 (75.2, 76.0)</td>
<td>-0.3 (-0.4, -0.3)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>15.7 (15.0, 16.5)</td>
<td>1.1 (1.1, 1.1)</td>
<td>1.7 (1.5, 2.0)</td>
<td>75.0 (74.5, 75.3)</td>
<td>-1.0 (-1.1, -0.9)</td>
</tr>
<tr>
<td>Jan 1, 2003 onwards</td>
<td>Immediate universal CD4 &lt;500</td>
<td>8.9 (8.6, 9.3)</td>
<td>1.04 (1.03, 1.1)</td>
<td>0.4 (0.3, 0.4)</td>
<td>78.6 (78.4, 78.7)</td>
<td>-0.2 (-0.2, -0.2)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;350</td>
<td>10.1 (9.8, 10.6)</td>
<td>1.1 (1.1, 1.2)</td>
<td>1.2 (1.1, 1.4)</td>
<td>78.1 (77.9, 78.3)</td>
<td>-0.7 (-0.7, -0.6)</td>
</tr>
</tbody>
</table>

*Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4 count, HIV-RNA and AIDS) and baseline characteristics (calendar period and age of HIV diagnosis, risk group, gender, geographical origin, ethnicity and cohort).
Survival curves from CEPAC and HIV-CAUSAL showed increased survival and AIDS-free survival over time with earlier treatment initiation. Figures 2.1 and 2.2 display the estimated survival and AIDS-free survival curves for each time period for HIV-CAUSAL and for the base case CEPAC runs, when the treatment effect multipliers for OIs and for chronic AIDS-related mortality are set to 1. The HIV-CAUSAL curves also indicate improved survival and AIDS-free survival over time in all periods. The CEPAC curves also show improved survival and AIDS-free survival over time, but to a lesser extent than in HIV-CAUSAL. In all three time periods, the CEPAC curves more closely resemble the HIV-CAUSAL curves for the intermediate period.
Figure 2.1: Survival over follow-up. (a) Baseline from Jan 1, 1996 - Dec 31, 1999, HIV-CAUSAL; (b) Baseline from Jan 1, 2000 - Dec 31, 2002, HIV-CAUSAL; (c) Baseline on or after Jan 1, 2003, HIV-CAUSAL; (d) Baseline from Jan 1, 1996 - Dec 31, 1999, CEPAC; (e) Baseline from Jan 1, 2000 - Dec 31, 2002, CEPAC; (f) Baseline on or after Jan 1, 2003, CEPAC. All CEPAC estimates use 1.0 for multipliers.
Figure 2.2: AIDS-free survival over follow-up. (a) Baseline from Jan 1, 1996 - Dec 31, 1999, HIV-CAUSAL; (b) Baseline from Jan 1, 2000 - Dec 31, 2002, HIV-CAUSAL; (c) Baseline on or after Jan 1, 2003, HIV-CAUSAL; (d) Baseline from Jan 1, 1996 - Dec 31, 1999, CEPAC; (e) Baseline from Jan 1, 2000 - Dec 31, 2002, CEPAC; (f) Baseline on or after Jan 1, 2003, CEPAC. All CEPAC estimates use 1.0 for multipliers.
Figures 2.3 and 2.4 display the survival and AIDS-free survival curves from all 36 CEPAC calibration runs. In these figures, the CEPAC estimates are shown in grey and the HIV-CAUSAL estimates are shown in black. For parsimony, we show only the late period which had the largest sample size in HIV-CAUSAL.

(a) Immediate universal

(b) CD4 < 500

(c) CD4 < 350

Figure 2.3: Survival over follow-up comparing CEPAC calibration runs, where multipliers for OI incidence and chronic AIDS-related mortality are varied from 0 to 1 by 0.2, (grey) to HIV-CAUSAL estimates (black) when baseline is on or after Jan 1, 2003. (a) Immediate universal initiation; (b) Initiation at CD4 <500 cells/mm³; and (c) Initiation at CD4 <350 cells/mm³.
Figure 2.4: AIDS-free survival over follow-up comparing CEPAC calibration runs, where multipliers for OI incidence and chronic AIDS-related mortality are varied from 0 to 1 by 0.2, (grey) to HIV-CAUSAL estimates (black) when baseline is on or after Jan 1, 2003. (a) Immediate universal initiation; (b) Initiation at CD4 <500 cells/mm³; and (c) Initiation at CD4 <350 cells/mm³.

Figures 2.5 and 2.6 visualize the 7-year mortality and AIDS or death risks in the 36 CEPAC calibration runs. The top left corner of each sub-figure represents the 7-year risk when both the multiplier for the effect of treatment on OIs and for the effect of treatment on chronic AIDS-mortality were set to 0, for a given treatment initiation strategy. This assumes that treatment completely eradicates these outcomes, separately from any effect of treatment on CD4 count changes. The bottom
left corner of each sub-figure represents the scenario were both multipliers are set to 1, which assumes that treatment has no effect on either OIs or chronic AIDS mortality, except that which operates through changes to CD4 cell count. In each sub-figure, the location in the heat map which is closest to the 7-year risk estimated from HIV-CAUSAL is indicated by the black box; the area of the heat map which produces estimates within the 95% confidence intervals estimated from HIV-CAUSAL is enclosed in grey boxes.

Figure 2.5: 7-year mortality risk from CEPAC calibration runs, when treatment effect multipliers for chronic AIDS-related mortality and opportunistic infections are varied from 0 to 1 by treatment strategy. Black box indicates closest match to HIV-CAUSAL estimates using the parametric g-formula applied to the subset with baseline on or after Jan 1, 2003; grey boxes indicate 95% confidence interval for parametric g-formula estimates using 500 bootstrap samples.
Figure 2.6: 7-year risk of AIDS or death from CEPAC calibration runs by treatment strategy, when treatment effect multipliers for chronic AIDS-related mortality and opportunistic infections are varied from 0 to 1. Black box indicates closest match to HIV-CAUSAL estimates using the parametric g-formula applied to the subset with baseline on or after Jan 1, 2003; grey boxes indicate 95% confidence interval for parametric g-formula estimates using 500 bootstrap samples.

Figure 2.7 shows the estimated mean CD4 cell count and mean HIV RNA levels from HIV-CAUSAL and from CEPAC for the late period, by treatment initiation strategy, among individuals remaining alive at each month over follow-up. The CEPAC runs shown here were obtained from the base case parameterization, where the treatment multipliers for OIs and for chronic AIDS mortality were both set to 1. Compared to the estimates from HIV-CAUSAL, the mean CD4 cell count from CEPAC increased more rapidly over time. In contrast, the mean HIV RNA level decreased more rapidly over time in CEPAC than in HIV-CAUSAL.
Figure 2.7: Mean of CD4 count and HIV viral load under intervention in CEPAC and estimated via the parametric g-formula in HIV-CAUSAL Collaboration, late baseline: on or after Jan 1, 2003. All CEPAC estimates use initial parameterization of 1.0 for multipliers. (a) Mean CD4 count in HIV-CAUSAL (cells/mm³); (b) Mean CD4 count in CEPAC (cells/mm³); (c) Mean HIV viral load in HIV-CAUSAL (copies/mL); (d) Mean HIV viral load in CEPAC (copies/mL).
When we used the g-formula to estimate mortality in HIV-CAUSAL under no intervention, as an assessment of the goodness of fit of our models, we found good agreement for all covariates and outcomes in the late baseline period, but poor fits for AIDS diagnosis and mean CD4 count in the other time periods, especially for the early baseline period (see Appendix). In the intermediate and early periods, the g-formula models over-estimated the incidence of AIDS diagnosis and under-estimated the mean CD4 count over time relative to the observed data. We performed a range of sensitivity analyses but were not able to improve the fit for AIDS diagnosis in the early period.

DISCUSSION

The strategy of immediate universal treatment initiation resulted in the lowest estimates of both mortality and a combined AIDS or death outcome in all time periods, regardless of modeling approach. Survival and AIDS-free survival improved dramatically between the three time periods, and with earlier treatment initiation in HIV-CAUSAL and to a lesser degree in CEPAC. The CEPAC model was most sensitive to changes in the inputs for the effect of treatment on OI incidence and on chronic AIDS-mortality, and calibration suggested these values may need to be close to 0.

Many CEPAC inputs, including natural history inputs, were obtained from the Multicenter AIDS Cohort Study (MACS)—a cohort study of HIV-positive men which began enrollment in April 1984.² Our calibration suggests several possible problems with the use of the MACS inputs. First, the population of individuals enrolled in MACS may no longer reflect the current population of HIV-positive individuals in ways that affect survival and AIDS progression, regardless of treatment status. We found that mortality and AIDS-progression was dramatically reduced between the early and late periods in HIV-CAUSAL. Mean CD4 count at baseline was lower in the intermediate period (2000-02), but similar in the early and late periods. Mean age at baseline was lowest in the early period.
Alternatively, the majority of HIV-CAUSAL participants live in Europe, while the CEPAC model is generally used to estimate outcomes in the USA. Differences in underlying mortality risk or infectious disease transmission between these regions may be driving the differences we observed. However, if this is the case, it would suggest that ABMs may not an appropriate choice for modeling mortality and AIDS progression among HIV-infected individuals, since ABMs are designed to address questions across multiple populations.

We estimated 4.4% mortality after 7 years under the strategy of initiation at CD4 count <500 cells/mm³ in HIV-CAUSAL. In the CEPAC base case run, the 7-year mortality estimate was 6.7% under this treatment strategy. In comparison, a recent paper by Edwards et al²⁷ used the parametric g-formula in an American cohort and found a 5-year mortality risk of 4.6% under the strategy of initiating treatment at a CD4 count less than 500 cells/mm³ and 10.8% at 10 years. The Edwards study used data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort and included individuals who enrolled between Jan 1 1998 and Dec 31 2013. The higher observed mortality may therefore reflect a pooling of mortality across these time periods, as we observed a nearly 6 percentage point decrease in mortality between our early (Jan 1 1996 - Dec 31 1999) and late (on or after Jan 1 2003) cohorts. There were also several differences in baseline covariates between our study and the Edwards study which may explain the differences in mortality. In particular, 82% of the study sample was men in the Edwards analysis, compared to between 74% and 79% in our study. T The distribution of transmission risk group also appears to differ, although a large proportion of our study had unknown transmission type. Finally, our study excluded individuals with a history of AIDS defining illnesses at baseline, while the Edwards study did not—5% of their study sample had an AIDS diagnosis at baseline. Together, this suggests that the mortality risk may not differ between American and European populations in a way that would invalidate the use of ABMs; rather differences in the distribution of
baseline covariates lead to differences in mortality estimates. A future calibration could confirm this by comparing estimates from the CNICS cohort to those from CEPAC when matched to CNICS at baseline.

