Impact of Tracing on LTFU HIV Patients – Final Report

David Chen & Max Murphy

12/12/2019

Group Introduction

- David Chen
  - Masters of Biostatistics interested in approaches to optimal dynamic treatment and applications in mental health
- Max Murphy
  - PhD. Biostatistics working on malaria transmission dynamics jointly with Dr. Rasmus Nielsen at UCB and Dr. Bryan Greenhouse at UCSF

Study Background

- A 2015-2017 study was conducted in Zambia to improve estimates of baseline mortality due to HIV
- A subset of individuals who were lost to follow up were randomized to receive extra care through follow up outreach by community health workers
- What are the impacts of this type of intervention
  - Returning people to care?
  - Retention in care over time?

Target Population

Pop 1

Zambian, HIV positive adult patients on ART who are lost to follow-up ($\geq$ 90 days late for their last appointment or $\geq$ 180 days without clinic visit for patients with no future appointment scheduled at their last visit).

Pop 2

The subset of patients satisfying the above criteria who have also returned to care in the study period.

Data 1

$O = (W, A, \tilde{T}, \Delta)$, where $\tilde{T} = \min(T, C)$ and $\Delta = \mathbb{I}(T \leq C)$

- $W =$ province, facility type, facility size, medication possession ratio (MPR, imputed), MPR Imputation Indicator, time on ART, number of prior lost events
- $A =$ Assignment to tracing as defined as in-depth review of paper and EMRs, phone calls, in-person tracing in community (using bicycles, public transport, study vehicles, or motorcycles) by peer health workers at least 3 times.
- $T =$ Time from loss to return (first post-LTFU clinic visit)
- $C =$ Time from loss to end of study

Data 2

Data $O = (W, A, \tilde{T}, \Delta)$, where $\tilde{T} = \min(T, C)$ and $\Delta = \mathbb{I}(T \leq C)$

- $W =$ same as above
- $A =$ same as above
- $T =$ Time from return to 2nd LTFU (as defined on Slide 4)
- $C =$ Time from return to end of study

