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The Use of the Restricted Mean Survival Time as a Treatment Measure in HIV/AIDS Clinical Trials: Reanalysis of the ACTG A5257 Trial

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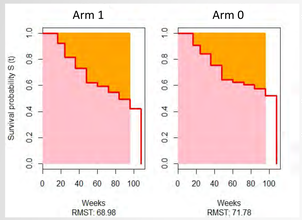
BACKGROUND

- The Restricted Mean Survival Time (RMST) has recently been proposed to estimate the event-free time over a given time period.
  - It is estimated as the area under the Kaplan-Meier (KM) curve as shown in pink below:



- *The average "event-free" time during 96 weeks of follow-up is 68.98 weeks on Arm 1 and is 74.11 weeks on Arm 0.*
- *The difference in RMST is 68.98-71.78=-2.8 weeks*
- *For future patients the "event-free " time on Treatment 1, is 2.8 weeks shorter than for those on Treatment 0 on average.*

- RMST measure has not been used as primary measure of efficacy in HIV/AIDS clinical trials.
- Under or over estimation of the hypothesized failure rates in the definition of non-inferiority bounds for a hazard ratio(HR) based analysis can significantly impact on the probability of a trial demonstrating non-inferiority for a HR and complicate the interpretation of the study findings. [1]
- ACTG A5257 was a US-based Phase III randomized trial comparing 3 modern NNRTI-sparing regimens for initial treatment of HIV-1. [2]
  - 1809 ART naive participants were randomized to FTC+TDF with ATV/RTV , RAL, DRV/RTV.
  - Primary efficacy endpoint: Time to virologic failure. Analysis based on the pairwise comparisons of difference in Kaplan-Meier estimates (RD_{KM}) by week 96 with equivalence accepted if the 97.5% CI was wholly contained within -/+10%.
  - Primary tolerability endpoint: Time to discontinuation of treatment for toxicity. Analysis based on RD_{KM} estimated by method Gray in the presence of the competing risk. A composite endpoint combining virologic and tolerability endpoint was also analyzed.
  - Based on an exponential distribution model, assuming rates of virologic failure and lost to follow-up of 25% and 12% respectively, a sample size of 600/arm was targeted.
  - Based on the RD_{KM} analysis, equivalence was demonstrated in all comparisons for the virologic endpoint, and for one comparison for the tolerability endpoint (DRV/RTV versus RAL).

1. *Abulizi X, Flandre P. Choice of treatment-effect measures when noninferiority margins originally defined in absolute difference translated into relative difference influenced the results of clinical trials. J Clin Epidemiol 2018;96:63–72. doi:10.1016/j.jclinepi.2017.12.010.*
2. *Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, et al. Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor–Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1: A Randomized, Controlled Equivalence Trial. Annals of Internal Medicine 2014;161:461. doi:10.7326/M14-1084.*

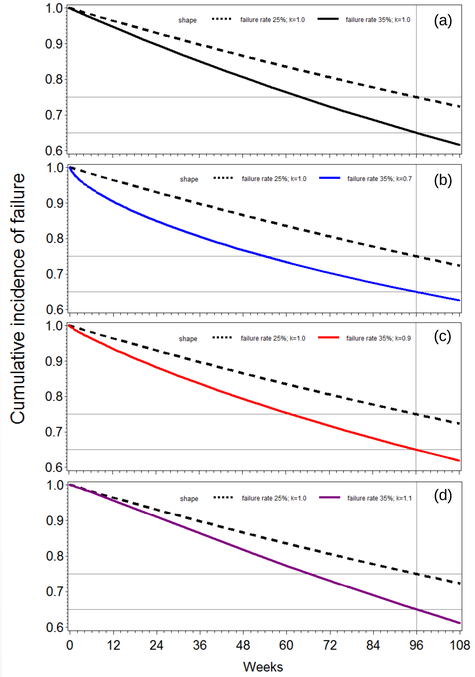
OBJECTIVES

- **To compare analysis based on the difference in RMST (Δ-RMST) measure to RD_{KM} and hazard ratio (HR) in the ACTG A5257 equivalence trial.**
- **To investigate the performance and characteristics of Δ-RMST-based analysis in the context of proportional and non-proportional hazards.**