Although randomized clinical trials are sometimes considered as the ideal source of calibration targets for ABMs, there are many potential limitations to using trial data for calibration, and the parametric g-formula provides an alternate method of estimating targets from observational data. Limitations of randomized trials include financial and logistic constraints, which will limit the number of intervention strategies compared in any given trial, and ethical constraints on which strategies are appropriate for randomization. Randomized trials may also not be available in the population for which the ABM is being calibrated, or conducted in a highly specific subset of the population of interest. Finally, even when randomized trials exist, appropriate calibration targets may require adjustment for non-compliance or analysis of intermediate outcomes, making intention to treat estimates insufficient and introducing the need to consider treatment-confounder feedback in the trial data. However, in this case, we can apply the parametric g-formula to the trial data to obtain valid calibration targets.

Finally, some caution is advised when using the parametric g-formula to calibrate an ABM. The parametric g-formula requires strong identifiability assumptions, and both ABMs and the parametric g-formula are potentially subject to model misspecification, which can lead to bias in the estimates of regime-specific outcomes. Furthermore, the g-formula estimates are limited in their generalizability to populations similar to that under study. When calibrating an ABM to use for inference in other populations, with other treatment strategies, or over longer follow-up time, differences between the target and calibration populations in unmeasured common causes of the outcome and time-varying confounders or in the distributions of effect modifiers can cause bias. Finally, the g-formula estimates can be limited by the quality or quantity of data available. Together, data collection issues or violations of modeling assumptions mean that the g-formula estimates from HIV-CAUSAL may not be a perfect
gold standard for calibrating CEPAC. However, the ability to calibrate CEPAC across a range of treatment initiation targets allowed identification of issues which might not have been detected had a single calibration target been used. In summary, when building an agent-based model, calibration is necessary to ensure that the model has been well designed and parameterized. Calibration should consider a range of outcomes and time-points in order to provide the best assessment of the model. In addition, calibration should be seen as an ongoing process in order to keep models up to date and relevant for the population of interest.
ACKNOWLEDGEMENTS

We are indebted to the contributors to the HIV-CAUSAL Collaboration. We thank Michael Girouard, Moses Flash, and Mingshu Huang for their support and advice on the CEPAC model. We also thank Dr. Sara Lodi, Dr. Lauren Cain, and Dr. Roger Logan for their technical assistance.
REFERENCES


TECHNICAL APPENDIX

Parametric modeling assumptions

The parametric g-formula results are based on the following modeling assumptions for the first step of the estimating algorithm described in the main text.

1. Models for the covariates, from k=2 to maximum length of follow-up:
   a. RNA measured at visit k:

   $logit\left(Pr[L_{1,k} = 1|\bar{L}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{y}_k = \bar{c}_{k+1} = 0]\right) = \beta_{l_1}^T x_{l_1,k}$

   where $\beta_{l_1}$ is a coefficient vector, $x_{l_1,k}$ is the vector

   $[1, V, h(k), s_2(L_{2,k-1}), s_2(L_{2,k-2}), s_4(L_{4,k-1}), s_4(L_{4,k-2}), L_{5,k-1}, t(L_{1,k-1}, L_{3,k-1}), A_{k-1}, A_{k-1} \times \sum_{j=0}^{k-1} A_j]$ and

   • $V$ is the vector of baseline covariates: sex, origin, race, RNA category, CD4 count category, cohort, mode of transmission, age, and year;

   • $h(k)$ is a transformation of k needed to fit a restricted cubic spline with knots at (6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120) months;

   • $s_2(L_{2,j})$ is a transformation of $L_{2,j}$ needed to create categories with cut-points at (51, 1000, 10000, 100000) copies per μl $s_2(L_{2,-1}) = 0$;

   • $s_4(L_{4,j})$ is a transformation of $L_{4,j}$ needed to fit a restricted cubic spline with knots at (4.25, 5.48, 6.17, 6.88, 7.26) natural log cells per mm$^3$ for $j = 0, ..., K$ and $s_4(L_{4,-1}) = 0$;

   • $t(L_{1,j}, L_{3,j})$ is the number of months since last measured viral load or CD4 cell count by month j for $j = 0, ..., K$, and $t(L_{1,-1}, L_{3,-1}) = 0$;

   • $\sum_{j=0}^{k-1} A_j$ is the number of months since treatment initiation by k-1, by definition of $A_j$. 

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b. RNA value at visit \( k \):

\[
\logit(\Pr[I(L_{2,k} = 0) = 1|\bar{L}_{k-1} = \bar{t}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0]) = \beta_{I(I_2)}^T X_l(I_2,k)
\]

\[
\ln(\Pr[I(L_{2,k}) = \bar{L}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0, L_{2,k} > 0) = \beta_{I_2}^T X_{I_2,k}
\]

where \( I(L_{2,k} = 0) \) is an indicator for a viral load of 0, \( \beta_{I(I_2)} \) and \( \beta_{I_2} \) are coefficient vectors, and \( X_l(I_2,k) = X_{I_2,k} = X_{I_1,k} \)

c. CD4 count measured at visit \( k \):

\[
\logit(\Pr[I(L_{3,k} = 1|\bar{L}_{k-1} = \bar{t}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0]) = \beta_{I_3}^T X_{I_3,k}
\]

where \( \beta_{I_3} \) is a coefficient vector, \( X_{I_3,k} = [X_{I_2,k}, s_2(L_{2,k}), L_{1,k}] \)

d. CD4 count at visit \( k \):

\[
\ln(\Pr[I(L_{4,k}) = \bar{L}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0) = \beta_{I_4}^T X_{I_4,k}
\]

where \( \beta_{I_4} \) is a coefficient vector, and \( X_{I_4,k} = X_{I_3,k} \)

e. AIDS diagnosis by month \( k \):

\[
\logit(\Pr[I(L_{5,k} = 1|\bar{L}_{k-1} = \bar{t}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0]) = \beta_{I_5}^T X_{I_5,k}
\]

where \( \beta_{I_5} \) is a coefficient vector, \( X_{I_5,k} = [X_{I_4,k}, s_4(L_{4,k}), L_{3,k}] \)

2. Model for the outcome, from \( k = 0 \) to maximum length of follow-up:

\[
\logit(\Pr[Y_{k+1} = 1|\bar{L}_k = \bar{t}_k, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{c}_{k+1} = 0]) = \beta_{Y}^T X_{y_k}
\]

where \( \beta_{Y} \) is the coefficient vector and \( X_{y_k} \) is the vector:

\[
[1, V, h(k), t(L_{1,k}), s(L_{2,k}), s(L_{2,k-1}), t(L_{2,k}), s(L_{4,k}), s(L_{4,k-1}), L_{5,k}, A_k, A_k \times \sum_{j=0}^{k} A_j]
\]

3. Model for treatment, from \( k = 0 \) to maximum length of follow-up:

\[
\logit(\Pr[A_k = 1|\bar{L}_k = \bar{t}_k, \bar{A}_{k-1} = 0, \bar{Y}_k = \bar{c}_{k+1} = 0]) = \beta_{a}^T X_{a_k}
\]

where \( \beta_{a} \) is the coefficient vector and \( X_{a_k} \) is the vector

\[
[1, V, h(k), s_2(L_{2,k}), s_2(L_{2,k-1}), s_2(L_{2,k-2}), s_4(L_{4,k}), s_4(L_{4,k-1}), s_4(L_{4,k-2}), L_{5,k}, L_{5,k-1}, t(L_{1,k-1}, L_{3,k-1})]
\]
**HIV-CAUSAL Collaboration detailed baseline characteristics**

The main text (Table 2.1) provides a summary of relevant HIV-CAUSAL cohort baseline covariates necessary for parameterizing the CEPAC runs. We provide additional information on the cohort profiles in Appendix Tables 2.5-2.8, to provide further context to our results.

**Table 2.5: Distribution of HIV-CAUSAL data by country of cohort.**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Early cohort: Jan 1 1996 to Dec 31 1999</th>
<th>Intermediate cohort: Jan 1 2000 to Dec 31 2002</th>
<th>Late cohort: on or after Jan 1 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>45.6</td>
<td>37.3</td>
<td>28.6</td>
</tr>
<tr>
<td>Greece</td>
<td>1.6</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.6</td>
<td>6.1</td>
<td>12.3</td>
</tr>
<tr>
<td>Spain</td>
<td>6.4</td>
<td>11.6</td>
<td>16.7</td>
</tr>
<tr>
<td>Switzerland</td>
<td>8.6</td>
<td>4.9</td>
<td>4.2</td>
</tr>
<tr>
<td>UK</td>
<td>17.3</td>
<td>21.3</td>
<td>24.3</td>
</tr>
<tr>
<td>USA</td>
<td>19.9</td>
<td>17.2</td>
<td>10.7</td>
</tr>
</tbody>
</table>
Table 2.6: Detailed baseline characteristics, HIV-CAUSAL Collaboration: Early baseline, Jan 1, 1996-Dec 31, 1999.

