Supplementary Materials

The simulated data and individual-level simulation model have been previously described (1).

Simulated data generation

Briefly, we created two simulated longitudinal datasets containing three time-varying covariates (treatment, a confounder, and the outcome), and one time-fixed covariate (U) using a structural nested accelerated failure time model. The data were simulated following the algorithm described by Robins (11) and Young et al (12). Briefly, for each of 10^5 simulated individuals:

Step 1: Simulate the counterfactual failure time in the absence of treatment $T_{\bar{0}}$ under an exponential distribution with hazard $\lambda_0(t)$, and set $U = T_{\bar{0}}$. Then for each $k \in [0,12]$ implement steps 2, 3, and 4:

Step 2: Simulate L_k using the probability model:
$$\Pr(L_k = 1 | \bar{A}_{k-1}, U, Y_k = 0) = (1 - \gamma_2) \times \exp[\gamma_1 + \kappa \times \ln(U + \tau)] / [1 + \exp(\gamma_1 + \kappa \times \ln(U + \tau))] + \gamma_2 A_{k-1}$$
, 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:
$\text{logit}\Pr(A_k = 1 | \bar{L}_k, \bar{A}_{k-1}, Y_k = 0) = \alpha_0 + \alpha_1 L_k + \alpha_2 L_{k-1} + \alpha_3 L_{k-2}$. Set A_k=1 if A_{k-1}=1.

Step 4: Generate the failure time as the solution to: $T_{\bar{0}} = \int_0^T \exp[\gamma(t, \bar{A}_t, \bar{L}_t, \psi)]dt$, where $\gamma(t, \bar{A}_k, \bar{L}_k, \psi) = -\psi A_k$. If $T \leq k+1$ 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. ψ is set to 0 for a null treatment effect and to -1 for a protective effect. By definition, everybody has Y_0=0.

Parameter values for the simulation are given in Appendix Table 1.

Appendix Table 1 Input Parameters Used in the Data Simulation

Model	Parameter Value
Exponential Parameter for $T_{\bar{0}}$ ($\lambda_0(t)$):	0.010
Treatment effect parameter Ψ	
No effect (sharp null)	0
Beneficial effect	-1
Conditional probability distribution for L_k	
A_{k-1}	0.675
γ_1	25
κ	-11.2
τ	0.38
Conditional probability distribution for A_k, logistic regression model parameters	
Intercept	0.1
L_k	-0.3
L_{k-1}	-0.25
L_{k-2}	-0.10

Individual-level simulation

The individual-level simulation model estimated the total effect of treatment on the outcome using a series of pooled logistic regression models.

Step 1: Fit the pooled logistic regression models to the simulated data to estimate the parameters $\text{logit}\Pr(L_k = 1|\bar{L}_{k-1}, \bar{A}_{k-1}, Y_k = 0) = \beta_{0,k} + \beta_1 L_{k-1} + \beta_2 L_{k-2} + \beta_3 A_{k-1} + \beta_4 A_{k-2}$, and $\text{logit}\Pr(Y_{k+1} = 1|\bar{L}_k, \bar{A}_k, Y_k = 0) = \theta_{0,t} + \theta_1 L_k + \theta_2 L_{k-1} + \theta_3 A_k + \theta_4 A_{k-1}$, where time is modeled using a spline with knots at 3, 6, 9, and 12 months.

Step 2: For each of 200 individual-level simulation models, replace the estimate of θ_4 with the specified guess for the direct effect of A_{k-1}, in the model for the outcome. The guess ranged, on the odds ratio scale, from 0.005 and 1.0 by increments of 0.005 (-5.30 to 0 on the natural scale).

Step 3: For each of 200 individual-level simulation models, simulate 10^5 individuals for 12 months by:

a. Draw baseline confounder values from the baseline distribution observed in the simulated data.
b. Set treatment to 1 at all time-points for “always treat” and 0 at all time-points for “never treat”

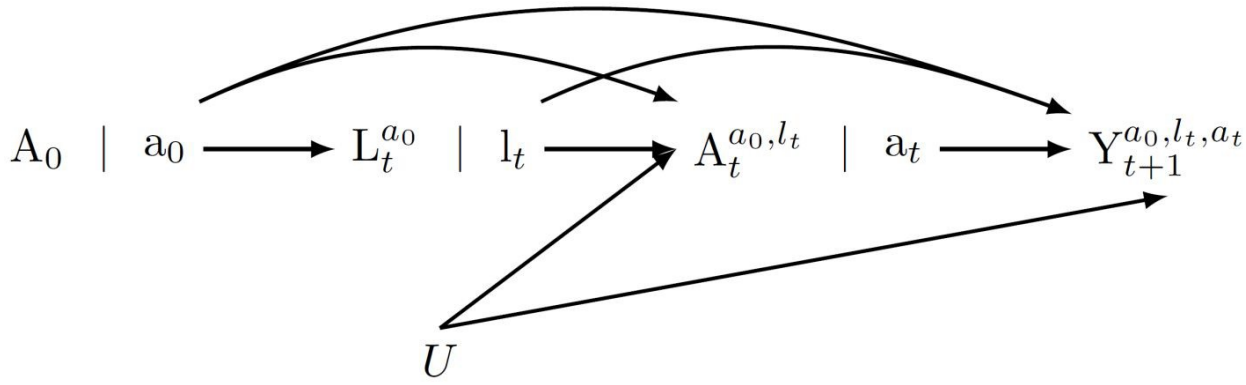
c. At each time point, generate the outcome probability and confounder value using the linear predictors of the regression models from Step 1, with the Step 2 parameter modification, the fixed value of treatment, and the prior simulated confoundervalues.

Step 4: Obtain the estimated 12-month survival probability under each intervention for each individual-level simulation model parameterization from the simulated individuals in Step 3 using the product-limit method, and calculate the estimated risk and risk difference.

Table 1 in the manuscript displays the range of total effect estimates obtained from these runs for each simulated dataset.

Single world intervention graph

Single world intervention graphs (SWIGS) are a tool for depicting the data generating structure, the interventions of interest, and the counterfactual outcomes in a single graphic (13). These graphs have similar rules to directed acyclic graphs, but add split nodes to specify the intervention value of interest and label all variables downstream of interventions with the counterfactual value that can be observed in a world where the intervention is performed. Appendix Figure 1 shows a SWIG that corresponds to an intervention that could allow estimation of the controlled direct effect of treatment when CD4 count is held constant. On this SWIG we can see that the counterfactual of relevance to the controlled direct effect depends on the value of CD4 count selected.



Appendix Figure 1 Single-world intervention graph (SWIG), showing the problem of estimating the direct effect. The controlled direct effect requires setting L_t to a specific value, and as a result all subsequent variables are counterfactual on the intervention value chosen. If an intervention on Lt cannot be specified the counterfactuals required for the controlled direct effect may not be identifiable.