Estimation of the Cumulative Incidence Function Under Multiple Dependent and Independent Censoring Mechanisms, with application to safety and efficacy of HIV treatment

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Background

ART recommended treatment for HIV-positive patients.

Many types of ART.

Goal:

Compare **efficacy** and **safety** of 3-drug versus 4-drug ART in the treatment of HIV-positive patients.

Efficacy: time to virologic failure (VF) while on initial treatment.

Safety: time to discontinuation of initial treatment because of a treatment-limiting adverse event (TLAE).

Competing risks setting

Event type:

- Virologic failure (VF)
- Discontinuation of initial treatment because of a treatment limiting adverse event (TLAE)
- Discontinuation of initial treatment because of clinical events, disallowed medications, pregnancy, or death (TLOE, Treatment Limiting Other Events).

Event time: time until VF, TLAE, or TLOE, whichever comes first.

Estimand: the Cumulative Incidence Function

$$P\left(\text{failure of type } j \text{ before time } t\right).$$

T: failure time. J: failure type.

$$CIF_j(t) = P\left(T \leq t, J = j\right).$$

Cumulative Incidence Function.

From the above:

$$P\left(T \leq t\right) = \sum_j P\left(T \leq t, J = j\right).$$

Counterfactual scenario of interest

Counterfactual scenario of interest:
"Had no one discontinued initial treatment for reasons other than virologic failure (VF), treatment limiting adverse events (TLAE), clinical events mandating treatment discontinuation, disallowed medications, pregnancy, or death (TLOE)."

Reasons:

1. Reasons other than these for treatment discontinuation might be avoided in clinical practice.
2. What would happen if initial treatment is taken as long as feasible?

Counterfactual scenario of interest

Counterfactual scenario of interest:
"Had no one discontinued initial treatment for reasons other than virologic failure (VF), treatment limiting adverse events (TLAE), clinical events mandating treatment discontinuation, disallowed medications, pregnancy, or death (TLOE)."

Censored patients when they were no longer following counterfactual scenario.

$\Rightarrow$

1. Administrative censoring.
2. Discontinuation of initial treatment because of dropout/patient decision.

Estimating the Cumulative Incidence Function without censoring

Possible estimating equations based on the full data are

$$P_n \left(1_{\{T \leq t, J=j\}} - P\left(T \leq t, J = j\right)\right) = 0,$$

where P_n indicates the empirical average over all patients.
Motivation:

$$E \left(1_{\{T \leq t, J=j\}} - P\left(T \leq t, J = j\right)\right) = 0.$$

Fix time t. Define:

$$Q\left(\text{full data}_i\right) = \left(1_{\{T_i \leq t, J=j\}} - P\left(T \leq t, J = j\right)\right).$$

Method: Inverse Probability of Censoring Weighting (IPCW) for competing risks

Common to discretize the data for Inverse Probability of Censoring Weighting (IPCW):

- L_k: covariates and outcomes at period k.
- A: treatment assignment.
- $C_k = 0$ if the patient was uncensored at period k (and $C_k = 1$ otherwise).
- K: last period of interest.

$\Rightarrow$ Full data (with overbars indicating history): $(\overline{L}_{K+1}, A)$.

Method: IPCW for competing risks

Full data (with overbar indicating history): $(\overline{L}_{K+1}, A)$.
Then:

$$E\left(\frac{1_{C_K=0}}{P(C_K=0|\overline{L}_{K+1},A)}Q(\overline{L}_{K+1},A\right)=0.$$

Need:

Assumption: (Positivity). $P\left(C_K=0|\overline{L}_{K+1},A\right)>0$ for all possible values of $(\overline{L}_{K+1},A)$.

No matter what a patient's full data, there is a positive probability of observing his/her full data.

Method: IPCW for competing risks

$$E\left(\frac{1_{C_K=0}}{P(C_K=0|\overline{L}_{K+1},A)}Q(\overline{L}_{K+1},A)\right)=0.$$

Re-write

$$P(C_K=0|\overline{L}_{K+1},A)=\prod_{k=1}^{K}P\left(C_k=0|\overline{L}_{K+1},A,C_{k-1}=0\right).$$

Method: IPCW for competing risks under MAR

Assumption: (Missing At Random (MAR)). See e.g. Robins et al. (1995). For every $k = 2, \ldots, K$, with $Y_k = 1$ if an event took place in period k or earlier and $Y_k = 0$ if not,

$$\bar{L}_{K+1} \perp\!\!\!\perp ADMIN_k | \bar{L}_{k-1}, \bar{Y}_k = 0, A, C_{k-1} = 0,$$

and

$$\bar{L}_{K+1} \perp\!\!\!\perp LTFU_k | \bar{L}_{k-1}, \bar{Y}_k = 0, A, C_{k-1} = 0, ADMIN_k = 0.$$

Here, $\perp\!\!\!\perp$ indicates conditional independence Dawid (1979).