<table>
<thead>
<tr>
<th>CD4 cell count, cells/mm³</th>
<th>Individuals (n)</th>
<th>Person-years</th>
<th>Proportion starting ART during follow-up (%)</th>
<th>Median (IQR) follow-up (months)</th>
<th>Deaths (n)</th>
<th>Incidence of death (per 1000 person-years)</th>
<th>AIDS events or deaths (n)</th>
<th>Incidence of AIDS events or death (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1523</td>
<td>9847.08</td>
<td>0.88247</td>
<td>61 (21, 139)</td>
<td>453</td>
<td>46</td>
<td>727</td>
<td>95.4</td>
</tr>
<tr>
<td>50-100</td>
<td>1138</td>
<td>7678.92</td>
<td>0.88928</td>
<td>64 (24, 145)</td>
<td>254</td>
<td>33.1</td>
<td>405</td>
<td>63.0</td>
</tr>
<tr>
<td>100-200</td>
<td>2741</td>
<td>18821.42</td>
<td>0.89055</td>
<td>66 (26, 145)</td>
<td>443</td>
<td>23.5</td>
<td>673</td>
<td>39.4</td>
</tr>
<tr>
<td>200-350</td>
<td>5593</td>
<td>39431.83</td>
<td>0.81942</td>
<td>68 (27, 147)</td>
<td>565</td>
<td>14.3</td>
<td>927</td>
<td>25.2</td>
</tr>
<tr>
<td>350-500</td>
<td>5780</td>
<td>40293.83</td>
<td>0.72249</td>
<td>65 (27, 147)</td>
<td>460</td>
<td>11.4</td>
<td>736</td>
<td>19.2</td>
</tr>
<tr>
<td>&gt;500</td>
<td>7935</td>
<td>51668.17</td>
<td>0.56799</td>
<td>56 (25, 136)</td>
<td>542</td>
<td>10.5</td>
<td>854</td>
<td>17.2</td>
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<tr>
<td>HIV-RNA, copies/mL</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10,000</td>
<td>8374</td>
<td>52470.17</td>
<td>0.56269</td>
<td>52 (24, 132)</td>
<td>661</td>
<td>12.6</td>
<td>949</td>
<td>18.8</td>
</tr>
<tr>
<td>≥10,000</td>
<td>10179</td>
<td>71578</td>
<td>0.77346</td>
<td>67 (27, 148)</td>
<td>1034</td>
<td>14.4</td>
<td>1672</td>
<td>25.0</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>6157</td>
<td>43693.08</td>
<td>0.88972</td>
<td>72 (27, 147)</td>
<td>1022</td>
<td>23.4</td>
<td>1701</td>
<td>44.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19156</td>
<td>132819.7</td>
<td>0.74765</td>
<td>65 (27, 146)</td>
<td>2431</td>
<td>18.3</td>
<td>3704</td>
<td>30.1</td>
</tr>
<tr>
<td>Women</td>
<td>5554</td>
<td>34921.58</td>
<td>0.67357</td>
<td>54 (24, 130)</td>
<td>286</td>
<td>8.2</td>
<td>618</td>
<td>18.9</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>11336</td>
<td>74210.33</td>
<td>0.69293</td>
<td>56 (25, 139)</td>
<td>557</td>
<td>7.5</td>
<td>1209</td>
<td>17.4</td>
</tr>
<tr>
<td>35-50</td>
<td>10636</td>
<td>74026.25</td>
<td>0.75611</td>
<td>66 (26, 147)</td>
<td>1367</td>
<td>18.5</td>
<td>2143</td>
<td>31.4</td>
</tr>
<tr>
<td>&gt;50</td>
<td>2738</td>
<td>19504.67</td>
<td>0.79109</td>
<td>75.5 (27, 146)</td>
<td>793</td>
<td>40.7</td>
<td>970</td>
<td>54.2</td>
</tr>
</tbody>
</table>
Table 2.6 (Continued)

<table>
<thead>
<tr>
<th>Transmission group</th>
<th>Individuals (n)</th>
<th>Person-years</th>
<th>Proportion starting ART during follow-up (%)</th>
<th>Median (IQR) follow-up (months)</th>
<th>Deaths (n)</th>
<th>Incidence of death (per 1000 person-years)</th>
<th>AIDS events or death (n)</th>
<th>Incidence of AIDS events or death (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterosexual</td>
<td>6738</td>
<td>45870.5</td>
<td>0.73969</td>
<td>64 (26, 143)</td>
<td>369</td>
<td>8</td>
<td>795</td>
<td>18.5</td>
</tr>
<tr>
<td>MSM or MSMW*</td>
<td>7701</td>
<td>62352.75</td>
<td>0.76198</td>
<td>95 (34, 160)</td>
<td>473</td>
<td>7.6</td>
<td>1041</td>
<td>18.1</td>
</tr>
<tr>
<td>Injection drug user</td>
<td>4071</td>
<td>22088.17</td>
<td>0.64873</td>
<td>45 (22, 94)</td>
<td>428</td>
<td>19.4</td>
<td>684</td>
<td>33.2</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>6200</td>
<td>37429.83</td>
<td>0.7371</td>
<td>51 (23, 131)</td>
<td>1447</td>
<td>38.7</td>
<td>1802</td>
<td>52.0</td>
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</tbody>
</table>

*MSM: men who have sex with men; MSMW: men who have sex with men and women
Table 2.7: Detailed baseline characteristics, HIV-CAUSAL Collaboration: Intermediate baseline, Jan 1, 2000-Dec 31, 2002.

<table>
<thead>
<tr>
<th>CD4 cell count, cells/mm³</th>
<th>Individuals (n)</th>
<th>Person-years</th>
<th>Proportion starting ART during follow-up (%)</th>
<th>Median (IQR) follow-up (months)</th>
<th>Deaths (n)</th>
<th>Incidence of death (per 1000 person-years)</th>
<th>AIDS events or deaths (n)</th>
<th>Incidence of AIDS events or death (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1276</td>
<td>7255.67</td>
<td>0.90674</td>
<td>66.5 (22, 113)</td>
<td>274</td>
<td>37.8</td>
<td>512</td>
<td>89.6</td>
</tr>
<tr>
<td>50-100</td>
<td>933</td>
<td>5551.08</td>
<td>0.94855</td>
<td>69 (28, 113)</td>
<td>149</td>
<td>26.8</td>
<td>272</td>
<td>87.2</td>
</tr>
<tr>
<td>100-200</td>
<td>2159</td>
<td>12831.83</td>
<td>0.93052</td>
<td>70 (27, 114)</td>
<td>232</td>
<td>18.1</td>
<td>400</td>
<td>33.6</td>
</tr>
<tr>
<td>200-350</td>
<td>4013</td>
<td>23780.67</td>
<td>0.84675</td>
<td>68 (27, 116)</td>
<td>272</td>
<td>11.4</td>
<td>474</td>
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<tr>
<td>350-500</td>
<td>3606</td>
<td>21067.5</td>
<td>0.70715</td>
<td>63 (27, 115)</td>
<td>214</td>
<td>10.2</td>
<td>386</td>
<td>19.3</td>
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<tr>
<td>&gt;500</td>
<td>4702</td>
<td>26458.08</td>
<td>0.53764</td>
<td>57 (26, 113)</td>
<td>183</td>
<td>6.9</td>
<td>414</td>
<td>16.4</td>
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<tr>
<td>HIV-RNA, copies/mL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10,000</td>
<td>4446</td>
<td>23614.42</td>
<td>0.5587</td>
<td>51 (24, 109)</td>
<td>249</td>
<td>10.5</td>
<td>398</td>
<td>17.4</td>
</tr>
<tr>
<td>10,000-100,000</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000</td>
<td>7221</td>
<td>42547.25</td>
<td>0.76347</td>
<td>66 (27, 115)</td>
<td>527</td>
<td>12.4</td>
<td>974</td>
<td>24.4</td>
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<tr>
<td>&gt;100,000</td>
<td>5022</td>
<td>30783.17</td>
<td>0.90203</td>
<td>73 (29, 117)</td>
<td>548</td>
<td>17.8</td>
<td>1086</td>
<td>39.6</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>12332</td>
<td>73938.17</td>
<td>0.76443</td>
<td>69 (28, 116)</td>
<td>1160</td>
<td>15.7</td>
<td>2005</td>
<td>29.1</td>
</tr>
<tr>
<td>Women</td>
<td>4357</td>
<td>23006.67</td>
<td>0.7115</td>
<td>50 (23, 110)</td>
<td>164</td>
<td>7.1</td>
<td>453</td>
<td>21.2</td>
</tr>
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<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
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<td>39391.83</td>
<td>0.69422</td>
<td>55 (25, 112)</td>
<td>187</td>
<td>4.7</td>
<td>604</td>
<td>16.3</td>
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<tr>
<td>35-50</td>
<td>7140</td>
<td>43085.67</td>
<td>0.78375</td>
<td>70 (28, 116)</td>
<td>586</td>
<td>13.6</td>
<td>1150</td>
<td>29.0</td>
</tr>
<tr>
<td>&gt;50</td>
<td>2436</td>
<td>14467.33</td>
<td>0.81814</td>
<td>73 (27, 113)</td>
<td>551</td>
<td>38.1</td>
<td>704</td>
<td>52.3</td>
</tr>
<tr>
<td>Transmission group</td>
<td>Individuals (n)</td>
<td>Person-years</td>
<td>Proportion starting ART during follow-up (%)</td>
<td>Median (IQR) follow-up (months)</td>
<td>Deaths (n)</td>
<td>Incidence of death (per 1000 person-years)</td>
<td>AIDS events or deaths (n)</td>
<td>Incidence of AIDS events or death (per 1000 person-years)</td>
</tr>
<tr>
<td>-------------------</td>
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<td>--------------------------------</td>
<td>------------</td>
<td>--------------------------------------------</td>
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<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>6131</td>
<td>34442.58</td>
<td>0.74164</td>
<td>58 (25, 113)</td>
<td>220</td>
<td>6.4</td>
<td>664</td>
<td>20.9</td>
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<tr>
<td>MSM or MSMW*</td>
<td>5241</td>
<td>35918.42</td>
<td>0.75921</td>
<td>89 (38, 123)</td>
<td>184</td>
<td>5.1</td>
<td>543</td>
<td>16.1</td>
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<tr>
<td>Injection drug user</td>
<td>1429</td>
<td>6269.83</td>
<td>0.6823</td>
<td>35 (19, 79)</td>
<td>146</td>
<td>23.3</td>
<td>247</td>
<td>42.3</td>
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<tr>
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<td>20314</td>
<td>0.77829</td>
<td>55 (23, 102)</td>
<td>774</td>
<td>38.1</td>
<td>1004</td>
<td>52.9</td>
</tr>
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</table>

*MSM: men who have sex with men; MSMW: men who have sex with men and women
Table 2.8: Detailed baseline characteristics, HIV-CAUSAL Collaboration: Late baseline, on or after Jan 1, 2003.