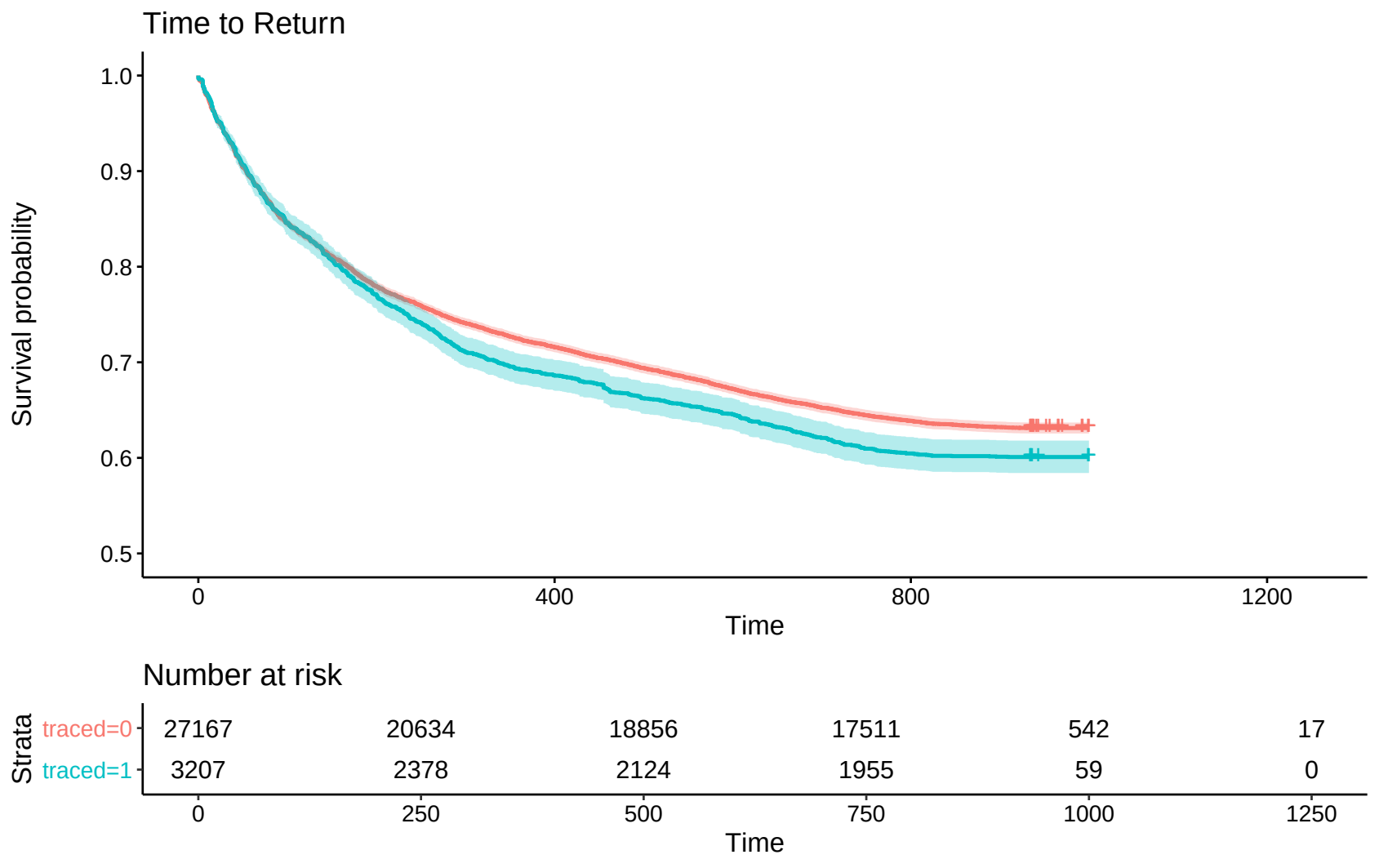
Characteristics

	Censored (n=18474)	Returned (n=11299)	Overall (n=29773)
Age			
Mean (SD)	38.2 (10.4)	38.4 (10.0)	38.3 (10.2)
Median [Min, Max]	37.0 [15.1, 84.6]	37.3 [16.1, 82.2]	37.1 [15.1, 84.6]
Province			
Eastern	2082 (11.3%)	1694 (15.0%)	3776 (12.7%)
Southern	1990 (10.8%)	1013 (9.0%)	3003 (10.1%)
Lusaka	11701 (63.3%)	6895 (61.0%)	18596 (62.5%)
Western	2701 (14.6%)	1697 (15.0%)	4398 (14.8%)
Facility Type			
hospital	5183 (28.1%)	2653 (23.5%)	7836 (26.3%)
rural	1467 (7.9%)	2017 (17.9%)	3484 (11.7%)
urban	11824 (64.0%)	6629 (58.7%)	18453 (62.0%)
Education Level			
none	1277 (6.9%)	957 (8.5%)	2234 (7.5%)
1-6	4030 (21.8%)	2684 (23.8%)	6714 (22.6%)
7-12	12214 (66.1%)	7132 (63.1%)	19346 (65.0%)
college/univ	953 (5.2%)	526 (4.7%)	1479 (5.0%)
HIV Stage at Enrollment			
1	7962 (43.1%)	5430 (48.1%)	13392 (45.0%)
2	3548 (19.2%)	2426 (21.5%)	5974 (20.1%)
3	6214 (33.6%)	3111 (27.5%)	9325 (31.3%)
4	750 (4.1%)	332 (2.9%)	1082 (3.6%)
Household Income			
<50K	2772 (15.0%)	2188 (19.4%)	4960 (16.7%)
50-99K	1438 (7.8%)	942 (8.3%)	2380 (8.0%)
100-199K	2271 (12.3%)	1429 (12.6%)	3700 (12.4%)
200-499K	5008 (27.1%)	2987 (26.4%)	7995 (26.9%)
>500K	6985 (37.8%)	3753 (33.2%)	10738 (36.1%)
Sex			
Female	10804 (58.5%)	7237 (64.0%)	18041 (60.6%)
Male	7670 (41.5%)	4062 (36.0%)	11732 (39.4%)
Traced Status			
Untraced	16606 (89.9%)	10019 (88.7%)	26625 (89.4%)
Traced	1868 (10.1%)	1280 (11.3%)	3148 (10.6%)