MAR: Censoring depends only on past observed values, and not further on prognosis.

Method: IPCW for competing risks: MAR

Missing At Random: MAR: Censoring only depends on past observed values, and not further on prognosis.

$\overline{L}_k$ needs to include whether an event took place before time k, and its type (for Q known given full data). Then, need enough covariates measured to make MAR plausible.

E.g., if current CD4 count $CD4_k$ predicts both censoring in the subsequent period and future events or their type, need current CD4 count in $\overline{L}_k$.

Method: IPCW for competing risks under MAR

Under MAR:

$$
\begin{aligned}
&P(C_K = 0 | \bar{L}_{K+1}, A) \\
&= \prod_{k=2}^{K} P\left(ADMIN_k = 0 | \bar{L}_{k-1}, Y_k = 0, A, C_{k-1} = 0\right) \\
&\qquad \cdot P\left(LTFU_k = 0 | \bar{L}_{k-1}, Y_k = 0, A, C_{k-1} = 0, ADMIN_k = 0\right).
\end{aligned}
$$

Common interpretation: weight of censored patients gets distributed over "similar" patients in follow-up, with "similar" determined at the last observed clinic visit (Robins et al. (1995), Cole and Hernán (2008)).

Continuous time: MAR

Discretizing the time may lead to some bias, so we also looked at a continuous time scale.

Assumptions: for both censoring types $r = 1, 2$ we assume MAR:

$$\lambda_{C,r}(t|\bar{V}_T, T, J, T > t) = \lambda_{C,r}(t|\bar{V}_t, T > t) \qquad (1)$$

where
$\lambda_{C,r}(t|\bar{V}_T, T, J, T > t) = \lim_{h \downarrow 0} \frac{P(t \leq C < t+h, R=r | C \geq t, \bar{V}_T, T, J, T > t)}{h}$.

In words, we assume that the hazard of censoring at time t for reason r, depends only on the measured variables up to time t and not on any future observed or unobserved variables, failure time, or failure type.

Continuous time: Modeling assumptions

Assumption: Information available until last time point of interest:

$$\lambda_{C,r}(t|\bar{V}_T, T, J, T > t) < \xi \tag{2}$$

with probability 1 for some constant ξ, for t in the interval $[0, \nu)$.

Cox's proportional hazards model for censoring:

$$\lambda_{C,r}(t|\bar{V}_t) = \lambda_{0,r}(t) \exp[\gamma_r' w_r(t, \bar{V}_t)], \tag{3}$$

where $\lambda_{0,r}(t)$ is an unknown, non-negative function of t, $w_r(t, \bar{V}_t)$ is a specified function of t and $\bar{V}_t$, and γ_r is an unknown parameter vector.

Reason: when $\bar{V}_t$ is high dimensional, we cannot estimate $\lambda_{C,r}(t|\bar{V}_t)$ nonparametrically due to the curse of dimensionality.

Continuous time: IPCW weights

Following Rotnitzky et al. (2007), we define the inverse weights $\pi(t|\bar{V}_t; \Lambda_0)$:

$$\begin{aligned}
\pi(t|\bar{V}_t; \Lambda_0) &= \exp\left(-\int_0^t \lambda_C(u|\bar{V}_T, T, J, T > u)du\right) \\
&= \exp\left(-\int_0^t \sum_{r=1}^{r^*} \lambda_{0,r}(u) \exp[\gamma_r' w_r(u, \bar{V}_u)]du\right) \\
&= \prod_{r=1}^{r^*} \prod_{0 \le u \le t} [1 - \exp[\gamma_r' w_r(u, \bar{V}_u)] d\Lambda_{0,r}(u)],
\end{aligned}$$

with the cumulative baseline hazard, $\Lambda_{0,r}(t)$, defined as $\Lambda_{0,r}(t) = \int_0^t \lambda_{0,r}(s)ds$.

Continuous time: IPCW estimator

An estimate of $F_j(t)$: solution to

$$\sum_{i=1}^{n} \frac{\tilde{\Delta}_i}{\pi_i(\tilde{T}_i|\bar{V}_{i,\tilde{T}_i};\Lambda_0)} \{\mathbf{1}(T_i \leq t, J_i = j) - F_j(t)\} = 0 \qquad (4)$$

where $\tilde{T}$ is the minimum time such that $\mathbf{1}(T \leq t, J = j)$ is observed, i.e. $\tilde{T} = \min(T, t)$, and $\tilde{\Delta} = \mathbf{1}(\tilde{T} < C)$.