<table>
<thead>
<tr>
<th>CD4 cell count, cells/mm³</th>
<th>Individuals (n)</th>
<th>Person-years</th>
<th>Proportion starting ART during follow-up (%)</th>
<th>Median follow-up (months)</th>
<th>Deaths (n)</th>
<th>Incidence of death (per 1000 person-years)</th>
<th>AIDS events or deaths (n)</th>
<th>Incidence of AIDS events or death (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>3134</td>
<td>10366.42</td>
<td>0.93331</td>
<td>34 (17, 59)</td>
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<td>32.5</td>
<td>1214</td>
<td>64.0</td>
</tr>
<tr>
<td>50-100</td>
<td>2615</td>
<td>8956.08</td>
<td>0.93614</td>
<td>36 (17, 63)</td>
<td>201</td>
<td>22.4</td>
<td>585</td>
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<tr>
<td>100-200</td>
<td>6606</td>
<td>22431.83</td>
<td>0.94111</td>
<td>34 (17, 61)</td>
<td>301</td>
<td>13.4</td>
<td>791</td>
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<tr>
<td>200-350</td>
<td>14391</td>
<td>48399.83</td>
<td>0.85262</td>
<td>34 (18, 59)</td>
<td>336</td>
<td>6.9</td>
<td>893</td>
<td>18.2</td>
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<tr>
<td>350-500</td>
<td>14351</td>
<td>46849.83</td>
<td>0.65877</td>
<td>32 (17, 57)</td>
<td>255</td>
<td>5.4</td>
<td>619</td>
<td>13.2</td>
</tr>
<tr>
<td>&gt;500</td>
<td>19081</td>
<td>60714.58</td>
<td>0.4385</td>
<td>31 (17, 55)</td>
<td>293</td>
<td>4.8</td>
<td>690</td>
<td>11.4</td>
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<table>
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<tr>
<th>HIV-RNA, copies/mL</th>
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<tr>
<td>&lt;10,000</td>
<td>15691</td>
<td>50002.17</td>
<td>0.52718</td>
<td>32 (17, 55)</td>
<td>301</td>
<td>6</td>
<td>672</td>
<td>13.1</td>
</tr>
<tr>
<td>10,000-100,000</td>
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<tr>
<td>100,000</td>
<td>27065</td>
<td>89223.08</td>
<td>0.70057</td>
<td>33 (17, 58)</td>
<td>686</td>
<td>7.7</td>
<td>1826</td>
<td>19.7</td>
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<tr>
<td>&gt;100,000</td>
<td>17422</td>
<td>58493.33</td>
<td>0.8293</td>
<td>34 (17, 60)</td>
<td>736</td>
<td>12.6</td>
<td>2294</td>
<td>33.6</td>
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<table>
<thead>
<tr>
<th>Sex</th>
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<tbody>
<tr>
<td>Men</td>
<td>47565</td>
<td>156920.2</td>
<td>0.68494</td>
<td>33 (17, 58)</td>
<td>1544</td>
<td>9.8</td>
<td>3883</td>
<td>23.2</td>
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<tr>
<td>Women</td>
<td>12613</td>
<td>40798.42</td>
<td>0.72164</td>
<td>32 (17, 57)</td>
<td>179</td>
<td>4.4</td>
<td>909</td>
<td>20.4</td>
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<table>
<thead>
<tr>
<th>Age, years</th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>26308</td>
<td>83413.83</td>
<td>0.62947</td>
<td>31 (17, 55)</td>
<td>205</td>
<td>2.5</td>
<td>1063</td>
<td>12.3</td>
</tr>
<tr>
<td>35-50</td>
<td>25190</td>
<td>86752.08</td>
<td>0.72461</td>
<td>35 (18, 61)</td>
<td>737</td>
<td>8.5</td>
<td>2218</td>
<td>23.5</td>
</tr>
<tr>
<td>&gt;50</td>
<td>8680</td>
<td>27552.67</td>
<td>0.79124</td>
<td>32 (16, 57)</td>
<td>781</td>
<td>28.3</td>
<td>1511</td>
<td>48.8</td>
</tr>
<tr>
<td>Transmission group</td>
<td>Individuals (n)</td>
<td>Person-years</td>
<td>Proportion starting ART during follow-up (%)</td>
<td>Median follow-up (months)</td>
<td>Deaths (n)</td>
<td>Incidence of death (per 1000 person-years)</td>
<td>AIDS events or deaths (n)</td>
<td>Incidence of AIDS events or death (per 1000 person-years)</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
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<td>------------------------------------------</td>
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<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>19530</td>
<td>65534.92</td>
<td>0.73968</td>
<td>33 (18, 59)</td>
<td>371</td>
<td>5.7</td>
<td>1647</td>
<td>22.3</td>
</tr>
<tr>
<td>MSM or MSMW*</td>
<td>28548</td>
<td>96532.75</td>
<td>0.65181</td>
<td>34 (18, 59)</td>
<td>337</td>
<td>3.5</td>
<td>1323</td>
<td>13.2</td>
</tr>
<tr>
<td>Injection drug user</td>
<td>2196</td>
<td>6538.42</td>
<td>0.66393</td>
<td>28 (15, 51)</td>
<td>150</td>
<td>22.9</td>
<td>326</td>
<td>43.9</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>9904</td>
<td>29112.5</td>
<td>0.72385</td>
<td>30 (15, 53)</td>
<td>865</td>
<td>29.7</td>
<td>1496</td>
<td>48.8</td>
</tr>
</tbody>
</table>

*MSM: men who have sex with men; MSMW: men who have sex with men and women
**Goodness of fit**

To assess the goodness of fit of our parametric g-formula model, we estimated the outcome distributions under no intervention. That is, we assigned treatment at each month based on the estimated conditional probability of treatment observed in the data following the model presented above. The estimated 7-year risks of mortality and the combined outcome of AIDS or death for each baseline subset are presented in Appendix Table 2.9.

**Table 2.9: Estimated 7-year risk in each baseline cohort under no intervention, HIV-CAUSAL Collaboration.**

<table>
<thead>
<tr>
<th>Baseline period</th>
<th>Outcome</th>
<th>Risk at 7 years, % (95% CI)</th>
<th>Restricted mean survival time (days; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 1, 1996 - Dec 31, 1999</td>
<td>Mortality</td>
<td>11.8 (11.1, 12.4)</td>
<td>78.5 (78.3, 78.9)</td>
</tr>
<tr>
<td></td>
<td>AIDS or death</td>
<td>19.8 (18.6, 20.5)</td>
<td>73.5 (73.3, 74.1)</td>
</tr>
<tr>
<td>Jan 1, 2000 - Dec 31, 2002</td>
<td>Mortality</td>
<td>9.0 (8.4, 9.4)</td>
<td>79.5 (79.2, 79.8)</td>
</tr>
<tr>
<td></td>
<td>AIDS or death</td>
<td>17.0 (16.3, 17.8)</td>
<td>74.4 (74.0, 74.7)</td>
</tr>
<tr>
<td>Jan 1, 2003 onwards</td>
<td>Mortality</td>
<td>4.8 (4.5, 5.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AIDS or death</td>
<td>10.6 (10.2, 11.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4 count, HIV-RNA and AIDS) and baseline characteristics (calendar period and age of HIV diagnosis, risk group, gender, geographical origin, ethnicity and cohort).

Appendix Figures 2.8-2.10 show graphs of cumulative incidence and covariate distributions over time that compare the observed values to the estimated values under no intervention for each baseline subset. We obtained good fits for all variables for the late baseline period. For the intermediate and early baseline periods our models over-estimated the incidence of AIDS and under-estimated the mean CD4 cell count under no intervention especially in the latter half of the follow-up period. We also
observed several anomalously high HIV RNA measurements in the intermediate baseline period which led to a spike in the mean observed viral load at approximately month 40.

We performed a number of sensitivity analyses in an attempt to improve the fit for the early and intermediate baseline period and to assess the impact of the modeling assumptions on the goodness of fit. We used the natural log of HIV viral load, the absolute value of CD4 count, and assessed including time since HIV diagnosis. None of the sensitivity analyses substantially altered the fit for AIDS incidence or CD4 count.
Figure 2.8: Mean of the main study variables under no intervention: observed (solid line) and estimated via the parametric g-formula (dotted line). HIV-CAUSAL Collaboration, late baseline: on or after Jan 1, 2003. (a) Cumulative incidence of death; (b) Cumulative incidence of AIDS; (c) Mean proportion on treatment; (d) Mean CD4 count, natural log scale; (e) Mean HIV viral load.
Figure 2.9: Mean of the main study variables under no intervention: observed (solid line) and estimated via the parametric g-formula (dotted line). HIV-CAUSAL Collaboration, intermediate baseline: Jan 1, 2000 – Dec 31, 2002. (a) Cumulative incidence of death; (b) Cumulative incidence of AIDS; (c) Mean proportion on treatment; (d) Mean CD4 count, natural log scale; (e) Mean HIV viral load.
Figure 2.10: Mean of the main study variables under no intervention: observed (solid line) and estimated via the parametric g-formula (dotted line). HIV-CAUSAL Collaboration, early baseline: Jan 1, 1996 – Dec 31, 1999. (a) Cumulative incidence of death; (b) Cumulative incidence of AIDS; (c) Mean proportion on treatment; (d) Mean CD4 count, natural log scale; (e) Mean HIV viral load.
Chapter 3 Using observational data to improve agent-based models: an application to the incidence of opportunistic diseases in HIV-positive individuals

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ABSTRACT

Agent-based models (ABMs) are increasingly popular tools for assessing the effects of complex interventions in epidemiology and health policy research. ABMs must model the relationships between treatments, outcomes, and time-varying confounders and mediators. To do so, modelers often require estimates of the direct effects of treatment, conditional on current covariate or mediator values. However, estimating these parameters requires strong identifiability and transportability assumptions. Here, we formally define the direct effect of interest for these inputs, and describe the assumptions required for identifiability and transportability of this effect. As an example, we use the Cost Effectiveness of Preventing AIDS Complications (CEPAC) ABM and data from the HIV-CAUSAL Collaboration observational study of HIV-positive individuals to show how a common approach to estimating these parameters can produce bias when the assumptions are violated, applied to the example of parameterizing the ABM for opportunistic disease incidence.
BACKGROUND

Agent-based models (ABMs), also known as microsimulation models, are increasingly being used in epidemiology and health policy research to estimate the causal effects of complex interventions. When properly designed and calibrated, these models can be used to make inferences about intervention strategies, time frames, or populations for which no directly observable data exist. Though the goal of ABMs is inherently causal, there has been little work assessing ABMs from a causal inference perspective.

In particular, ABMs are generally interpreted as mechanistic causal models: some of their parameters are conceptualized as the changes on one variable would bring about on another variable, that is, as the direct effect of one variable on another not mediated through the other variables in the model. Direct effects have been extensively studied in the causal inference literature, but these studies have not generally been used to inform the design and construction of ABMs.

A relevant finding for ABMs is that some direct effects are not well defined and, even if so, the conditions under which they can be estimated from actual data are quite strong. Therefore, it is possible that the construction of ABMs relies on parameter estimates that are ill-defined or very sensitive to bias in the original studies from which they were obtained, or both. In addition, even if we could obtain unbiased estimates of these parameters in one population, we often cannot expect these to provide transportable estimates of treatment effects to other populations. That is, even if we could estimate these inputs without bias, knowing the correct value in one population may not help us make inferences in a second population.