Time to Return Characteristics

	Untraced (n=26625)	Traced (n=3148)	Overall (n=29773)
Age			
Mean (SD)	38.2 (10.2)	38.7 (10.5)	38.3 (10.2)
Median [Min, Max]	37.1 [15.1, 84.4]	37.5 [18.1, 84.6]	37.1 [15.1, 84.6]
Province			
Eastern	3211 (12.1%)	565 (17.9%)	3776 (12.7%)
Southern	2438 (9.2%)	565 (17.9%)	3003 (10.1%)
Lusaka	17187 (64.6%)	1409 (44.8%)	18596 (62.5%)
Western	3789 (14.2%)	609 (19.3%)	4398 (14.8%)
Facility Type			
hospital	6992 (26.3%)	844 (26.8%)	7836 (26.3%)
rural	2753 (10.3%)	731 (23.2%)	3484 (11.7%)
urban	16880 (63.4%)	1573 (50.0%)	18453 (62.0%)
Education Level			
none	1947 (7.3%)	287 (9.1%)	2234 (7.5%)
1-6	5943 (22.3%)	771 (24.5%)	6714 (22.6%)
7-12	17410 (65.4%)	1936 (61.5%)	19346 (65.0%)
college/univ	1325 (5.0%)	154 (4.9%)	1479 (5.0%)
HIV Stage at Enrollment			
1	11979 (45.0%)	1413 (44.9%)	13392 (45.0%)
2	5234 (19.7%)	740 (23.5%)	5974 (20.1%)
3	8460 (31.8%)	865 (27.5%)	9325 (31.3%)
4	952 (3.6%)	130 (4.1%)	1082 (3.6%)
Household Income			
<50K	4370 (16.4%)	590 (18.7%)	4960 (16.7%)
50-99K	2074 (7.8%)	306 (9.7%)	2380 (8.0%)
100-199K	3239 (12.2%)	461 (14.6%)	3700 (12.4%)
200-499K	7129 (26.8%)	866 (27.5%)	7995 (26.9%)
>500K	9813 (36.9%)	925 (29.4%)	10738 (36.1%)
Sex			
Female	16157 (60.7%)	1884 (59.8%)	18041 (60.6%)
Male	10468 (39.3%)	1264 (40.2%)	11732 (39.4%)