Shown: (4) is unbiased estimating equation for $F_j(t)$ since under MAR, $\Pr(\tilde{\Delta} = 1|V_{\tilde{T}}) = \pi(\tilde{T}|\bar{V}_{\tilde{T}};\Lambda_0)$.

Without regularity condition (2), we would be dividing by 0; a positivity violation, where some patients have probability 0 of remaining uncensored, and IPCW fails (Robins et al., 1995).

Continuous time: towards Doubly Robust IPCW estimator

Can improve efficiency of previous IPCW estimator by introducing augmentation term (Tsiatis (2006); Rotnitzky et al. (2005)): solve

$$\sum_{i=1}^{n} \left\{ \frac{\tilde{\Delta}_i}{\pi_i(\tilde{T}_i | \bar{V}_{\tilde{T}_i}; \Lambda_0)} \{\mathbf{1}(T_i \leq t, J_i = j) - F_j(t)\} - A_i\{F_j(t), \gamma, b(\cdot)\} \right\} = 0 \tag{5}$$

with augmentation term

$$A\{F_j(t), \gamma, b(\cdot)\} \equiv \sum_{r=1}^{r^*} \int \frac{b(u, \bar{V}_u)}{\pi(u\text{-}|\bar{V}_u; \Lambda_0(u))} dM_{C,r}(u), \tag{6}$$

with $b(u, \bar{V}_u)$ a user specified, left-continuous function of u and $\bar{V}_u$, $\pi\left(u\text{-}|\bar{V}_u; \Lambda_0(u)\right)$ the left-continuous version of π,

$$M_{C,r}(u) = N_{C,r}(u) - \int_0^u 1(X \geq s) \exp\left\{\gamma_r' w_r(s, \bar{V}_s)\right\} d\Lambda_{0,r}(s). \tag{7}$$

(5) is unbiased estimating equation for $F_j(t)$.

Continuous time: Doubly Robust IPCW estimator

For efficiency reasons, we choose

$$b(u, \bar{V}_u) = -\mathbf{E}\left[\left\{\mathbf{1}(T \leq t, J_i = j) - F_j(t)\right\}\middle| \bar{V}_{u-}, T \geq u\right]. \quad (8)$$

If we can consistently estimate $b(u, \bar{V}_u)$ as defined in (8) then we can find an estimate of $F_j(t)$ as the solution to

$$\sum_{i=1}^{n}\left\{\frac{\tilde{\Delta}_i}{\hat{\pi}_i(\tilde{T}_i|\bar{V}_{\tilde{T}_i};\hat{\Lambda}_0)}\{\mathbf{1}(T_i \leq t, J_i = j) - F_j(t)\} - \hat{A}_i(F_j(t), \hat{b}(u, \bar{V}_u), \hat{\gamma})\right\} \quad (9)$$

$$\hat{A}(F_j(t), \hat{b}(u, \bar{V}_u), \hat{\gamma})$$

$$= \sum_{r=1}^{r^*}\int_0^{\tilde{T}} \frac{-\hat{\mathbf{P}}[(T \leq t, J = j)|\bar{V}_{u-}, T \geq u] + F_j(t)}{\hat{\pi}(u-|\bar{V}_u;\hat{\Lambda}_0(u))} d\hat{M}_{C,r}(u),$$

$$\hat{M}_{C,r}(u) = N_{C,r}(u) - \int_0^u \exp\left\{\hat{\gamma}_r' w_r(s, \bar{V}_s)\right\} d\hat{\Lambda}_{0,r}(s).$$

Continuous time: Doubly Robust IPCW estimator

In practice, estimating the conditional expectation $\mathbf{E}[\{\mathbf{1}(T \leq t, J = j) - F_j(t)\}|\bar{V}_{u\text{-}}, T \geq u]$ can be difficult, because $\bar{V}_u$ is time-dependent. To make the problem more tractable, in practice we estimated

$$\mathbf{E}[\{\mathbf{1}(T \leq t, J = j) - F_j(t)\}|\bar{V}_0, T \geq u], \tag{10}$$

where $\bar{V}_0$ are the baseline covariates. One way to estimate (10) is:

$$\hat{\mathbf{P}}[(T \leq t, J = j)|\bar{V}_0, T \geq u] = \frac{\int_u^t \hat{S}(a\text{-}|\bar{V}_0) d\hat{\Lambda}_j(a|\bar{V}_0)}{\hat{S}(u\text{-}|\bar{V}_0)}, \tag{11}$$

with $\hat{\Lambda}_j(a|\bar{V}_0) = \hat{\Lambda}_{0,j}(a) \exp\left\{\hat{\beta}_j' f(\bar{V}_0)\right\}$ and $\hat{\beta}_j'$ the estimated parameter vector from a Cox proportional hazards model.

