METHODS

To compare analysis based on the difference in RMST (Δ-RMST) measure to R0.3 and hazard ratio (HR) in the ACTG A5257 equivalency trial.

To investigate the performance and characteristics of Δ-RMST-based analysis in the context of proportional and non-proportional hazards.

RESULTS

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Endpoint</th>
<th>Combined endpoint (Virologic or tolerability failure endpoint)</th>
<th>ATV/r vs RAL</th>
<th>DRV/r vs RAL</th>
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<tbody>
<tr>
<td>RMST</td>
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<tr>
<td>Δ-RMST</td>
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<td>HR</td>
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<td>RDKM</td>
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</table>

- Table 2. RMST estimate for each endpoint and randomized groups of ACTG 5257 study, with alternative analyses.

- Table 3. Probability of concluding equivalence using the Δ-RMST measure at different time points under 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).

- 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 an underlying 96-week failure rate of 25% (i.e., power).

CONCLUSIONS

- Analyses based on Δ-RMST globally led to similar conclusions as the published ACTG 5257 analyses based on R0.3.

- Analyses based on the RMST equivalence bounds for the original trial design were concordant with either the initial analyses based on R0.3 and the Δ-RMST.

- The performance of Δ-RMST-based analyses with proportional and non-proportional hazards, in terms of power of the study and false positive rate investigated in simulation study.

- Assumption 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.

- Parameters for the simulation study were determined using Weibull model parameters fit for each randomized group of A5257.

ACKNOWLEDGMENTS

- The use of the restricted mean survival time as a measure in HIV/AIDS clinical trials: Reanalysis of the ACTG A5257 Trial

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The primary efficiency and tolerability as well as the combined outcome measures from ACTG A5257 trial were standardized using hazard ratio(HR) and difference in RMST (Δ-RMST) and compared to the original study findings based on R0.3. 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 investigated in simulation study.

- Assumption 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.

- Parameters for the simulation study were determined using Weibull model parameters fit for each randomized group of A5257.

- 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 recommend using the RMST measure as a potential tool for the clinical and regulatory processes.

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