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D:A:D

Investigating the causal impact of PI- and NNRTI-containing cART on the risk of mortality: methodological challenges

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BACKGROUND

- Use of standard multivariable models to assess the impact of cART on death is problematic as CD4 count is both a confounder (those with low values are at the greatest risk of death, and also more likely to receive ART) and on the causal pathway between cART and death.
- Marginal Structural Models (MSMs) have been successfully used as an alternative method to investigate the association between death and use of cART and similar questions. Rather than multivariable adjustment, they account for potential confounding by weighting the relative importance of individuals' follow-up using Inverse Probability Weights (IPWs) (analogous to propensity scores).
- We used MSMs to investigate whether PI- and NNRTI-containing cART were associated differently with all-cause mortality compared to receipt of no cART.

METHODS

- All D:A:D study participants who were ART-naive at study entry were followed until the earlier of 1st February 2012, last clinic visit or death.
- We assessed the association between PI-containing and NNRTI-containing cART (vs. no cART) with all-cause mortality using:
  1. Standard univariable Cox Proportional Hazards regression model (unadjusted model)
  2. Standard multivariable Cox Proportional Hazards regression model adjusted for baseline factors (including CD4 count)
  3. Standard multivariable Cox Proportional Hazards regression model adjusted for baseline and time-updated factors (including CD4 count)
  4. MSM: Proportional Hazards regression with adjustment using IPWs
- MSMs can only be used in situations where reasonable numbers of individuals start ART across the whole spectrum of CD4 counts (the **positivity assumption**). We assess this by calculating the mean IPW, which should be close to unity (one) if this assumption is met.

RESULTS

- There were 511 deaths in 13,645 individuals and 67,467 person-years (rate=7.57/1,000 person-years; **Table 1**).
- The mean IPW from the MSM including all HIV-positive individuals, which is much greater than one, suggests violation of the positivity assumption. This occurs primarily due to two individuals who had very low CD4 counts (<100 cells/mm^3) for an extended time without starting cART (**Table 2**).
- We re-analysed our data removing these two "outliers" ("restricted dataset"), and censoring IPWs greater than 10 ("truncated dataset", a standard approach to ensure that no one individuals' follow-up is given undue importance), which resulted in improved model fit (**Table 2**).
- Hazard ratios obtained using standard methods and the full dataset MSM suggested both PI- and NNRTI-containing cART were associated with an increased or similar risk of death compared to no cART (**Table 3**).
- In contrast, results from the "truncated" and "restricted" datasets suggested approximately a halving of risk with both regimens, but estimates were imprecise with wide confidence intervals.

CONCLUSIONS

- Methodological problems can arise when fitting MSMs if some individuals have an experience for which there is very low probability. This was the case with our I ndividuals who survived for a long period with very low CD4 counts.
- This led to erroneous findings; results were highly affected by two individuals.
- All analyses using MSMs should report the mean IPW obtained, to allow ascertainment of whether the positivity assumption is appropriate.
- Alternative analytical approaches (e.g. dynamic MSMs, structured nested models) may be more appropriate to address this research question in this and other cohorts.
- A further assumption of MSMs is that there is no unmeasured confounding
- Furthermore, care must be taken when interpreting the results from any MSM analysis.

Table 1

Baseline Characteristics

		Number (%)
Number		13645 (100.0)
Gender	Male	10224 (74.9)
Risk of HIV acquisition	MSM IDU Heterosexual Other	6726 (49.3) 1599 (11.7) 4471 (32.8) 849 (6.2)
Hepatitis B positive [a]	Yes	1503 (11.0)
Hepatitis C positive [b]	Yes	1453 (10.7)
Smoking status	Current Ex Unknown Never	4906 (36.0) 1523 (11.2) 4112 (30.1) 3104 (22.8)
AIDS diagnosis	Yes	950 (7.0)
Age	Median (range)	36 (16-79)
Systolic BP	Median (range)	120 (65-20) n=9297
BMI	Median (range)	23 (11-45) n=9962
CD4 count	Median (range)	453 (0-2950)
HIV RNA viral load	Median (range)	4.9 (1.7-7.3) n=12932

[a] HBsAg positive, HBeAg positive or HBV DNA positive/anti-Hbe positive; [b] HCV antibody positive and HCV-RNA positive/unknown

Table 2

Inverse Probability Weights (IPW)

	Mean IPW	SD	1st and 99th percentiles	Maximum IPW
All individuals	455.3	123913	0.06, 7.75	22,000,000
Restricted dataset [a]	2.16	141	0.06, 7.45	10,000
Truncated dataset [b]	1.00	1.18	0.06, 7.75	10

[a] Removal of two individuals from dataset
[b] All IPWs greater than 10 are assigned a value of 10

Table 3

Association between ART and death, estimated using different statistical approaches

	PI-containing cART vs. no cART			NNRTI-containing cART vs. no cART		
	HR	95% CI	P-value	HR	95% CI	P-value
Standard methods						
Unadjusted	1.88	1.46-2.41	<.0001	1.51	1.20-1.89	0.0004
Adjusted for baseline factors [a]	1.11	0.84-1.47	0.47	0.93	0.72-1.21	0.60
Adjusted for baseline & time-updated factors [b]	0.92	0.69-1.23	0.57	0.86	0.66-1.13	0.28
MSM [c]						
All HIV-positive individuals	11.6	9.63-14.0	<.0001	2.46	2.01-3.01	<.0001
Restricted dataset [d]	0.33	0.26-0.41	<.0001	0.53	0.41-0.68	<.0001
Truncated dataset [e]	0.60	0.47-0.77	<.0001	0.48	0.38-0.60	<.0001

[a] Adjusted for: CD4 count and HIV viral load at study entry, AIDS diagnosis at study entry, Calendar year, Age, Gender and Mode of HIV acquisition
[b] Adjusted for: factors in [a] plus 2 most recent CD4 counts (non linear, fitted using spline curves), current HIV-RNA viral load, in a period of not accessing care, AIDS event in previous 3 months
[c] Separate weighting model fitted for each contributing cohort. Treatment and censoring model includes factors listed in [a] and [b]
[d] Removal of two HIV- positive individuals from dataset
[e] All IPWs greater than 10 are assigned a value of 10

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