Continuous time: Doubly Robust IPCW estimator

If we can consistently estimate $b(u, \bar{V}_u)$ as defined in (8), then $\hat{F}_j^A(t)$ would be doubly robust (Rotnitzky et al., 2005).

That is, $\hat{F}_j^A(t)$ is consistent and asymptotically normal if the model for the censoring process, $\pi(t|\bar{V}_t; \Lambda_0)$, is correctly specified or the outcome model, $\mathbf{E}[\mathbf{1}(T \leq t, J = j)|\bar{V}_{u^-}, T \geq u]$ is correctly specified.

Also, if both the model for the censoring process and outcome model are correctly specified then $\hat{F}_j^A(t)$ is locally semi-parametric efficient (Robins and Rotnitzky, 1992; Tsiatis, 2006).

HIV illustration: Data

ACTG 5095 (Gulick et al. (2004, 2006)).

3-drug regimen: zidovudine/lamivudine plus efavirenz.
4-drug regimen: zidovudine/lamivudine/abacavir plus efavirenz.

Double blind RCT, 3-drug versus 4-drug ART for HIV-positive patients.

758 patients, and in first 3 years:
146 VF, 58 TLAE, 26 TLOE, 96 LTFU, 432 ADMIN.

HIV illustration: nuisance paramter models

Model for lost to follow-up (LTFU): literature review of variables that might predict LTFU in HIV-positive patients.

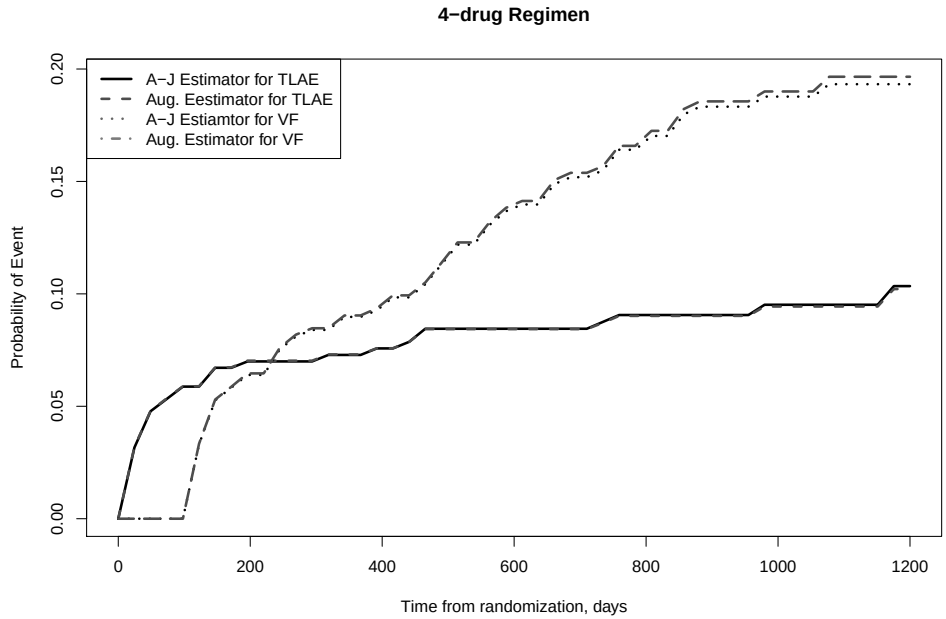
Model for administrative censoring: only needed characteristics whose distribution was different in patients enrolled earlier than in patients enrolled later. Including more variables that may be predictive of the outcome of interest might increase precision (Rotnitzky et al. (2010)).

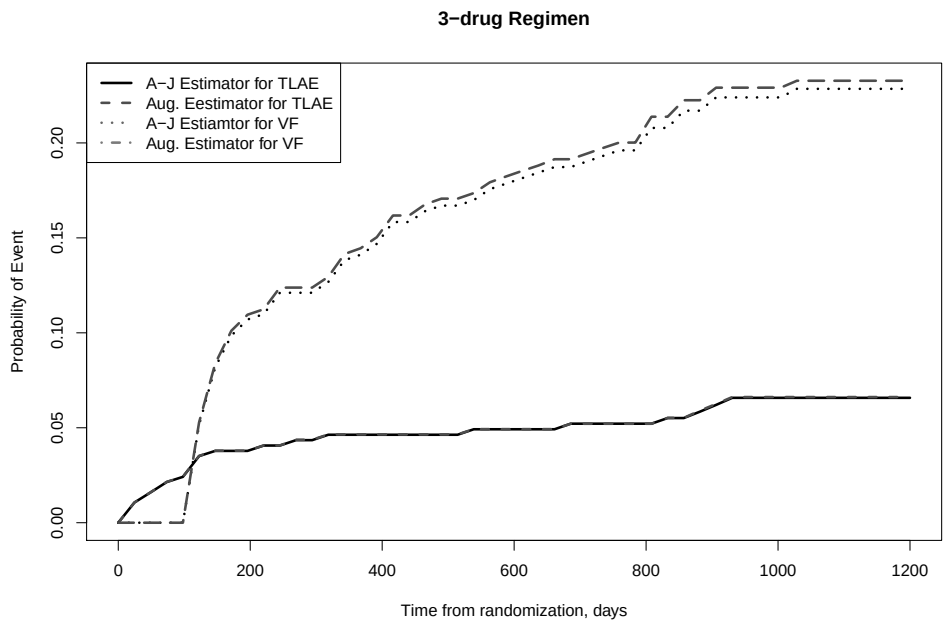
HIV illustration: nuisance paramter models