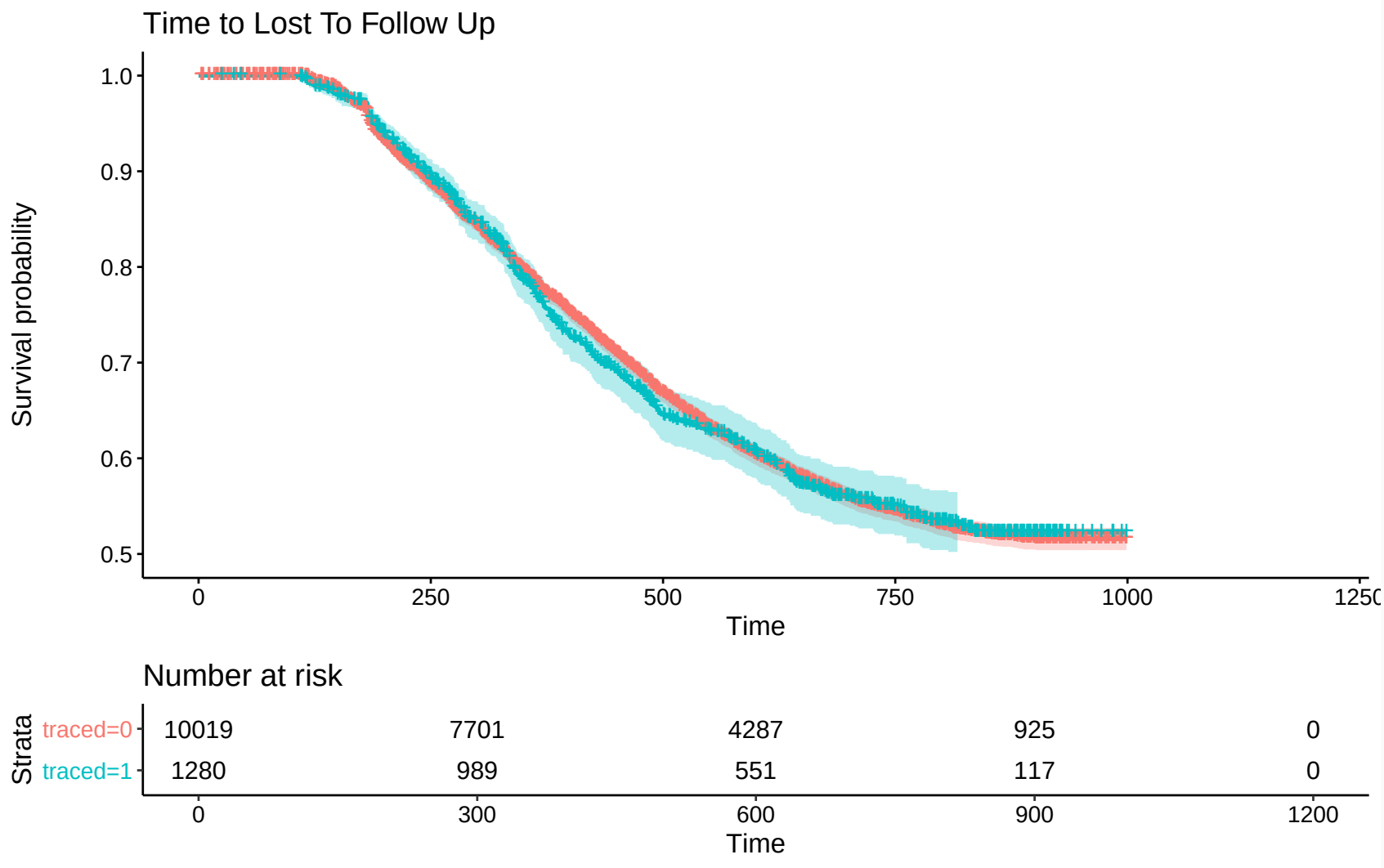
Time to Return Kaplan Meier



Time to ReLoss Characteristics

	Censored (n=6823)	Re-LTFU (n=4476)	Overall (n=11299)
Age			
Mean (SD)	38.3 (10.1)	38.4 (9.84)	38.4 (10.0)
Median [Min, Max]	37.2 [16.1, 81.8]	37.4 [18.4, 82.2]	37.3 [16.1, 82.2]
Province			
Eastern	976 (14.3%)	718 (16.0%)	1694 (15.0%)
Southern	603 (8.8%)	410 (9.2%)	1013 (9.0%)
Lusaka	4191 (61.4%)	2704 (60.4%)	6895 (61.0%)
Western	1053 (15.4%)	644 (14.4%)	1697 (15.0%)
Facility Type			
hospital	1665 (24.4%)	988 (22.1%)	2653 (23.5%)
rural	1190 (17.4%)	827 (18.5%)	2017 (17.9%)
urban	3968 (58.2%)	2661 (59.5%)	6629 (58.7%)
Education Level			
none	555 (8.1%)	402 (9.0%)	957 (8.5%)
1-6	1624 (23.8%)	1060 (23.7%)	2684 (23.8%)
7-12	4340 (63.6%)	2792 (62.4%)	7132 (63.1%)
college/univ	304 (4.5%)	222 (5.0%)	526 (4.7%)
HIV Stage at Enrollment			
1	3353 (49.1%)	2077 (46.4%)	5430 (48.1%)
2	1485 (21.8%)	941 (21.0%)	2426 (21.5%)
3	1794 (26.3%)	1317 (29.4%)	3111 (27.5%)
4	191 (2.8%)	141 (3.2%)	332 (2.9%)
Household Income			
<50K	1324 (19.4%)	864 (19.3%)	2188 (19.4%)
50-99K	559 (8.2%)	383 (8.6%)	942 (8.3%)
100-199K	856 (12.5%)	573 (12.8%)	1429 (12.6%)
200-499K	1814 (26.6%)	1173 (26.2%)	2987 (26.4%)
>500K	2270 (33.3%)	1483 (33.1%)	3753 (33.2%)
Sex			
Female	4295 (62.9%)	2942 (65.7%)	7237 (64.0%)
Male	2528 (37.1%)	1534 (34.3%)	4062 (36.0%)
Traced Status			
Untraced	6049 (88.7%)	3970 (88.7%)	10019 (88.7%)
Traced	774 (11.3%)	506 (11.3%)	1280 (11.3%)

