To Dose-Adjust or Not to Dose-Adjust: 3TC Dose in Renal Impairment

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Background
• Lamivudine (3TC) is generally well tolerated
• 70% of oral 3TC is excreted by kidney
• Current guidelines suggest 3TC dose adjustment (150mg daily vs. 300 mg daily) for PLWH with decreased renal function (eGFR 30 to <60 mL/min/1.73 m²)
  🟠 Prevalence of estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² in people living with HIV (PLWH): 4%-16% 1,2
  🟠 Incompatible with fixed-dose combinations

Objective
To assess the risks associated with the full (300mg) vs adjusted 3TC dose (150mg) in PLWH with eGFR ≥ 30 to < 49 mL/min/1.73m²

Methods
Study population
• OPERA Cohort: Prospectively captured, routine clinical data from electronic health records (EHR) in the US (85 clinics, 19 states, 1 US territory)
• Inclusion criteria
  🟠 PLWH aged 13 years or older
  🟠 Prescribed 3TC (150 mg or 300 mg daily dose) for the first time between 11/17/1995 and 12/31/2018
  🟠 eGFR ≥ 30 to 49 mL/min/1.73m² at 3TC initiation
• Person-time censored at 3TC discontinuation/dose change, loss-to-follow-up, death, 31/Mar/2019, or first out-of-range eGFR

Outcomes
Table 1. Composite unintended events definitions*

<table>
<thead>
<tr>
<th>Composite Unintended Events</th>
<th>Composite Unintended Events 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific diagnoses of interest†</td>
<td>✔</td>
</tr>
<tr>
<td>• Lactic Acidosis; Pneumonia; Peripheral Neuropathy; Pancreatitis; Rhabdomyolysis; Anemia; Neutropenia; Thrombocytopenia; Nausea</td>
<td>✔</td>
</tr>
<tr>
<td>Neurological abnormalities</td>
<td>✔</td>
</tr>
<tr>
<td>• Neuropathy; Herpeszoster; Paresthesia; A/C TH; Total Inability; Lactates +</td>
<td>✔</td>
</tr>
<tr>
<td>• Blood glucose &gt;150 mg/dL; P/Creatinine &gt;3.5</td>
<td>✔</td>
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<tr>
<td>Laboratory abnormalities</td>
<td>✔</td>
</tr>
<tr>
<td>• Diagnoses of gastrointestinal (GI) symptoms†</td>
<td>✔</td>
</tr>
<tr>
<td>• Hematocrit; Anemia; Varicose; Abdominal Pain</td>
<td>✔</td>
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</tbody>
</table>

* *Diagnostic codes used in conjunction with text entries of the diagnosis field of the electronic health records

Statistical analyses
• Prevalence of Unintended Events at baseline
• Among PLWH without prevalent Unintended Events at baseline
  • Incidence rates of composite Unintended Events: Univariate Poisson regression
  • Association between 3TC dose and incident Unintended Events: Poisson regression adjusted for drug/alcohol abuse and hemoglobin
  • Sensitivity analysis: person-time not censored at first out-of-range eGFR

Results
Table 2. Demographic and clinical characteristics at ART initiation

<table>
<thead>
<tr>
<th>Age, median (IQR)</th>
<th>3TC Daily Dose: 150 mg (n=103)</th>
<th>3TC Daily Dose: 300 mg (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 (48, 61)</td>
<td>54 (47, 60)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>40 (39)</td>
<td>119 (27)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>67 (65)</td>
<td>202 (46)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>11 (11)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>ART-naive, n (%)</td>
<td>12 (12)</td>
<td>49 (11)</td>
</tr>
<tr>
<td>Log2 Viral load, median (IQR)</td>
<td>2.1 (1.3, 4.5)</td>
<td>1.7 (1.2, 3.9)</td>
</tr>
<tr>
<td>eGFR, median (IQR)</td>
<td>39.9 (36.4, 45.5)</td>
<td>43.3 (38.6, 46.5)</td>
</tr>
<tr>
<td>Drug/Alcohol abuse, n (%)</td>
<td>28 (27)</td>
<td>79 (18)</td>
</tr>
<tr>
<td>Low hemoglobin (female: &lt;8.5g/dL; male: &lt;9g/dL), n (%)</td>
<td>17 (17)</td>
<td>28 (6)</td>
</tr>
</tbody>
</table>

Note: HIV with eGFR ≥30 to <50 mL/min/1.73 m²

Discussion
• Dose adjustment more frequently prescribed to women, African Americans, and sicker PLWH (Table 2)
  🟠 Suggests that physicians weighed the risks and benefits of prescribing a full dose, including tradeoff between potential unintended events with the full dose vs. potentially lower adherence and effectiveness with the adjusted dose
• Untended events of interest were common at baseline (Figure 1)
  🟠 Grade 2 lab abnormalities were most prevalent
• No statistically significant difference in select diagnoses/severe lab abnormalities with 300mg vs 150mg 3TC (Figure 2)
  🟠 Robust to sensitivity analysis without censoring person-time at first out-of-range eGFR
• Statistically significantly higher rate of select diagnoses/moderate lab abnormalities/GI symptoms with 300mg vs 150mg 3TC (Figure 2)
  🟠 Dose adjustment may be considered for PLWH experiencing moderate lab abnormalities or GI symptoms
• Frequency of 3TC discontinuation and dose modification did not differ by dose
dose
• OPERA cohort reflects routine clinical care in the U.S., where the 3TC dose-adjustment recommendation is not always followed in PLWH with renal impairment

Key Findings
• Among PLWH with eGFR 30-49 mL/min/1.73 m²:
  🟠 No statistical difference in risk of select incident diagnoses/severe lab abnormalities by daily 3TC dose
  🟠 Increased risk of incident GI symptoms/moderate lab abnormalities with full (300 mg) vs. adjusted (150 mg) 3TC dose
• Clinical judgement is key in weighing the benefits of a single tablet regimen vs. the risks of mild/moderate unintended events without dose adjustment

References

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