Included in the IPCW models for LTFU: randomized treatment group, age (indicator for ≤ 30 years old), sex, injection drug use (ever/never), black non-hispanic, hispanic, baseline $\log_{10}$ viral load, time-dependent indicator of CD4 count ≤ 200, and period variables: "period 3", "period 4", "period 5-8", "period 9-13", and "period 14-18", with period 2 representing the reference group for these variables (in period 1, only one patient had no visit after baseline and thus was LTFU, and we modeled that separately without including covariates).

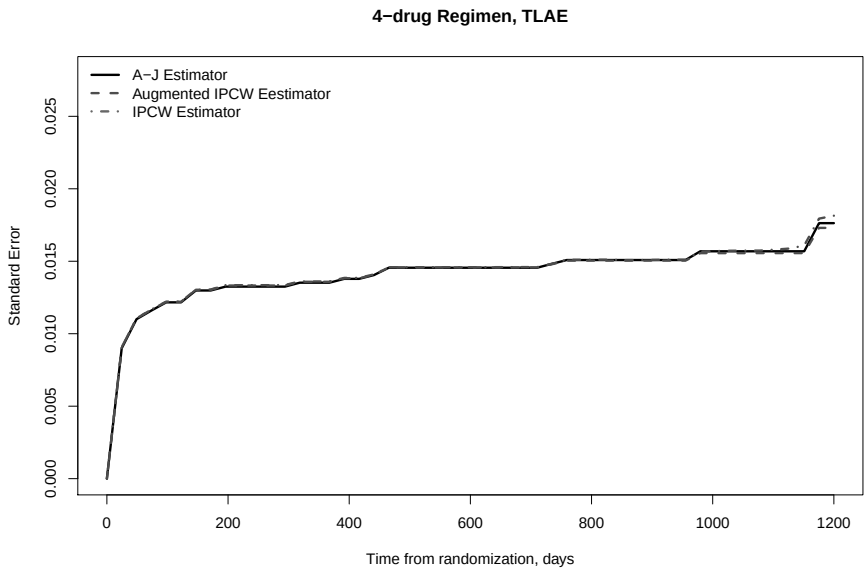
Included in the IPCW models for ADMIN: same, but with period variables indicator variables were included for "period 17" and "period 18". First periods: virtually no administrative censoring, and we only included period as a categorical variable; this effectively reduces to Efron's redistribute-to-the-right algorithm (Efron (1967)).