As an example consider the Cost-Effectiveness of Prevention of AIDS Complications (CEPAC) model.\textsuperscript{1-4} CEPAC models the health status of individuals over time, as well as how these changes affect the risk of health events, such as opportunistic diseases or death, at each time point. To do this, CEPAC
requires information on the direct effects of treatment on the incidence of opportunistic diseases (ODs) and the probability of death within 30 days on an OD diagnosis, both conditional on current CD4 cell count and history of past ODs, as well as the direct effect of treatment on chronic AIDS mortality, conditional on current CD4 cell count only.

Here, we discuss conditions under which such direct effects: (1) are well defined, (2) can be estimated without bias in a particular population, and (3) are transportable across populations. To illustrate these issues, we use the CEPAC model and data from the HIV-CAUSAL Collaboration, a consortium of prospective studies of HIV-positive individuals.

AN EXAMPLE OF AN ABM: CEPAC

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC)\textsuperscript{1-4} model is described by three general health states—chronic infection and acute health events including ODs, which are both stratified by current CD4 count and viral load, and death—as well as time-varying covariates which govern transitions between these states. Figure 3.1 provides a flow chart of the CEPAC decision process for each month.
Figure 3.1: Summary of the CEPAC decision process for determining infection (I) with each of j opportunistic diseases in a given month k.
Recently, we calibrated the CEPAC model to data from a consortium of observational cohort studies\(^5\). We obtained a good fit between CEPAC and the observational data for 7-year mortality, across a range of treatment strategies. This supports our claim that a carefully designed and well parameterized ABM can be used for valid inference. However, we did not identify a unique set of inputs that produced a good fit for all outcomes and strategies assessed. Specifically, this calibration effort suggested that the input probabilities of ODs used in CEPAC may be higher than those observed in current HIV-positive populations.

CEPAC simulations require inputting monthly conditional probabilities of each of several ODs: *pneumocystis jirovecii* pneumonia (PCP), *mycobacterium avium complex* (MAC), *cytomegalovirus* (CMV), toxoplasmosis, fungal infections, and other infections. CEPAC also requires specification of the multiplicative effect of treatment on the probability of each OD, within CD4 count strata. Specifically, CEPAC requires an estimate of the 1-month probability for each OD of interest conditional on CD4 count, OD history, and treatment status:

\[
P[I(j)_{k+1} = 1|CD4_k = cd4_k, H_k, A_k = 0]
\]

where \(I(j)_{k+1}\) is an indicator for infection with OD of type \(j\) at the start of month \(k+1\); \(CD4_k\) is the current CD4 stratum at the start of month \(k\); \(H_k\) is an indicator for a history of any OD, including but not limited to the OD of interest, up to the end of the previous month; and \(A_k\) is an indicator for treatment history up to month \(k\), with \(A_k = 0\) denoting an individual who has never been treated at any time between baseline and month \(k\).
CEPAC also includes a “rate multiplier” for each OD of interest, in an attempt to model the direct effect of treatment on OD incidence that does not operate through changes in CD4 count or viral load.

The CEPAC rate multipliers are defined as:

\[
\frac{\lambda^a=1(k|CD4_k = cd4_k)}{\lambda^a=0(k|CD4_k = cd4_k)} = \frac{\ln(1 - P[I(j)_{k+1} = 1|CD4_k = cd4_k])}{\ln(1 - P[I(j)_{k+1} = 1|CD4_k = cd4_k])}
\]

where \(\lambda^a=1(k|CD4_k = cd4_k)\) is the counterfactual rate of infection that would have been observed between times \(k\)-1 and \(k\) if everyone had been treated, conditional on CD4 stratum in month \(k\), and \(\lambda^a=0(k|CD4_k = cd4_k)\) is the counterfactual rate of infection that would have been observed between times \(k\)-1 and \(k\) if no one had been treated, conditional on current CD4 stratum in month \(k\).

CEPAC estimates these rates by conversion from counterfactual probabilities, where \(I(j)_{k+1} = 1\) represents the counterfactual infection status for OD \(j\) at the start of month \(k+1\) that would have been observed under treatment in month \(k\), using the relationship \(\lambda(k) = -\ln(1 - P_k)\) (see Appendix for more information). This rate multiplier is assumed constant for all time periods for a given OD, and is conditional only on CD4 count, not OD history. In recent CEPAC publications, the multiplier has generally been assumed constant across CD4 counts.6

CEPAC uses these input parameters to determine whether an individual has an OD in each month, and if so, which OD (see Appendix for algorithm). If an OD occurs, the probability of death may be increased during that month. Otherwise, if alive at the next month, the OD is assumed to have resolved.
THE DIRECT EFFECT

The directed acyclic graph (DAG) in Figure 3.2 shows the relationship between treatment (A), CD4 count, and an opportunistic disease (I) at time k in the CEPAC model. Treatment can affect the OD in two ways: directly, as shown by the arrow from \( A_{k-1} \) to \( I_{k+1} \), or indirectly through changes to CD4 count which in turn affects OD incidence, as shown by the sequence of arrows from \( A_{k-1} \) to \( CD4_k \) and from \( CD4_k \) to \( I_{k+1} \). ABMs need to model each of these relationships. CEPAC does so by using the risk under no treatment within CD4 count strata and a multiplier for the change in risk when treated conditional on CD4 count strata, as well as, separately, modeling changes in CD4 count due to treatment.

Figure 3.2: Causal directed acyclic graph depicting two arbitrary time points from a setting with time-varying treatment A, outcome I, and confounder L or CD4 count, with an unmeasured common cause of CD4 count and OD incidence. Conventional adjustment for L is expected to introduce bias because L is affected by prior treatment and shares a cause (U) with the outcome.
The (controlled) direct effect of treatment on OD incidence not mediated via CD4 count that we are interested in estimating for CEPAC is the change in the probability of an OD that would be observed if an individual had been treated compared to if she had not been treated, while her CD4 count remained fixed at some value. This can be represented using counterfactual notation as

\[
\frac{\Pr(I(g, L=l))}{\Pr(I(g', L=l))} = \frac{\Pr(I(g, L=l))}{\Pr(I(g', L=l))}, \quad g \neq g' \quad \text{where } I(g, L=l) \text{ is the counterfactual value of the opportunistic disease indicator when the individual is treated according to strategy } g \text{ and the CD4 count is fixed to some value } L=l, \text{ and } g' \text{ is some other treatment strategy with no treatment in the current month. The identifiability conditions for this effect have been well-described.}^{7,8}

Identification of the direct effect requires two assumptions about the structure of the causal relationships.\(^8\) These assumptions are: A.1) no unmeasured common causes of treatment and the outcome; and A.2) no unmeasured common causes of the mediator, CD4 count, and the outcome.\(^8,9\) Well-defined ABMs typically include information on treatment-outcome confounders, or attempt to replicate scenarios in which treatment was randomized, so assumption A.1 may hold. Here, we focus on the assumption A.2 in order to provide some intuition for identifying potential violations.

Consider a trial in which we randomize individuals to some treatment initiation strategy delivered at multiple time-points. This trial is described by the DAG in Figure 3.2 and we can see that, although assumption A.1 is met, assumption A.2 may still be violated by the presence of an open path between the outcome and CD4 count through the unmeasured common cause of CD4 count and OD incidence, \(U\). Intuitively, individuals with low CD4 count at time \(k\) must have some reason for their low CD4 count. This might be because they were untreated in the past, or it might be because of some other factor, \(U\), such as longer time since initial HIV infection. If treatment improves CD4 count, then the distribution of \(U\) among people who have low CD4 counts and have previously been untreated will differ from the distribution of \(U\) among people who have low CD4 counts and have previously been treated. As
a result, the risk of ODs in the two groups— that is, people previously treated and with low CD4 counts, and people previously untreated and with low CD4 counts—will be expected to differ simply because of the difference in the distribution of $U$ between the two groups. Any attempt to assess the relationship between treatment and OD incidence, conditional on current CD4 count, from a trial where only treatment was randomized may still have a common cause of CD4 count and OD incidence. If this is the case, we will find an association even if no direct effect exists, and will produce a biased estimate of the effect size when a direct effect does exist.\textsuperscript{10,11}

Now consider a second hypothetical trial in which we randomize treatment status and then randomize CD4 cell count, although this trial would not be feasible in a real world setting. For example, we might randomize individuals to: (1) fix CD4 count at an individual’s baseline value; or to (2) fix CD4 count to the value the individual had the month before starting treatment. Setting aside the plausibility of such an intervention, this trial would now have no common causes of either treatment and OD incidence nor CD4 count and OD incidence, and we could therefore obtain estimates of the direct effect of treatment, conditional on CD4 count.\textsuperscript{11-13} In reality, we cannot manipulate CD4 count to fix it to a constant level, regardless of treatment status. Therefore, even though we could in theory estimate the direct effect of treatment on OD incidence, not mediated through CD4 count, in practice we cannot obtain an estimate of this effect.

In summary, if there are no unmeasured common causes of the treatment and outcome or of the mediator and outcome; or if we could intervene on both the treatment and the mediator, then we could estimate the direct effect of treatment on OD incidence, not mediated by CD4 cell count. Estimation of the effect under these assumptions could be performed using a number of approaches including regression\textsuperscript{6} or the parametric g-formula.\textsuperscript{11} If any of these assumptions are violated, then we cannot obtain unbiased estimates of the direct effect of treatment. In the example of parameterizing
CEPAC, there could be several potential common causes of CD4 count and OD incidence, such as time since HIV diagnosis or other genetic determinants of immune function.

TRANSPORTABILITY OF THE DIRECT EFFECT

Consider two scenarios in the DAGs in Figures 3.3 and 3.4. In Figure 3.3, there is an unknown or unmeasured cause of CD4 count which does not affect the outcome, and in Figure 3.4 the unmeasured variable is a cause only of the outcome, and so the assumptions required for estimating the direct effect are met. In a population where either of these graphs represents the true causal structure, and we had data from the population, we could obtain an estimate of the direct effect of treatment to parameterize our ABM for that population.

Figure 3.3: Causal directed acyclic graph depicting two arbitrary time points from a setting with time-varying treatment $A$, outcome $I$, and confounder $L$ or CD4 count in our example, with an unmeasured cause of CD4 count only.
However, when we parameterize an ABM, it is not sufficient to have an estimate of the direct effect of treatment only in one population. The goal of an ABM is to provide inferences across a range of populations. Therefore, we must assess whether the direct effect of treatment will be transportable to other populations in order to ensure that our ABM returns valid estimate of OD incidence in any population of interest.