Time to ReLoss Kaplan Meier



Target Parameter

- The treatment specific survival curve, where $d(W)$ is a rule of interest.
- Our intervention $d(W)$ is actually a single time point static intervention - fixed to 1 or 0, reflecting the treatment specific survival curve of everyone receiving treatment vs. no one receiving treatment.
- Interested in comparing the impact of tracing assignment on
  - (1) time to return to care
  - (2) duration of retention in care (assuming tracing has no effect on return to care)

Target Parameter

$$\Psi(P_0) = \mathbb{E}_{P_0}[S_0(t_0|A = a, W)]\,,\ a \in \{0, 1\}$$
$$S_0(t_0|A, W) = \prod_{t \in [0, t_0]} (1 - \Lambda_0(dt|A, W))$$

Thus our target parameter of interest only depends on Q_W and λ.

- Plug-in Estimation

$$\Psi(Q_{W,n}, \lambda_n^*) = \frac{1}{n} \sum_{i=1}^{n} S_{\lambda_n^*}(t_0|A = a, W)\,,\ a \in \{0, 1\}$$

Loss Function

- Log-likelihood loss
  - Event (Return / Reloss) Hazard

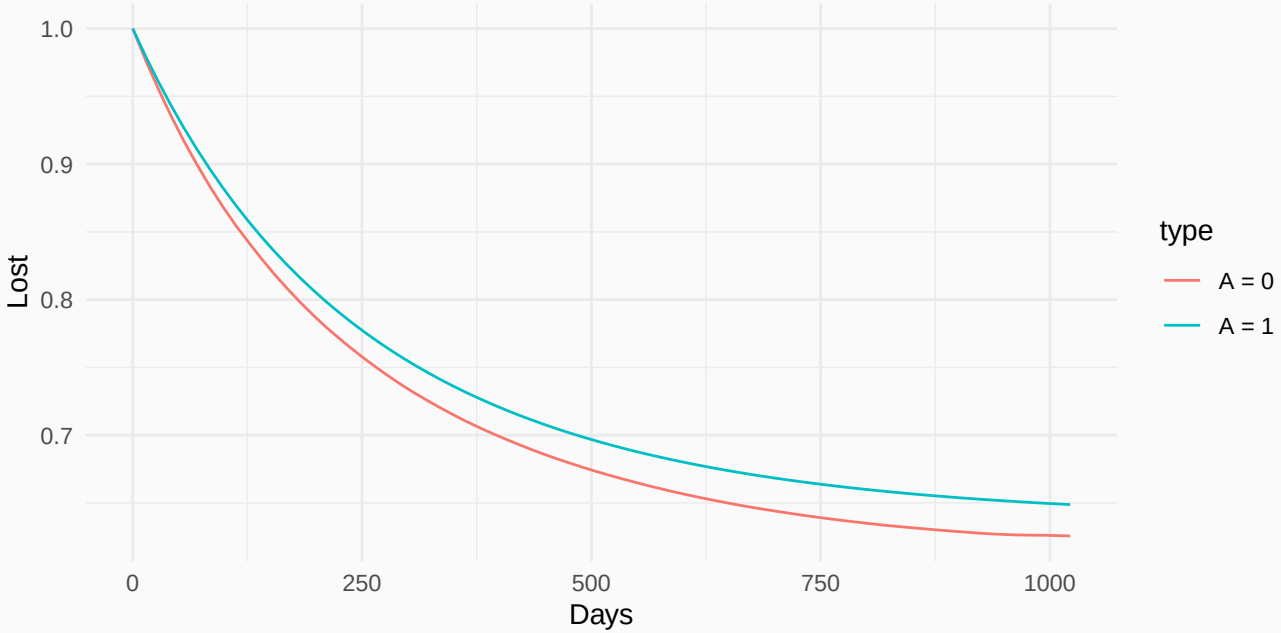
$$L(\lambda)(O) = -\left\{ \prod_{t \leq \tilde{T}} \lambda(t \mid A, W)^{dN(t)} (1 - \lambda(t \mid A, W))^{1 - dN(t)} \right\}$$