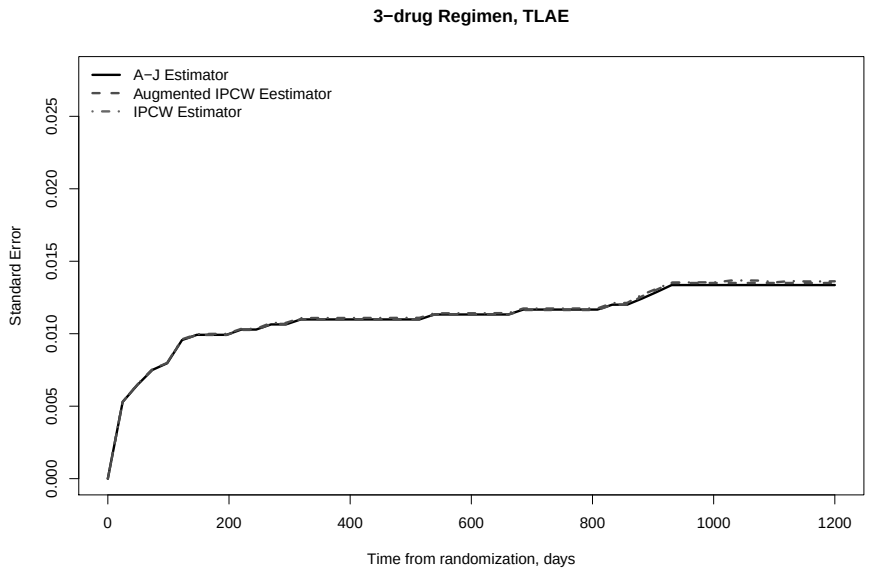
Cumulative Incidence Curves, by regimen

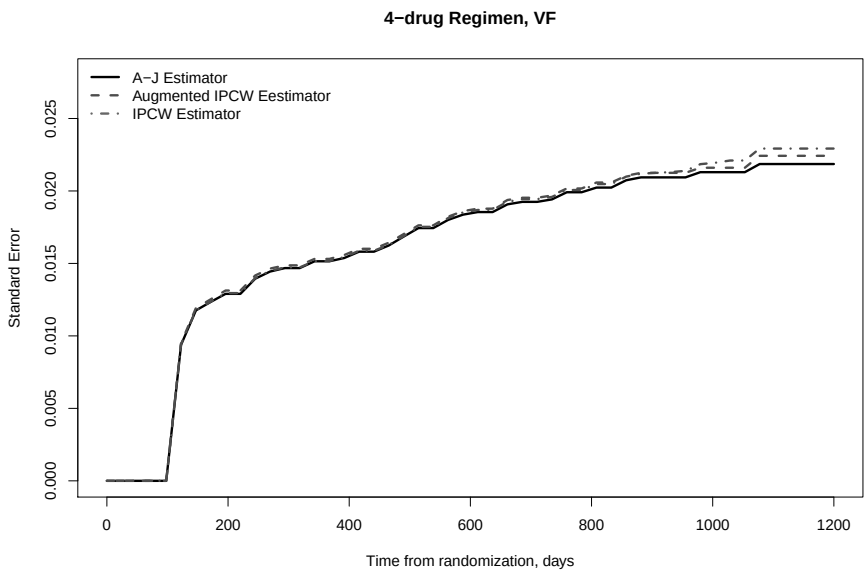


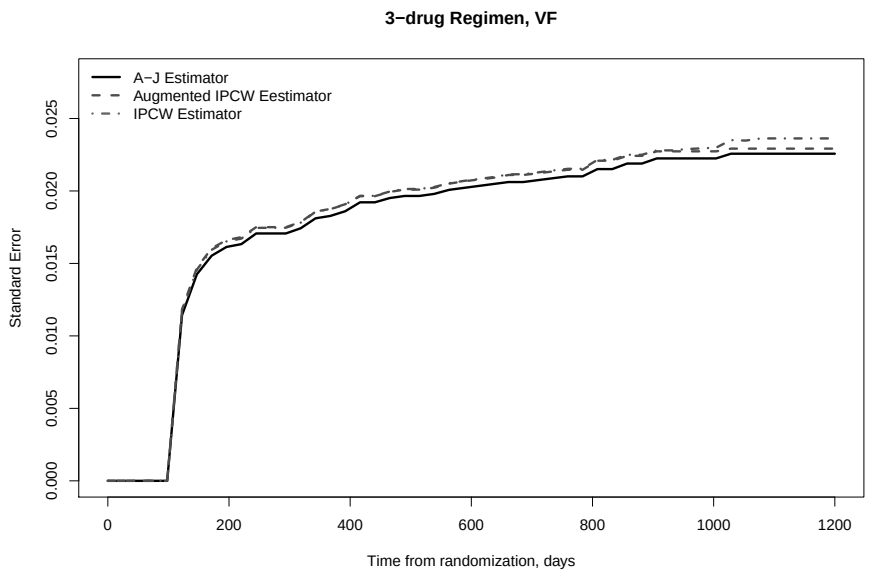


Standard Errors, by regimen and failure type (bootstrap)









HIV illustration: Results

We compared our augmented and non-augmented IPCW estimators with the standard estimate of the cumulative incidence function (Andersen et al., 1993) which assumes independent censoring, the Aalen-Johansen estimator.

We conclude that IPCW and augmented IPCW doesn't substantially decrease the precision compared to an unweighted analysis.

Useful since IPCW and augmented IPCW more robust to informative censoring.

We also predicted the CIF based on baseline covariates

For this, we discretized the time. We fit the following prediction model for the CIFs (τ fixed here):

$$P\left(\text{failure of type } j \text{ before time } \tau | X = x\right) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}.$$

T: failure time. J: failure type. X: baseline covariates.

$$P\left(T \leq \tau, J = j | X = x\right) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}.$$

Type-specific logistic regression model. Results:

Table 3: Multivariate analysis. Estimated odds ratios for events within 144 weeks of starting treatment (95%-confidence intervals).