However, in Figures 3.3 and 3.4, OD incidence also depends not only on the effect of treatment and CD4 count but also on some other unmeasured variable. If either of these Figures represents the true causal relationships in all populations of interest, the OD incidence estimated for a given population when the ABM is parameterized with the direct effect from another population may not be correct. The direct effect estimate from one population will likely not be transportable to another population where the distribution of the unmeasured causes of CD4 cell count or the outcome differ from the original population. This is because differences in the distributions of the unmeasured cause of CD4 cell
count or of the outcome will lead changes to the underlying risk of ODs between these two populations which the ABM will not be parameterized to detect.

**DATA ANALYSIS**

Next, we demonstrate the bias that can occur when attempting to estimate the direct effect of treatment on OD incidence if any of the required assumptions are violated. As we have described, we expect that there may be unmeasured common causes of CD4 count and OD incidence, violating assumption A.2.

We first describe the HIV-CAUSAL data which we use to demonstrate the bias. We then describe two approaches to inference about the effect of treatment on OD incidence. The first approach is a naïve approach to estimating the direct effect which is expected to be biased. The second approach provides some intuition about the likely direction of the direct effect but does not estimate this effect, which cannot be estimated because of the potential violations of A.2.

**An observational cohort: the HIV-CAUSAL Collaboration**

The HIV-CAUSAL Collaboration \(^5\text{–}^{16}\) combines data from prospective studies of HIV-infected individuals in nine countries: Brazil, Canada, France, Greece, the Netherlands, Spain, Switzerland, UK, and USA. All studies are based on clinical data collected within universal health care systems.\(^5\) We excluded data from Brazil from our analyses because a separate parameterization of the CEPAC model exists for Brazil. Cohort enrollment began between 1982 and 1998; administrative end of follow-up is cohort-specific and occurs between February 2010 and March 2013.

To estimate inputs for CEPAC, we restricted our analyses to individuals 18 or older, who were antiretroviral naïve, had no history of an AIDS-defining illness, were not pregnant (if known), and had a CD4 cell count and HIV viral load measurement within 3 months of baseline. The start of follow-up for
each individual was defined as the first month in which all eligibility criteria were met from Jan 1, 2003 onwards. Follow-up continued until first occurrence of the OD of interest, death, or censoring; individuals were considered censored 12 months after the last recorded CD4 cell count and HIV viral load measurements, at pregnancy (if known), or at the cohort-specific administrative end of follow-up.

Antiretroviral therapy (ART) was defined as a regimen of antiretroviral drugs including at least two nucleoside reverse transcriptase inhibitors (NRTIs) and either one or more protease inhibitors, one or more non-nucleoside reverse transcriptase inhibitor (NNRTI), one entry or fusion inhibitor, or one integrase inhibitor. We consider three ART interventions: (1) immediate universal initiation; (2) initiation delayed until the CD4 count first falls below 500 cells/mm³; and (3) initiation delayed until the CD4 count first falls below 350 cells/mm³.

Preliminary analysis of HIV-CAUSAL data suggested that the most common serious ODs in this cohort were Kaposi’s sarcoma, AIDS-related lymphoma, and tuberculosis. The incidence of PCP, MAC, toxoplasmosis, CMV, and fungal infections was too low to estimate the risk of these infections individually, so we combined these infections in an ‘other OD’ category.

**Naive approach to estimating ABM inputs**

We fit multivariable pooled logistic regression models for first diagnosis of each OD conditional on current CD4 count, and additionally include history of prior OD infection and treatment initiation status. These models include product terms between treatment status and CD4 count, and OD history and CD4 count, to mimic the strata of inputs required by CEPAC (see Appendix for details).

**The parametric g-formula approach**

The parametric g-formula is a generalization of standardization to settings with time-varying covariates affected by treatment where traditional regression methods may cause bias. We cannot
use the parametric g-formula to estimate the direct effect of treatment on ODs because, as we saw previously, the identifiability criteria are not met for this effect. Instead, we estimate use the g-formula to provide some intuition about the impact of treatment on OD incidence when treatment initiation depends on CD4 count.

We estimate the 7-year risk of each OD and the 7-year restricted mean OD survival time\textsuperscript{20} under three treatment intervention strategies: (1) immediate universal initiation; (2) initiation delayed until the CD4 count first falls below 500 cells/mm\textsuperscript{3}; and (3) initiation delayed until the CD4 count first falls below 350 cells/mm\textsuperscript{3}. By estimating the OD incidence under these strategies, we can obtain some evidence by which to assess the conclusions of our naïve regression analysis. We could also use the g-formula estimates as benchmarks against which to calibrate the CEPAC model.

Briefly, we adjusted for baseline and time-dependent confounders using the parametric g-formula under the three ART interventions. We included baseline CD4 count, HIV viral load, sex, race, geographical origin, transmission risk group, age, calendar year, and cohort. For each OD of interest, we fit logistic regression models for time-varying indicators for first diagnosis of that OD, diagnoses of each of the other three OD types, death, and treatment initiation, and linear regression models for the natural logarithms of HIV viral load and CD4 cell count. All regression models included the two most recent values of the time-varying covariates, as well as time since last CD4 count and HIV viral load measurements, prior diagnosis of an OD, and all baseline covariates. Models for CD4 count and HIV viral load also included interaction terms for the number of months since ART initiation (see Appendix for details). We created simulated populations based on the estimated regression models and each treatment strategy of interest using Monte-Carlo simulation. We used non-parametric bootstraps with 500 samples to obtain 95% confidence intervals for risk estimates. Parametric g-formula analyses were done using the GFORMULA macro\textsuperscript{21} in SAS 9.4.
RESULTS

The HIV-CAUSAL Collaboration included 66,562 individuals eligible for our analysis, after applying our exclusion criteria. The analyses presented here are based on data pooled in September 2013. The baseline cohort characteristics are described in Table 3.1. There were 482 individuals with at least one diagnosis of Kaposi’s sarcoma, 304 with AIDS-related lymphoma, 748 with tuberculosis, and 831 with at least one of the other ODs—PCP, MAC, CMV or toxoplasmosis (Table 3.2). The incidence rate for first diagnosis of an OD was higher among individuals with lower baseline CD4 counts, higher baseline viral loads, and older age (Table 3.2).
Table 3.1: Baseline characteristics of eligible individuals in the HIV-CAUSAL Collaboration 2003-2013.

<table>
<thead>
<tr>
<th></th>
<th>Individuals (n)</th>
<th>Person-years (py)</th>
<th>Proportion starting ART during follow-up (%)</th>
<th>Median (IQR) follow-up (months)</th>
<th>Deaths (n)</th>
<th>Incidence (per 1000 py)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, cells/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>3,344</td>
<td>10,557</td>
<td>90.4</td>
<td>32 (14, 57)</td>
<td>337</td>
<td>31.9</td>
</tr>
<tr>
<td>50-100</td>
<td>2,810</td>
<td>9,134</td>
<td>90.5</td>
<td>32 (13, 61)</td>
<td>201</td>
<td>22.0</td>
</tr>
<tr>
<td>100-200</td>
<td>7,082</td>
<td>22,864</td>
<td>90.5</td>
<td>32 (15, 58)</td>
<td>301</td>
<td>13.2</td>
</tr>
<tr>
<td>200-350</td>
<td>15,666</td>
<td>49,562</td>
<td>80.3</td>
<td>31 (14, 57)</td>
<td>336</td>
<td>6.8</td>
</tr>
<tr>
<td>350-500</td>
<td>15,921</td>
<td>4,8271</td>
<td>60.1</td>
<td>29 (13, 54)</td>
<td>255</td>
<td>5.3</td>
</tr>
<tr>
<td>&gt;500</td>
<td>21,587</td>
<td>62,981</td>
<td>39.2</td>
<td>27 (13, 51)</td>
<td>293</td>
<td>4.7</td>
</tr>
<tr>
<td>HIV-RNA, copies/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10000</td>
<td>17,910</td>
<td>52,012</td>
<td>47.3</td>
<td>27 (13, 50)</td>
<td>301</td>
<td>5.8</td>
</tr>
<tr>
<td>10,000-100,000</td>
<td>29,982</td>
<td>91,869</td>
<td>64.5</td>
<td>29 (14, 55)</td>
<td>686</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>18,518</td>
<td>59,487</td>
<td>79.7</td>
<td>31 (14, 58)</td>
<td>736</td>
<td>12.4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>52,265</td>
<td>161,179</td>
<td>63.5</td>
<td>30 (14, 55)</td>
<td>1,544</td>
<td>9.6</td>
</tr>
<tr>
<td>Women</td>
<td>14,145</td>
<td>42,187</td>
<td>66.3</td>
<td>27 (13, 53)</td>
<td>179</td>
<td>4.2</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>29,346</td>
<td>86,167</td>
<td>57.7</td>
<td>27 (13, 51)</td>
<td>205</td>
<td>2.4</td>
</tr>
<tr>
<td>35-50</td>
<td>27,658</td>
<td>88,991</td>
<td>67.4</td>
<td>31 (14, 58)</td>
<td>737</td>
<td>8.3</td>
</tr>
<tr>
<td>&gt;50</td>
<td>9,406</td>
<td>28,210</td>
<td>74.6</td>
<td>29 (13, 55)</td>
<td>781</td>
<td>27.7</td>
</tr>
<tr>
<td>Transmission group</td>
<td>Individuals (n)</td>
<td>Person-years</td>
<td>Proportion starting ART during follow-up (%)</td>
<td>Median (IQR) follow-up (months)</td>
<td>Deaths (n)</td>
<td>Incidence (per 1000 py)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>---------------------------------------------</td>
<td>--------------------------------</td>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>21,843</td>
<td>67,637</td>
<td>68.0</td>
<td>29 (14, 55)</td>
<td>371</td>
<td>5.5</td>
</tr>
<tr>
<td>MSM or MSMW*</td>
<td>30,790</td>
<td>98,560</td>
<td>61.0</td>
<td>31 (15, 57)</td>
<td>337</td>
<td>3.4</td>
</tr>
<tr>
<td>Injecting drug user</td>
<td>2,714</td>
<td>7,008</td>
<td>57.6</td>
<td>20 (11, 45)</td>
<td>150</td>
<td>21.4</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>11,063</td>
<td>30,162</td>
<td>66.5</td>
<td>26 (11, 49)</td>
<td>865</td>
<td>28.7</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western countries</td>
<td>46,518</td>
<td>143,924</td>
<td>63.9</td>
<td>30 (14, 55)</td>
<td>1,464</td>
<td>10.2</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>10,057</td>
<td>30,890</td>
<td>69.5</td>
<td>28 (13, 55)</td>
<td>112</td>
<td>3.6</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>6,622</td>
<td>19,192</td>
<td>61.5</td>
<td>27 (13, 50)</td>
<td>85</td>
<td>4.4</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>3,213</td>
<td>9,361</td>
<td>55.3</td>
<td>26 (12, 52)</td>
<td>62</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*MSM: men who have sex with men; MSMW: men who have sex with men and women
Table 3.2: First diagnosis of opportunistic diseases and AIDS by baseline variables, HIV-CAUSAL Collaboration 2003-2013.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incidence</th>
<th>AIDS-related lymphoma</th>
<th>Tuberculosis</th>
<th>Other ODs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma (n)</td>
<td>2.4</td>
<td>1.5</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>AIDS- related lymphoma (n)</td>
<td>2.7</td>
<td>2.4</td>
<td>3.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Tuberculosis (n)</td>
<td>1.7</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Other ODs* (n)</td>
<td>0.9</td>
<td>1.0</td>
<td>1.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 cell count, cells/mm3</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>6.3</td>
<td>2.7</td>
<td>14.7</td>
<td>32.0</td>
</tr>
<tr>
<td>50-100</td>
<td>4.2</td>
<td>3.6</td>
<td>7.6</td>
<td>12.9</td>
</tr>
<tr>
<td>100-200</td>
<td>2.5</td>
<td>2.4</td>
<td>5.9</td>
<td>5.2</td>
</tr>
<tr>
<td>200-350</td>
<td>2.2</td>
<td>1.7</td>
<td>3.9</td>
<td>2.2</td>
</tr>
<tr>
<td>350-500</td>
<td>1.8</td>
<td>1.0</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>&gt;500</td>
<td>2.0</td>
<td>0.9</td>
<td>1.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-RNA, copies/mL</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10,000</td>
<td>1.0</td>
<td>0.8</td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>10,000-100,000</td>
<td>2.2</td>
<td>1.3</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>3.9</td>
<td>2.3</td>
<td>5.6</td>
<td>7.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.8</td>
<td>1.6</td>
<td>3.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Women</td>
<td>0.7</td>
<td>1.0</td>
<td>5.6</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, years</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>1.7</td>
<td>0.9</td>
<td>3.2</td>
<td>1.8</td>
</tr>
<tr>
<td>35-50</td>
<td>2.6</td>
<td>1.6</td>
<td>3.7</td>
<td>5.1</td>
</tr>
<tr>
<td>&gt;50</td>
<td>3.7</td>
<td>3.0</td>
<td>5.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>