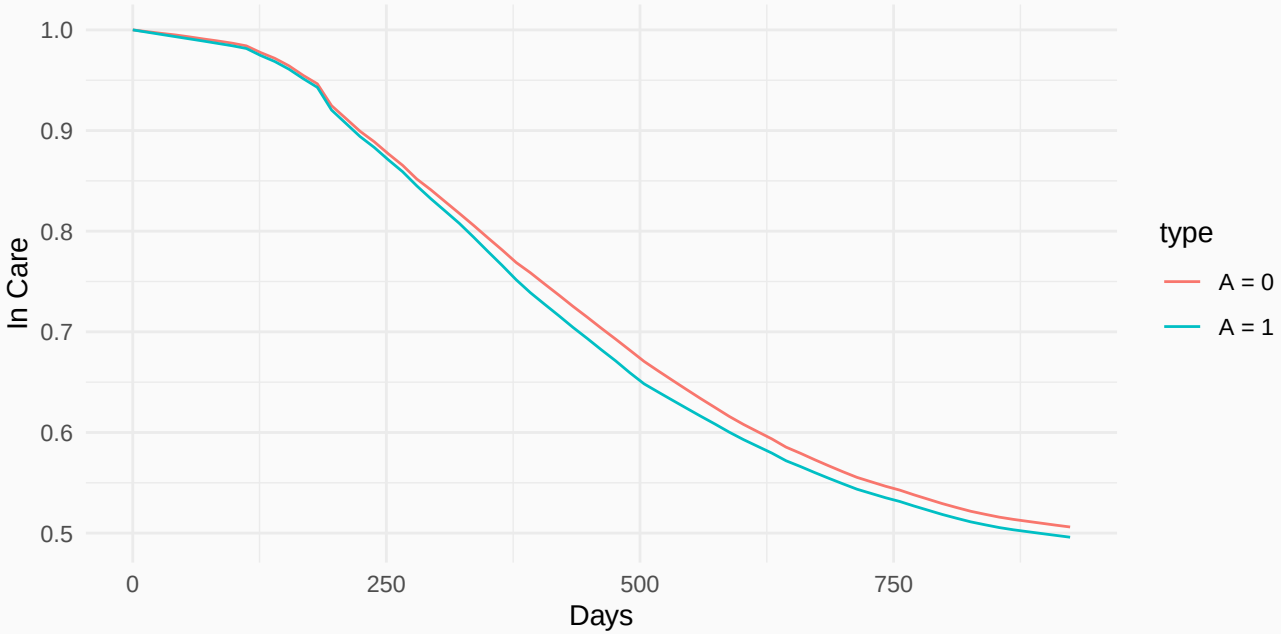
  - Censoring Hazard

$$L(\lambda_c)(O) = -\left\{ \prod_{t \leq \tilde{T}} \lambda_c(t \mid A, W)^{dA_c(t)} (1 - \lambda_c(t \mid A, W))^{1 - dA_c(t)} \right\}$$

- Candidate Estimators
  - mean, glm, bayes glm*, xgboost*, stepwise forward regression

