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The effect of antiretroviral therapy on all-cause mortality in the CNICS, generalized to persons diagnosed with HIV in the United States, 2009-2011

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Introduction

The effect of antiretroviral therapy (ART) on survival among recently HIV-diagnosed persons in the United States is unknown because published estimates of the effect of ART[1-3] have been based on cohorts that are not representative of this target population.[4-6]

Study Sample

HIV-infected patients ≥18 years of age who attended at least 2 clinic visits at one of eight Center for AIDS Research Network of Integrated Clinical Systems (CNICS) sites between 1 January 1998 and 30 December 2011.

Target population

Persons diagnosed with HIV infection in the United States (US) from 2009 to 2011.

Statistical Analysis

- Patients followed from enrollment (2nd clinic visit) to death from any cause, administrative censoring at 5 years or end of follow up (12/31/2011).
- ART initiation defined by prescription of 3+ drugs for at least 30 days.
- 5-year risk of all-cause mortality calculated from adjusted Kaplan-Meier survival curves.[7] Standard error for risk, risk differences, and risk ratios estimated from 200 nonparametric bootstrap resamples.[8] Hazard ratios obtained from a Cox regression model[9] using Efron's approximation for tied death times[10] and robust standard error.[11]
- Inverse probability of exposure[12] and censoring weights[13] used to control for confounding and possibly informative censoring.
- Inverse probability of sampling weights (IPSW)[5] used to standardize effect estimates to the target population.

Inset: IPSW

$$w_i^S = \begin{cases} \dfrac{P(S_i = 1)}{P(S_i = 1 | V = v_i)}, & S_i = 1 \\ 0, & S_i = 0 \end{cases}$$

Where:
S is an indicator of inclusion in the CNICS cohort
V is the vector of time-fixed covariates measured at baseline. V should include all covariates that:

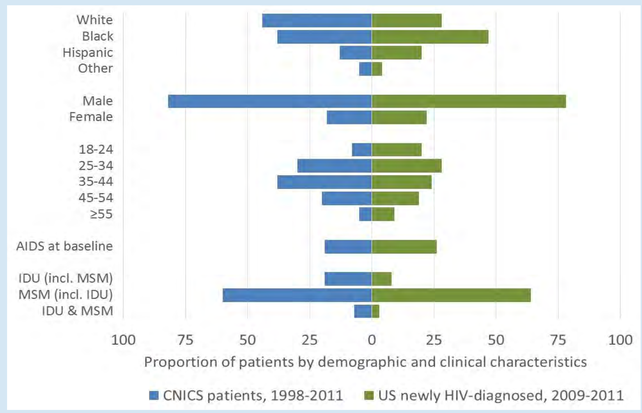
1. Predict inclusion in the CNICS
2. Modify the effect of treatment on mortality

References

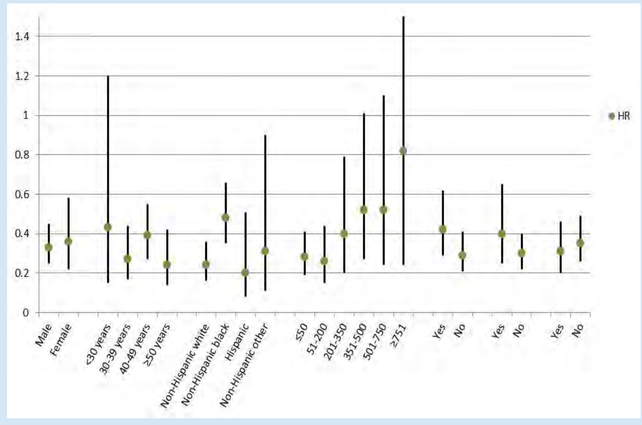
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Results

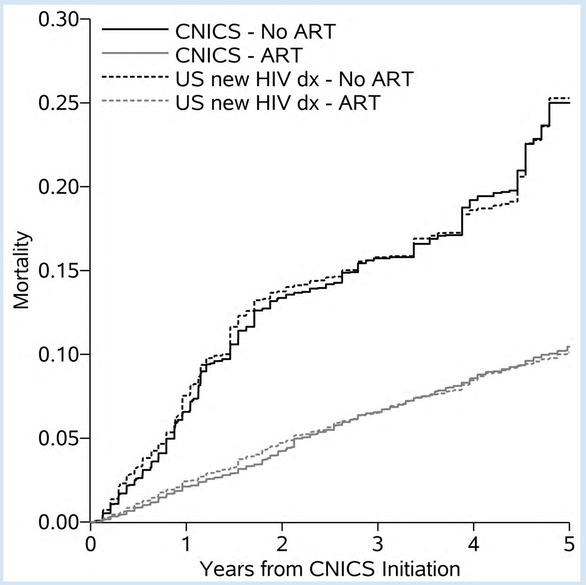
1) CNICS and target population have different distributions of key covariates



2) Those same covariates modify the effect of ART on mortality;



Yet, 3) the effect of ART observed in the CNICS was similar to that which we would have expected to see if everyone in the target population had been treated immediately or had treatment delayed ≥5 years



	5-year Risk, % (95% CI)	Risk Difference, % (95% CI)	Risk Ratio (95% CI)	Hazard Ratio (95% CI)
CNICS sample				
Crude				
No ART	12.1 (10.0, 14.3)	0.	1.	1.
ART	11.3 (10.4, 12.1)	-0.9 (-3.2, 1.5)	0.93 (0.76, 1.13)	1.01 (0.87, 1.17)
Weighted				
No ART	28.3 (19.1, 37.5)	0.	1.	1.
ART	10.6 (9.3, 11.9)	-17.7 (-27.0, -8.4)	0.37 (0.26, 0.53)	0.33 (0.25, 0.43)
Target population				
No ART	29.5 (18.2, 40.8)	0.	1.	1.
ART	10.4 (9.2, 11.6)	-19.1 (-30.5, -7.8)	0.35 (0.23, 0.53)	0.32 (0.23, 0.45)

Discussion

- Effect estimates from a study sample may not directly generalize to a target population due to: 1) differences in the prevalence of other causes of the outcome; 2) differences in versions of treatment; 3) differences in interference patterns.
- Unmeasured causes of both the outcome and inclusion in the study sample may threaten generalized estimates; sensitivity analyses for the effect of different distributions of CD4 cell count and viral load between the sample and target population showed limited impact on the estimated HR for ART on mortality.

Conclusions

ART initiation substantially lowers mortality in the CNICS, and this benefit is expected to be similar for the cohort of HIV-diagnosed persons in the US from 2009 to 2011.

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