Baseline covariate	VF[2]	TLAE[3]	events (VF[2]/TLAE[3]/TLOE[4])
ART: 4 drugs (vs 3 drugs)	0.94 (0.62,1.43), p=0.78	1.59 (0.88,3.05), p=0.12	1.07 (0.75,1.54), p=0.70
age (per 10 years older)	0.93 (0.74,1.16), p=0.53	1.36 (0.99,1.87), p=0.05	1.14 (0.95,1.39), p=0.16
black non-Hispanic[1]	2.11 (1.43,3.19), p<0.001	0.85 (0.43,1.49), p=0.56	1.55 (1.10,2.20), p=0.01
viral load (per $\log_{10}$ copies/ml higher)	1.29 (0.99,1.73), p=0.06	1.03 (0.70,1.52), p=0.89	1.17 (0.93,1.48), p=0.18
injection drug use: ever (vs never)	3.75 (1.64,9.44), p=0.003	1.64 (0.000,5.05)[5], p=0.55	3.53 (1.60,9.99), p=0.003
ART*injection drug use	0.32 (0.07,1.09), p=0.07	0.25 (0.000,7×10^5)[5], p=0.21	0.27 (0.06,0.87), p=0.03

[1] versus white non-Hispanic/other/Hispanic. [2] Virologic Failure. [3] Treatment Limiting Adverse Event. [4] Treatment Limiting Other Event. [5] Confidence interval may be unreliable because of small number of events (see text). Number of bootstrap samples: 20000.

We also predicted the CIF based on baseline covariates

In the multivariate model for VF, the interaction of injection drug use and randomized treatment suggests:

Among patients who never injected drugs, adding a fourth drug to the antiviral regimen has little impact on the odds of VF ($OR = 0.94$, $p = 0.78$).

Among patients who reported ever injecting drugs, adding a fourth drug to the ART regimen significantly decreases the odds of VF ($OR = 0.29$, $p = 0.03$) (and the odds of the composite outcome, $OR = 0.29$, $p = 0.03$).

Summary

- Counterfactual scenario where no one discontinues treatment for reasons other than VF, TLAEs, or TLOEs (clinical events, disallowed medications, pregnancy, or death): when deciding between different treatment regimens, if initial treatment will be taken as long as it works.
- $\Rightarrow$ Censored patients when they were no longer following counterfactual scenario.
- $\Rightarrow$ Informative censoring.
- $\Rightarrow$ Inverse Probability of Censoring Weighting (IPCW), adapted to the competing risk setting.
- $\Rightarrow$ Derived Doubly-Robust estimators.

Future directions

- Consider testing whether the two cumulative incidence functions for VFs and TLAEs are the same in both treatment groups, in the presence of TLOEs, using a 2-dimensional version of Gray's test (Gray (1988)) taking dependencies into account.
  ((I have shown: if the cause specific hazard for TLOEs is the same in both treatment groups, the null hypothesis of no difference in the cumulative incidence functions for VFs and TLAEs is equivalent to the null hypothesis of no difference in any of the cumulative incidence functions, provided the sum of the cause specific hazard functions for VFs and TLAEs is a piecewise analytic function (for both treatment groups))).

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Andersen, P. K., Ø. Borgan, R. D. Gill, and N. Keiding (1993). *Statistical models based on counting processes*. Springer series in statistics. New York: Springer–Verlag.

Cole, S. R. and M. A. Hernán (2008). Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology 186*(6), 656–664.

Dawid, A. P. (1979). Conditional independence in statistical theory (with discussion). *Journal of the Royal Statistical Society B 41*, 1–31.

Efron, B. (1967). The two sample problem with censored data. In *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*, Volume 4, pp. 831–853. New York: Prentice Hall.

Gray, R. J. (1988). A class of k-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics 16*, 1141–1154.

Gulick, R., H. Ribaudo, C. Shikuma, C. Lalama, B. Schackman, W. M. III, E. Acosta, J. Schouten, K. Squires, C. Pilcher, R. L. Murphy, S. L. Koletar, M. Carlson, R. C. Reichman, B. Bastow, K. L. Klingman, D. R. Kuritzkes, and for the AIDS Clinical Trials Group (ACTG) A5095 Study Team (2006). Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection. *Journal of the American Medical Association 296*(7), 769–781.

Gulick, R., H. Ribaudo, C. Shikuma, S. Lustgarten, K. Squires, W. M. III, E. Acosta, B. Schackman, C. Pilcher, R. Murphy, W. E. Maher, M. D. Witt, R. C. Reichman, S. Snyder, K. L. Klingman, D. R. Kuritzkes, and for the AIDS Clinical Trials Group Study A5095 Team (2004). Triple-nucleoside regimens versus Efavirenz-containing regimens for the initial treatment of HIV-1 infection. *New England Journal of Medicine 350*, 1850–1861.