Initial SL Estimates





TMLE Update

Efficient Influence Curve

$$D^*(P)(O) = D_0^*(Q) + \sum_{t=1}^{\tau} D_t^*(Q, G)$$

$$D_t^*(Q, G) = C_t(Q, G)\, I(\tilde{T} \geq t)(dN(t) - \lambda(t \mid A, W))$$

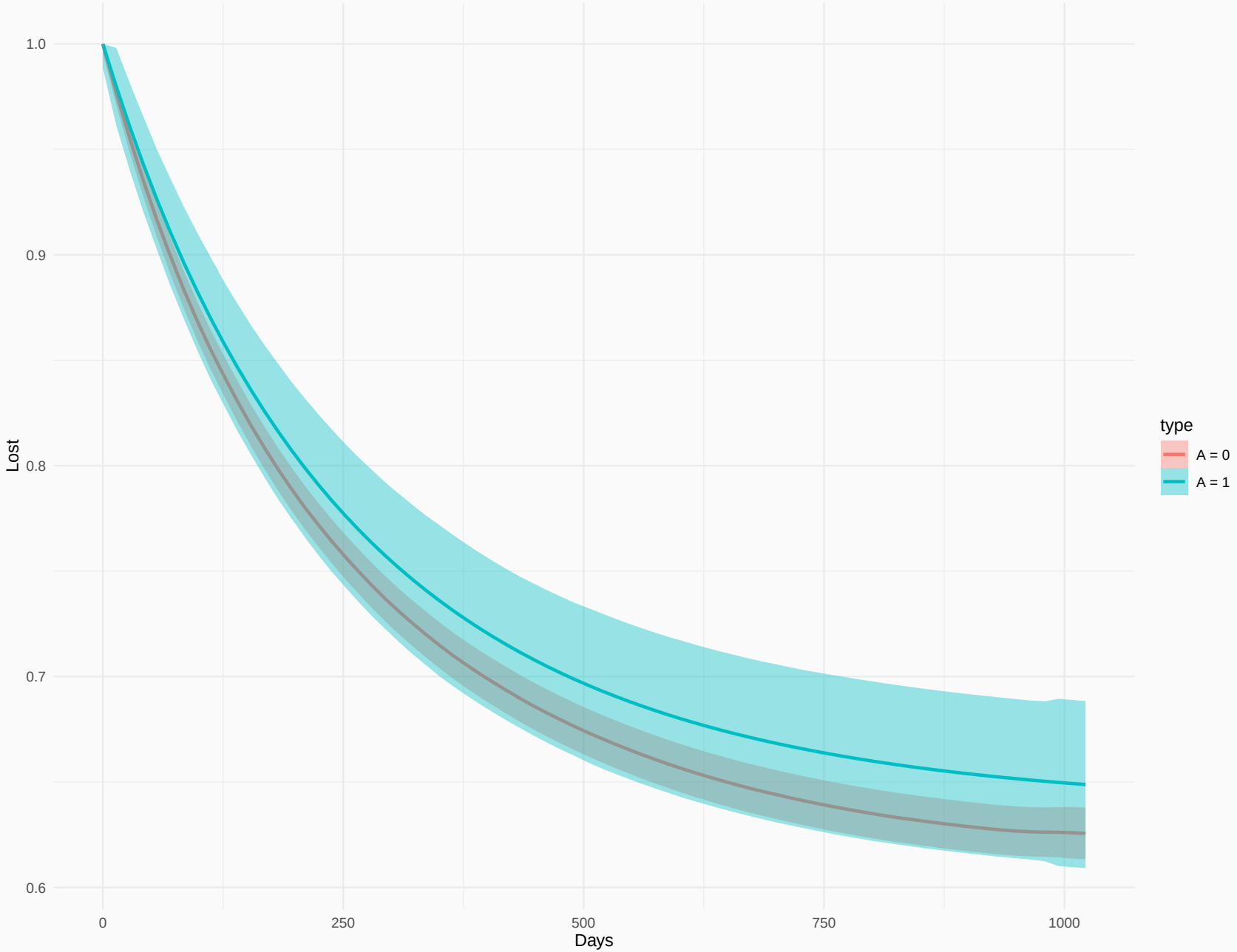
Clever Covariate

$$C_t(Q, G) = \frac{I(A = a, \bar{A}_c(t-1) = 0)}{g(a \mid W) \prod\limits_{s \leq t-1} (1 - \lambda_c(s \mid A, W))} \frac{S(t_0 \mid A, W)}{S(t \mid A, W)}\,,\ t \leq t_0$$

