The Effect of Antiretroviral Therapy Use Among HIV-1 Positive Children on the Hazard of AIDS Using Calendar Year as an Instrumental Variable

Andrew Anglemyer¹, Amy Sturt, Yvonne Maldonado²
1 – Operations Research, Naval Postgraduate School, Monterey, California
2 – Department of Pediatrics, Division of Infectious Diseases, Stanford University School of Medicine

Background

Although coverage of HIV-1 infected children with antiretroviral therapy (ART) is improving worldwide, only 32% of children are treated compared to 40% of adults. Early combination antiretroviral therapy (ART) for pediatric populations with human immunodeficiency virus type-1 (HIV-1) infection decreases mortality and progression to Stage 3 disease.

Given the lack of RCT data regarding when to start ART in asymptomatic older children with HIV-1 population, recommendations regarding initiation of ART in children >1 year of age vary by organization.

Instrumental variable (IV) analyses are now a common causal inference technique used in the absence of randomized data. The celebrated instrumental variable (IV) analyses require local independence of the treatment and the instrument and exclusion of the instrument from the error term.

Methods

To estimate the effect of ART on the hazard of progression to C category B symptoms, as defined by the 1994 MMWR classification system, later progressed to Stage 3 illness or death and were included in this analysis.

- 46% were male
- 34% were White
- 41% of their mothers were known to have received prenatal care
- 30% were low birth weight

In the pre-ART era, of the 31,519 person-days, 3,305 (9.6%) were misclassified (classified as time the children were actually receiving an ART regimen during the pre-ART era).

During the ART era, 7 out of 18 events (38.9%) and 8,244 out of 16,861 person-days (48.9%) were misclassified as the participants did not use ART during this period.

Figure 1: Traditional Instrumental Variable Approach

Figure 2: Weighted Instrumental Variable Approach

Results

Of 267 identified, eligible children, 106 diagnosed with clinical category B symptoms, as defined by the 1994 MMWR classification system, later progressed to Stage 3 illness or death and were included in this analysis.

- In the pre-ART era, the calendar period as the instrument (Figure 1) in our primary analysis using a traditional IV approach (ITT). Secondly, we adapted non-compliance or treatment misclassification methods in RCTs for use in IV analysis, which requires estimating rate rather than the risk.
- \( Y \) is the outcome variable\( = \text{Diagnosis or death} \)
- \( C \) is the confounding variable\( = \text{Calendar period} \)
- \( (a) \) represents the pre-ART era and \( (b) \) represents the ART era.

Table 1: Distribution of Events (First Stage 3 Diagnosis or Death) and Person-Days by Calendar Period Among Children With Previous Stage 2 Diagnosis

<table>
<thead>
<tr>
<th>Calendar Period (Before 1998/ After 1998)</th>
<th>No. of events</th>
<th>No. of Person-Days</th>
<th>Rate ( a )</th>
<th>Rate Difference</th>
<th>95% CI</th>
<th>Intent To Treat (ITT) Rate Ratio</th>
<th>95% CI</th>
<th>Instrumental Variable (IV) Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ART</td>
<td>88</td>
<td>31,519</td>
<td>2.79</td>
<td>1.72</td>
<td>0.96, 2.48</td>
<td>2.62</td>
<td>1.58, 4.35</td>
<td>3.93</td>
<td>2.37, 6.53</td>
</tr>
<tr>
<td>ART</td>
<td>18</td>
<td>16,861</td>
<td>1.07</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>48,380</td>
<td>2.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unweighted

| Pre-ART                                     | 86.2         | 31,376            | 2.75        | 1.20            | -1.04, 2.78 | 1.78                          | 0.71, 4.41 | 2.46                             | 0.93, 10.33 |
| ART                                         | 21.8         | 14,113            | 1.55        | 0               | 1               | 1                             | 1               |                                   | 1               |
| Total                                       | 108.0        | 45,489            | 2.37        |                 |                 |                               |                 |                                   |                 |

Weighted

Unweighted

| Pre-ART                                     | 86.2         | 31,376            | 2.75        | 1.20            | -1.04, 2.78 | 1.78                          | 0.71, 4.41 | 2.46                             | 0.93, 10.33 |
| ART                                         | 21.8         | 14,113            | 1.55        | 0               | 1               | 1                             | 1               |                                   | 1               |
| Total                                       | 108.0        | 45,489            | 2.37        |                 |                 |                               |                 |                                   |                 |

Weighted

Results (continued)

During 48,380 person-days, 106 HIV-positive children progressed to Stage 3 or death.

- The intention to treat (ITT) rate ratio of Stage 3 diagnosis or death comparing the pre-ART and ART era was estimated at 2.62 (95% confidence interval (CI): 1.58, 4.35).
- An IV estimator was used to adjust for ART use misclassification, yielding an IV rate ratio of 3.93 (95% CI: 2.37, 6.53).
- Weighting by the inverse probability of calendar era, given covariates, did not significantly alter the results.

Conclusions

- Our study provides further evidence that ART decreases progression to Stage 3 or death among children with perinatal HIV-1.
- In children with perinatal HIV-1, the use of calendar year as a surrogate for ART use under-represented the risk of progression to Stage 3 disease or death when compared to the IV analysis.
- ITT rate ratios are biased toward the null when exposure misclassification is not considered.
- ART use of noncompliance adjustments for ART misclassification in IV analyses may provide more robust evidence of ART's effectiveness than traditional ITT analysis.

Literature Cited