Lok, J. J. and M. D. Hughes (2016). Evaluating predictors of competing risk outcomes when censoring depends on time-dependent covariates, with application to safety and efficacy of HIV treatment. *Statistics in Medicine 35*(13), 2183–2194.

Lok, J. J., S. Yang, B. Sharkey, and M. D. Hughes (2017). Estimation of the cumulative incidence function under multiple dependent and independent censoring mechanisms. *Lifetime Data Analysis*, 1–23.

Robins, J. M. and A. Rotnitzky (1992). Recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS epidemiology*, pp. 297–331. Springer.

Robins, J. M., A. Rotnitzky, and L. P. Zhao (1995). Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *Journal of the American Statistical Association 90*(429), 106–121.

Rotnitzky, A., A. Farall, A. Bergesio, and D. Scharfstein (2007). Analysis of failure time data under competing censoring mechanisms. *Journal of the Royal Statistical Society, Series B 69*, 307–327.

Rotnitzky, A., L. Li, and X. Li (2010). A note on overadjustment in inverse probability weighted estimation. *Biometrika 97*(4), 997–1001.

Rotnitzky, A., J. Robins, P. Armitage, and T. Colton (2005). Encyclopedia of biostatistics. *Inverse probability weighted estimation in survival analysis. Wiley, New York*.

Tsiatis, A. A. (2006). *Semiparametric theory and missing data*. New York: Springer.

In many cases, analysts assume that administrative censoring, or equivalently date of randomization in the study, is independent of $(\bar{L}_K, Y_{K+1}, Y_{K+1}J, \overline{LTFU}_K)$. In that case, no covariates are needed in the model for administrative censoring, because

$$\begin{aligned} & P\left(ADMIN_k = 0 | \bar{L}_{k-1}, \bar{Y}_k, C_{k-1} = 0\right) \\ = & \frac{P\left(ADMIN_k = 0 \text{ and } LTFU_{k-1} = 0 | \bar{L}_{k-1}, \bar{Y}_k\right)}{P\left(ADMIN_{k-1} = 0 \text{ and } LTFU_{k-1} = 0 | \bar{L}_{k-1}, \bar{Y}_k\right)} \\ = & \frac{P\left(ADMIN_k = 0 | LTFU_{k-1} = 0, \bar{L}_{k-1}, \bar{Y}_k\right)}{P\left(ADMIN_{k-1} = 0 | LTFU_{k-1} = 0, \bar{L}_{k-1}, \bar{Y}_k\right)} \\ = & \frac{P\left(ADMIN_k = 0\right)}{P\left(ADMIN_{k-1} = 0\right)}, \end{aligned} \tag{12}$$

independent of $(\bar{L}_{k-1}, \bar{Y}_k)$. One may however want to include some covariates in the prediction model for ADMIN to increase precision (Rotnitzky et al. (2010)).

In our application, it is possible that simplification (12) does not necessarily hold.

It is possible that patients with characteristics which suggest that they might be harder to follow, may be under-represented in the patient population enrolling early, if clinical sites target enrollment first on patients who might be easier to follow.

May still assume: administrative censoring, or, equivalently, date of randomization in the study, depends on some selection of baseline covariates but not further on the prognosis of patients under the scenario of interest, or on their LTFU pattern:

$$\left(\bar{L}_K, \bar{Y}_{K+1}, Y_{K+1}J, \overline{LTFU}_{k-1}\right) \perp\!\!\!\perp \overline{ADMIN}_k | V, \qquad (13)$$

where V is a subset of the baseline covariates thought to predict date of enrollment.

Under equation (13), since V is part of L_0,

$$\overline{ADMIN}_k|V, \overline{LTFU}_{k-1} \sim \overline{ADMIN}_k|V, \bar{L}_K, \bar{Y}_{K+1}, Y_{K+1}J, \overline{LTFU}_{k-1},$$

where $\sim$ indicates that the left hand side has the same distribution as the right hand side, so that we have the following simplification:

$$\begin{aligned} & P\left(ADMIN_k = 0|\bar{L}_{k-1}, \bar{Y}_k, C_{k-1} = 0\right) \\ = \quad & P\left(ADMIN_k = 0|V, C_{k-1} = 0\right). \end{aligned}$$

$\Rightarrow$ only covariates that potentially predict randomization date need to be included in the model for administrative censoring.

Stabilized weights

Why not stabilize weights?

1. Can only stabilize for variables included in the prediction model, not for the unconditional CIFs.
2. Would need to go on stabilizing after an event took place, instead of carrying the weight forward. Would be different if focus was on the cause specific hazard instead of the cumulative incidence functions.