METHODS

- The primary efficacy and tolerability as well as the combined outcome measures from ACTG A5257 trial were reanalyzed using hazard ratio(HR) and difference in RMST (Δ-RMST) and compared to the original study findings based on RD_{KM}.
- A5257 equivalence bounds were transformed for each measure assuming exponential time-to-event distribution and A5257 design characteristics.
- The performance of Δ-RMST-based analyses with proportional and non-proportional hazards in terms of power of the study and false positive rate was investigated in simulation study.
- Assuming 25% of failure rate by week 96 in the reference arm and a sample size of 600/arm, clinical trial dataset with time-to-event outcomes were generated with Weibull shape parameters to simulate proportional and non-proportional hazards for hypothetical pairwise comparisons (Figure 1).
  - Parameters for the simulation study were determined using Weibull parametric models fit for each randomized group of A5257.

Figure 1. Simulation study time-to-event distributions. *In each case the time-to-event outcome for the reference group (dashed line) follows an exponential distribution (shape parameter k=1.0) with a failure rate at 96 weeks of 25%. In the other group the failure rate at 96 weeks is 35% and the time-to-event outcome follows an exponential (k=1.0) (a) or Weibull (k=0.7, 0.9 and 1.1) distribution (b-d, respectively).*



RESULTS

Table 1. Summary of the analyses in the ACTG 5257 study and alternative analyses.

		Comparaison ATV/r vs RAL		Comparaison DRV/r vs RAL		Comparaison ATV/r vs DRV/r	
Method	Equivalence Bounds	Point estimate	97.5% CI	Point estimate	97.5% CI	Point estimate	97.5% CI
Virologic failure endpoint							
RD_{KM}	-/+10%	3.4%	[-0.6 to 7.4]**	5.6%	[1.4 to 9.8]**	-2,2%	[-6.7 to 2.2]**
HR	0.56; 1.50	1.4	[0.82 to 1.58]	1.40	[1.0 to 1.93]	0.81	[0.6 to 1.10]**
Δ-RMST	-5.18; +5.43	2.3wk	[-0.08 to 4.7]**	3.7wk	[1.1 to 6.2]	-1.4wk	[-4.1 to 1.4]**
Tolerability failure endpoint							
RD_{KM}	-/+7%	12.7%	[9.4 to 16.1]	3.6%	[1.4 to 5.8]**	9.2%	[5.5 to 12.9]
HR	0.29; 1.77	12.7	[5.6 to 29.1]	4.07	[1.7 to 9.9]	3.14	[2.0 to 4.9]
Δ-RMST	-3.44; +3.53	7.9wk	[5.5 to 10.3]	1.6wk	[0.1 to 3.0]**	6.4wk	[3.8 to 9.0]
Combined endpoint (Virologic or tolerability failure endpoint)							
RD_{KM}	-/+10%	14.9%	[10.2 to 19.6]	7.5%	[3.2 to 11.8]	7.5%	[2.3 to 12.7]
HR	0.63; 1.43	2.4	[1.7 to 3.0]	1.55	[1.1 to 2.1]	1.46	[1.1 to 1.9]
Δ-RMST	-5.30; +5.57	9.5wk	[6.3 to 12.6]	4.1wk	[1.4 to 6.8]	5.4wk	[1.9 to 8.5]

- Analyses of Δ-RMST globally led to similar conclusions as the published A5257 findings based on RD_{KM}.
- Analyses based on HR provided some discordant equivalence conclusions compared both with the initial analyses bases on RD_{KM} and the Δ-RMST

***Equivalence shown.*

Table 2. RMST estimate for each endpoint and randomized groups of ACTG 5257 study, with Δ-RMST estimate for pairwise comparisons.