*OD: opportunistic diseases; PCP: *pneumocystis* pneumonia; MAC: *mycobacterium avium* complex; CMV: cytomegalovirus
In Table 3.3, we report the estimated monthly risks of each OD type from the pooled logistic regression model. The regression results suggest that, within each stratum of current CD4 count, treated individuals have a higher risk of first diagnosis of Kaposi’s sarcoma, AIDS-related lymphoma, and other ODs than untreated individuals. Only the results for tuberculosis suggest treatment might be beneficial. However, it has been well established that treatment improves both survival and progression to AIDS. In the absence of bias, we would therefore expect that treatment should have either a neutral or a beneficial effect on OD incidence, conditional on current CD4 count.

Table 3.3: Biased estimates of the 1-month probability for first diagnosis with each OD (cases /10,000 individuals) by current CD4 count and treatment status from multivariate logistic regression with induced collider bias, HIV-CAUSAL Collaboration 2003-2013.

<table>
<thead>
<tr>
<th>Current CD4 cell count (cells/mm³)</th>
<th>Kaposi’s Sarcoma</th>
<th>AIDS-related Lymphoma</th>
<th>Tuberculosis</th>
<th>Other ODs: PCP, MAC, CMV, toxoplasmosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>Untreated</td>
<td>15.6</td>
<td>8.6</td>
<td>54.1</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>21.4</td>
<td>10.7</td>
<td>49.8</td>
</tr>
<tr>
<td>50-100</td>
<td>Untreated</td>
<td>15.8</td>
<td>7.0</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>15.5</td>
<td>12.5</td>
<td>22.6</td>
</tr>
<tr>
<td>100-200</td>
<td>Untreated</td>
<td>3.7</td>
<td>4.1</td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>5.0</td>
<td>4.1</td>
<td>10.0</td>
</tr>
<tr>
<td>200-350</td>
<td>Untreated</td>
<td>1.9</td>
<td>1.2</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>3.0</td>
<td>2.4</td>
<td>3.6</td>
</tr>
<tr>
<td>350-500</td>
<td>Untreated</td>
<td>1.0</td>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>1.8</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Untreated</td>
<td>0.8</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>0.9</td>
<td>0.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*OD: opportunistic diseases; PCP: pneumocystis pneumonia; MAC: mycobacterium avium complex; CMV: cytomegalovirus
When we use the parametric g-formula to control for treatment-confounder feedback, immediate universal treatment from baseline decreases the 7-year risk of first diagnosis with all ODs compared to treatment delayed based on CD4 cell count thresholds (Table 3.4). This agrees with previous research that earlier treatment improves AIDS-free survival. The difference in results between these two methods is sometimes called Simpson’s paradox. However, in reality, no paradox exists. In the naïve analysis, we have conditioned on a descendent of treatment that shares a common cause with the outcome and in doing so have induced bias in our own analyses. In contrast, the g-formula avoids this bias and, under identifiability assumptions, provides us an unbiased estimate of the causal effect of early treatment initiation on first diagnosis of ODs.

Table 3.4: 7-year risk (%) and restricted mean survival time (days) for each OD by treatment initiation strategy, using the parametric g-formula, HIV-CAUSAL Collaboration 2003-2013.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Treatment initiation strategy, cells/mm³</th>
<th>Risk at 7 years, %</th>
<th>Risk difference</th>
<th>Risk ratio</th>
<th>Difference in RMST (days)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Immediate</td>
<td>0.9 (0.8, 1.1)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 500</td>
<td>1.0 (0.9, 1.2)</td>
<td>0.1 (0.03, 0.2)</td>
<td>1.1 (1.03, 1.2)</td>
<td>-0.1 (-0.2, 0.01)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 350</td>
<td>1.2 (1.0, 1.4)</td>
<td>0.3 (0.2, 0.3)</td>
<td>1.3 (1.2, 1.4)</td>
<td>-0.2 (-0.3, -0.1)</td>
</tr>
<tr>
<td>AIDS-related lymphoma</td>
<td>Immediate</td>
<td>0.6 (0.5, 0.8)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 500</td>
<td>0.7 (0.6, 0.9)</td>
<td>0.1 (0.1, 0.1)</td>
<td>1.2 (1.1, 1.2)</td>
<td>-0.1 (-0.1, -0.01)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 350</td>
<td>0.9 (0.7, 1.0)</td>
<td>0.2 (0.2, 0.3)</td>
<td>1.4 (1.3, 1.5)</td>
<td>-0.2 (-0.3, -0.1)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Immediate</td>
<td>1.7 (1.5, 2.0)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 500</td>
<td>2.0 (1.8, 2.2)</td>
<td>0.2 (0.2, 0.3)</td>
<td>1.1 (1.1, 1.2)</td>
<td>-0.2 (-0.3, -0.1)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 350</td>
<td>2.1 (1.9, 2.3)</td>
<td>0.4 (0.3, 0.5)</td>
<td>1.2 (1.1, 1.3)</td>
<td>-0.3 (-0.4, -0.2)</td>
</tr>
<tr>
<td>Other ODs: PCP, MAC, CMV, toxoplasmosis*</td>
<td>Immediate</td>
<td>1.5 (1.3, 1.7)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 500</td>
<td>1.6 (1.5, 1.8)</td>
<td>0.1 (0.1, 0.2)</td>
<td>1.1 (1.1, 1.1)</td>
<td>-0.1 (-0.2, -0.1)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 350</td>
<td>1.8 (1.6, 2.0)</td>
<td>0.3 (0.2, 0.4)</td>
<td>1.2 (1.1, 1.3)</td>
<td>-0.3 (-0.3, -0.2)</td>
</tr>
</tbody>
</table>

*OD: opportunistic diseases; PCP: *pneumocystis* pneumonia; MAC: *mycobacterium avium* complex; CMV: cytomegalovirus

**RMST: restricted mean survival time
Agent-based models have received attention recently in epidemiology as analytic tools for understanding complex systems. However, despite the fact that they are intended as tools for making evidence-based decisions, the design of ABMs from a causal inference perspective has not been widely considered. We have previously reported on the potential for bias when ABM inputs are selected from multiple populations, and described a method for obtaining a range of calibration targets for validating parameterized ABMs. Here, we describe in detail a single decision step from a prominent HIV-progression ABM, the CEPAC model, and describe a scenario in which some of the required inputs cannot be validly estimated directly from data.

When assessing HIV progression, updating CD4 counts over time in the model is crucial. CD4 count is associated with both mortality and treatment decisions, and an ABM which ignores CD4 count could fail to capture important dynamics. However, we may not be able to directly estimate inputs conditional on time-varying CD4 count if CD4 count shares a cause with the outcome of interest. When we attempt to estimate these inputs using a conditional regression approach, we expect bias due to the unmeasured common cause.

ABMs use microsimulation to estimate the impact of treatment strategies on an outcome of interest, and by necessity must condition on time-dependent covariates affected by prior treatment. Although we showed that this treatment-confounder feedback can result in bias in the traditional regression model, the parametric g-formula uses microsimulation to obtain unbiased estimates of the treatment effect. It does this by using only parameters estimated from a single population. Although the parametric g-formula cannot solve the problem of estimating the direct effect of treatment, we could use the g-formula to estimate calibration targets for the incidence of opportunistic infections under a range of treatment strategies and adjust the ABM inputs until the output matches these targets.
However, this process would provide inputs that are appropriate only for populations in which the distribution of the unmeasured common cause of the confounder and outcome is the same. Recalibration would be required whenever inference in a population with a different distribution of this variable is desired.