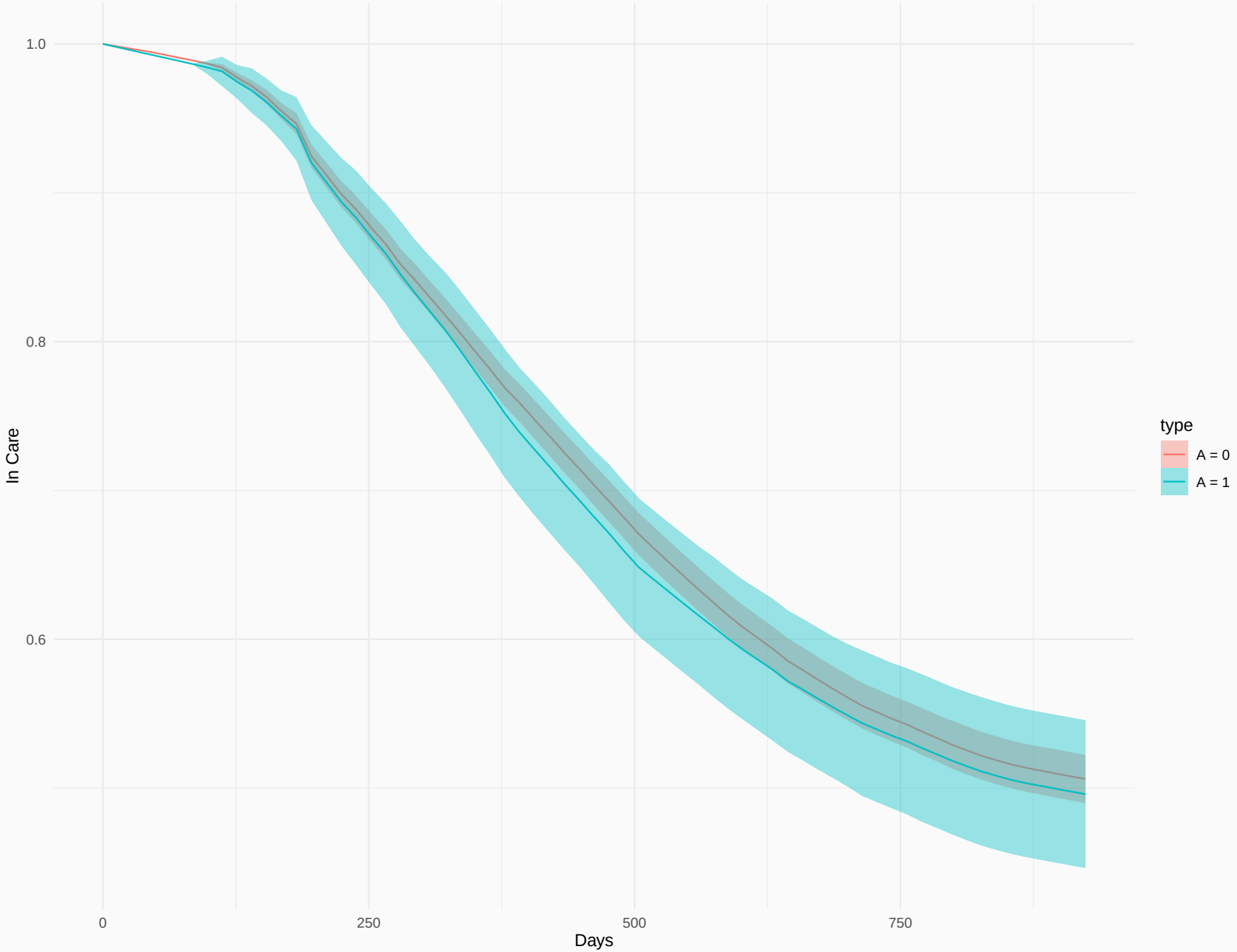
Least Favorable Submodel with Log-Likelihood Loss

$$\operatorname{logit} \lambda_{n,\epsilon}(t \mid A, W) = \operatorname{logit} \lambda_n(t \mid A, W) + \epsilon\, C_t(Q_n, G_n)$$

Time to Return – MOSS Estimate



Lost To Follow Up – MOSS Estimate



Results

- We find no significant effect of follow up tracing assignment on return to care in this population
- We also find no significant effect of follow up tracing assignment on remaining in care amongst those that do return to care at some point during the study

Limitations

- The primary purpose of the tracing intervention was information gathering rather than behavioral change
- Our adjustment set has been heavily reduced due to computational burden
- To interpret our second question causally, we require treatment to be independent of return

Conclusion

- Thanks to Wilson Cai for MOSS, Mark and Rachel for facilitating this course, and Elvin Geng et. al. for our data.
- Questions?