Endpoint	Arm	RMST by week 96 (weeks)	Pairwise comparison	Δ-RMST Estimate (weeks)
Virologic failure	ATV/r	89.2	ATV/r vs. RAL	2.3 [-0.08 to 4.7]
	RAL	91.5	DRV vs. RAL	3.7 [1.1 to 6.2]
	DRV/r	87.5	ATV/r vs. DRV/r	-1.4 [-4.1 to 1.4]
Tolerability failure	ATV/r	87.1	ATV/r vs. RAL	7.9 [5.5 to 10.3]
	RAL	95.0	DRV vs. RAL	1.6 [0.1 to 3.0]
	DRV/r	93.4	ATV/r vs. DRV/r	6.4 [3.8 to 9.0]
Combined endpoint	ATV/r	81.5	ATV/r vs. RAL	9.5 [6.3 to 12.6]
	RAL	90.9	DRV vs. RAL	4.1 [1.4 to 6.8]
	DRV/r	86.9	ATV/r vs. DRV/r	5.4 [1.9 to 8.8]

Table 3. Probability of concluding equivalence using the Δ-RMST* when time-to-event outcomes follow exponential (shape parameter =1) or Weibull (shape parameter ≠ 1) distributions and treatment groups have an underlying 96-week failure rate of 25% (i.e., power).

		35% failure rate shape parameter (*k*)			
	Shape parameter (*k*)	0.7	0.9	1.0	1.1
25% failure rate	0.7	81.5	66.5	51.2	38.3
	0.9		89.4	86.8	77.4
	1.0			**93.6**	89.9
	1.1				95.2

- With an exponential distribution, the expected power for the pairwise comparison with the Δ-RMST analysis is 93.6%.
- When the PH assumption is valid (same shape parameter in both groups), power decreases (increases) with monotonic decreasing (increasing) hazard (i.e., Weibull shape parameter).
- When the PH assumption is not valid (i.e., a shape parameter that is greater in one group), the power of the study is markedly decreased.

Table 4. Probability of concluding equivalence using Δ-RMST* when time-to-event outcomes follow exponential (shape parameter =1) or a Weibull (shape parameter ≠ 1) distributions and treatment groups have underlying 96-week failure rates of 35% and 25% failure rates (i.e., false positive rate).

		35% failure rate shape parameter (*k*)			
	Shape parameter (*k*)	0.7	0.9	1.0	1.1
25% failure rate	0.7	1.6	19.6	38.9	61.3
	0.9	0,1	3.9	12.2	27.7
	1.0	0.1	1.6	**5.4**	15.2
	1.1	0.0	0.7	2.5	9.2

- With an exponential distribution, the false positive rate for the pairwise comparison with the Δ-RMST analysis is 5.4%.
- When the PH assumption is valid, the false positive rate decreases (increases) with monotonic decreasing (increasing) hazard.
- When the PH assumption is not valid, with a shape parameter that is greater (lower) in the group with the highest failure rate, the false positive rate is markedly increased (decreased).

** RD_{KM} and HR-based analyses were not evaluated as part of the simulation study since the RD_{KM} estimate will not change as the difference in the rate of failure is the same whatever the time-to-event distribution (see Figure 1), and the HR estimate is not appropriate in the case of non-proportional hazards.*

CONCLUSIONS

- Analyses based on Δ-RMST globally led to similar conclusions as the published findings of ACTG A5257 study based on RD_{KM}. In contrast, analyses based on HR provided some discordant equivalence conclusions compared both with initial analysis based on RD_{KM} and the Δ-RMST. Such discordance is mainly explained by violation of the PH assumption and by an under- or over-estimation of the hypothesized failure rates in the study design.
- Though there are some advantages to use the RMST measure, further discussion is needed with clinicians involved in the HIV/AIDS field to determine which estimand best informs the clinical question and to suggest equivalence bounds. We also show that finding provided by RMST-based analyses are sensitive to departures from the PH assumption.

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