ABMs ideally rely on the assumption that all inputs are unbiased for the population of interest. However, the goal of ABMs is to provide information for decision-making when complete data do not exist for the population, question, or time period of interest. As a result, there is often no alternative to making strong assumptions about input validity and transportability. Careful assessment of the inputs to determine which can and cannot be estimated without bias, coupled with calibration of a range of outcomes and intervention strategies to the population of interest, can provide support for these assumptions and improve the ability of ABMs to be used for causal inference.
REFERENCES


CEPAC decision process for assigning OD incidence

CEPAC uses the 1-month conditional probabilities of each OD to determine whether an individual has an OD, and if so, which type, in each month. This decision process is as follows:

1. If $A_k = 1$, convert the probability of each OD when off treatment,
   
   $$ P[I(j)_{k+1} = 1|CD4_k = cd4_k, \bar{H}_k = \bar{h}_k, \bar{A}_k = 0], $$
   
   to a rate, $\lambda$,

   using the relationship $\lambda = -\ln(1 - P)$

2. Multiply this rate by the rate multiplier:

   $$ \lambda = -\ln(P[I(j)_{k+1} = 1|CD4_k = cd4_k, \bar{H}_k = \bar{h}_k, \bar{A}_k = 0]) 
   \times \frac{\ln(1 - P[I(j)_{k+1} = 1|CD4_k = cd4_k, \bar{A}_k = 1])}{\ln(1 - P[I(j)_{k+1} = 1|CD4_k = cd4_k, \bar{A}_k = 0])} $$

3. Convert back to a probability, using the inverse of the previous relationship $P = 1 - e^{-\lambda}$

4. Calculate the probability of not having any OD as:

   $$ P[I_{k+1} = 0|CD4_k, \bar{H}_{k-1}, \bar{A}_k] = \prod_{j=1}^{j} (1 - P[I(j)_{k+1} = 1|CD4_k = cd4_k, \bar{H}_{k-1} = \bar{h}_{k-1}, A_k = a_k]) $$

5. Calculate the probability of having any OD:

   $$ P[I_{k+1} = 1|CD4_k, \bar{H}_{k-1}, A_k] = 1 - P[I_{k+1} = 0|CD4_k, \bar{H}_{k-1}, A_k] $$
6. Draw for OD in month $k$. If OD occurs, determine which OD by:

   a. Calculate the probability of having each OD and none of the others as

   
   $$P[I(j)_{k+1} = 1, I(j')_{k+1} = 0|CD4_k, \bar{H}_{k-1}, A_k]$$

   $$= P[I(j)_{k+1} = 1|CD4_k, \bar{H}_{k-1}, A_k] \times \prod (1 - P[I(j')_{k+1} = 1|CD4_k, \bar{H}_{k-1}, A_k])$$

   where $I(j')_{k+1}$ indicates each OD other than OD $j$

   b. Normalize the individual OD probabilities by dividing by their sum

   c. Determine which OD occurs by drawing randomly from this distribution, under the assumption that at most 1 OD can occur in a given month

**Parametric modeling assumptions**

*Naive regression analysis*

Model for the probability of first diagnosis of each OD, conditional on joint CD4 count and OD history strata and treatment status (Table 3.3):

$$logit P[I(j)_{k+1} = 1|CD4_k, \bar{H}_k, \bar{A}_k]$$

$$= \beta_0 + \beta_1 \bar{H}_k + \beta_2 \bar{A}_k + \beta_3 \bar{H}_k * \bar{A}_k + \beta_i^T I(CD4_{k,i}) + \beta_i^T I(CD4_{k,i}) * \bar{A}_k$$

where $\beta_i^T I(CD4_{k,i})$ represents a vector of coefficients for indicator variables for each of the CD4 count strata.
The parametric g-formula results are based on the following modeling assumptions for the first step of the estimating algorithm described in the main text.

1. Models for the covariates, from $k=2$ to maximum length of follow-up:
   
   f. RNA measured at visit $k$:

   $$
   \text{logit}(\Pr[L_{1,k} = 1 | \bar{I}_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{y}_k, \bar{C}_{k+1} = 0]) = \beta_{l1}^T X_{l1,k}
   $$

   where $\beta_{l1}$ is a coefficient vector, $X_{l1,k}$ is the vector

   $$
   [1, V, h(k), s_2(L_{2,k-1}), s_2(L_{2,k-2}), s_4(L_{4,k-1}), s_4(L_{4,k-2}), L_{5i,k-1}, t(L_{1,k-1}, L_{3,k-1}), A_{k-1}, A_{k-1} \times \sum_{j=0}^{k-1} A_j]
   $$

   • $V$ is the vector of baseline covariates: sex, origin, race, RNA category, CD4 count category, cohort, mode of transmission, age, and year;

   • $h(k)$ is a transformation of $k$ needed to fit a restricted cubic spline with knots at (6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120) months;

   • $s_2(L_{2,j})$ is a transformation of $L_{2,j}$ needed to create categories with cut-points at (51, 1000, 10000, 100000) copies per μl $s_2(L_{2,-1}) = 0$;

   • $s_4(L_{4,j})$ is a transformation of $L_{4,j}$ needed to fit a restricted cubic spline with knots at (4.25, 5.48, 6.17, 6.88, 7.26) natural log cells per mm$^3$ for $j = 0, ..., K$ and $s_4(L_{4,-1}) = 0$;

   • $L_{5i,j}$ is a set of indicators for prior diagnosis with each of the four other OD types

   • $t(L_{1,j}, L_{3,j})$ is the number of months since last measured viral load or CD4 cell count by month $j$ for $j = 0, ..., K$, and $t(L_{1,-1}, L_{3,-1}) = 0$;

   • $\sum_{j=0}^{k-1} A_j$ is the number of months since treatment initiation by $k-1$, by definition of $A_j$. 

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g. RNA value at visit $k$:

\[
\logit(\Pr[I(L_{2,k} = 0)] = 1 | L_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0]) = \beta_{l1}^{T} X_{l1(k)}
\]

\[
\ln(L_{2,k} | L_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0, L_{2,k} > 0) = \beta_{l2}^{T} X_{l2,k}
\]

where $I(L_{2,k} = 0)$ is an indicator for a viral load of 0, $\beta_{l1}$ and $\beta_{l2}$ are coefficient vectors, and $X_{l1(k)} = X_{l1,k}$

h. CD4 count measured at visit $k$:

\[
\logit(\Pr[L_{3,k} = 1 | L_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0]) = \beta_{l3}^{T} X_{l3,k}
\]

where $\beta_{l3}$ is a coefficient vector, $X_{l3,k} = [X_{l3,k}, s_2(L_{2,k}), L_{1,k}]$

i. CD4 count at visit $k$:

\[
\ln(L_{4,k} | L_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0) = \beta_{l4}^{T} X_{l4,k}
\]

where $\beta_{l4}$ is a coefficient vector, and $X_{l4,k} = X_{l3,k}$

j. Any OD diagnosis by month $k$, modeled with separate logistic regression models for each of the four OD types other than the outcome of interest for that model

\[
\logit(\Pr[L_{5i,k} = 1 | L_{k-1} = \bar{l}_{k-1}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0]) = \beta_{l5}^{T} X_{l5,k}
\]

where $\beta_{l5}$ is a coefficient vector, $X_{l5,k} = [X_{l5,k}, s_4(L_{4,k}), L_{3,k}, L_{5i,k-1}]$ and $L_{5i,k-1}$ is an indicator for diagnosis of each of the other 3 ODs before that month.

2. Model for the outcome, $Y_{k+1}$, from $k = 0$ to maximum length of follow-up:

\[
\logit(\Pr[Y_{k+1} = 1 | L_k = \bar{l}_k, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0]) = \beta_{y}^{T} X_{y_k}
\]

where $\beta_{y}$ is the coefficient vector and $X_{y_k}$ is the vector:

\[
[1, V, h(k), t(L_{1,k}), s(L_{2,k}), s(L_{2,k-1}), t(L_{2,k}), s(L_{4,k}), s(L_{4,k-1}), L_{5i,k}, A_k, A_k \times \sum_{j=0}^{k} A_j]
\]

and $Y_{k+1}$ represents the OD of interest
3. Model for treatment, from \( k = 0 \) to maximum length of follow-up:

\[
\logit(\Pr[A_k = 1|L_k = \tilde{l}_k, A_{k-1} = 0, \tilde{y}_k = \tilde{c}_{k+1} = 0]) = \beta_a^T X_{a_k}
\]

where \( \beta_a \) is the coefficient vector and \( X_{y_k} \) is the vector:

\[
[1, V, h(k), s_2(L_{2,k}), s_2(L_{2,k-1}), s_4(L_{4,k}), s_4(L_{4,k-1}), s_4(L_{4,k-2}), s_4(L_{4,k-1}), L_{5,i,k}, L_{5,i,k-1}, \ldots]
\]

**Goodness of fit**

To assess the goodness of fit of our parametric g-formula model, we estimated the outcome distributions under no intervention. That is, we assigned treatment at each month based on the estimated conditional probability of treatment observed in the data following the model presented above. Figures 3.5-3.8 present graphs of cumulative incidence and covariate distributions over time, comparing the observed values to the estimated values under no intervention, for each of the ODs of interest.
Figure 3.5: Mean of the main study variables under no intervention, when first diagnosis of Kaposi’s sarcoma is the outcome of interest: observed (solid line) and estimated via the parametric g-formula (dotted line), HIV-CAUSAL Collaboration. (a) Cumulative incidence of Kaposi’s sarcoma; (b) cumulative incidence of death; (c) mean proportion on treatment; (d) mean CD4 count, natural log scale; (e) mean HIV viral load; (f) proportion with AIDS-related lymphoma in month $k$; (g) proportion with tuberculosis in month $k$; (h) proportion with other ODs in month $k$. 
Figure 3.6: Mean of the main study variables under no intervention, when first diagnosis of AIDS-related lymphoma is the outcome of interest: observed (solid line) and estimated via the parametric g-formula (dotted line), HIV-CAUSAL Collaboration. (a) Cumulative incidence of AIDS-related lymphoma; (b) cumulative incidence of death; (c) mean proportion on treatment; (d) mean CD4 count, natural log scale; (e) mean HIV viral load; (f) proportion with Kaposi's sarcoma in month $k$; (g) proportion with tuberculosis in month $k$; (h) proportion with other ODs in month $k$. 
Figure 3.7: Mean of the main study variables under no intervention, when first diagnosis of tuberculosis is the outcome of interest: observed (solid line) and estimated via the parametric g-formula (dotted line), HIV-CAUSAL Collaboration. (a) Cumulative incidence of tuberculosis; (b) cumulative incidence of death; (c) mean proportion on treatment; (d) mean CD4 count, natural log scale; (e) mean HIV viral load; (f) proportion with Kaposi’s sarcoma in month k; (g) proportion with AIDS-related lymphoma in month k; (h) proportion with other ODs in month k.
Figure 3.8: Mean of the main study variables under no intervention, when first diagnosis of any other OD is the outcome of interest: observed (solid line) and estimated via the parametric g-formula (dotted line), HIV-CAUSAL Collaboration. (a) Cumulative incidence of other ODs; (b) cumulative incidence of death; (c) mean proportion on treatment; (d) mean CD4 count, natural log scale; (e) mean HIV viral load; (f) proportion with Kaposi’s sarcoma in month k; (g) proportion with AIDS-related lymphoma in month k; (h) proportion with tuberculosis in month k.