PEB0217

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

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OPERA® The Longitudinal Cohort

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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 <50 mL/min/1.73 m^2)
  - Prevalence of estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2 in people living with HIV (PLWH): 4%-16% [1-3]
  - 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/1.73m^2

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/1.73m^2 at 3TC initiation
- Person-time censored at 3TC discontinuation/dose change, loss-to-follow-up, death, 31Mar2019, or first out-of-range eGFR

Outcomes

Table 1. Composite unintended events definitions*

	Composite Unintended Events 1	Composite Unintended Events 2
Specific diagnoses of interest† Lactic Acidosis; Paresthesia; Peripheral Neuropathy; Pancreatitis; Rhabdomyolysis; Anemia; Neutropenia; Thrombocytopenia; Nausea	✔	✔
Laboratory abnormalities Neutrophils; Hemoglobin; Platelets; ALT; AST; Total bilirubin; Lactate + pH; Creatinine kinase	✔ DAIDS grade 3-4	✔ DAIDS grade 2-4
Laboratory abnormalities Red blood count (♂: <4.52 x10^{12}/L, ♀: <4.10 x10^{12}/L); Mean corpuscular volume > 96	✘	✔
Diagnoses of gastrointestinal (GI) symptoms† Hyperlactatemia; Nausea; Vomiting; Abdominal Pain	✘	✔

* Event present at first incident event listed during follow-up
† Diagnosis codes used in conjunction with text searches 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

	3TC Daily Dose: 150 mg n=103	3TC Daily Dose: 300 mg n=436
Age, median (IQR)	54 (48, 61)	54 (47, 60)
Female, n (%)	40 (39)	119 (27)
Black, n (%)	67 (65)	202 (46)
Hispanic, n (%)	11 (11)	55 (13)
ART-naïve, n (%)	12 (12)	49 (11)
Log_{10} Viral load, median (IQR)	2.1 (1.3, 4.5)	1.7 (1.3, 2.9)
eGFR, median (IQR)	39.9 (36.4, 45.5)	43.3 (38.4, 46.5)
Drug/alcohol abuse, n (%)	28 (27)	79 (18)
Low hemoglobin (female: <8.5g/dL; male: <9g/dL), n (%)	17 (17)	28 (6)

Figure 1. Prevalence of unintended events within 12 months before or at 3TC initiation

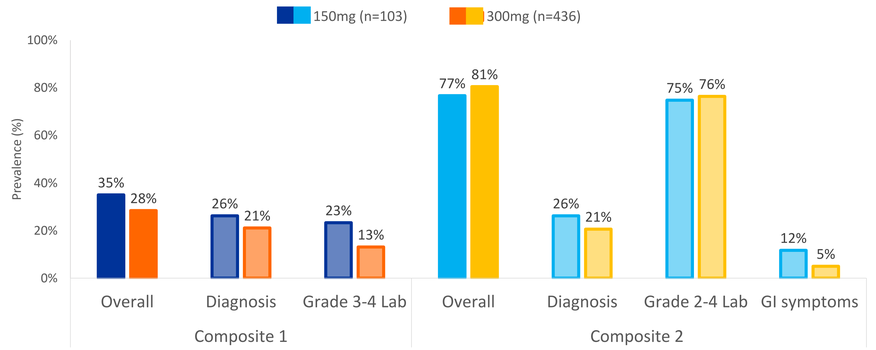
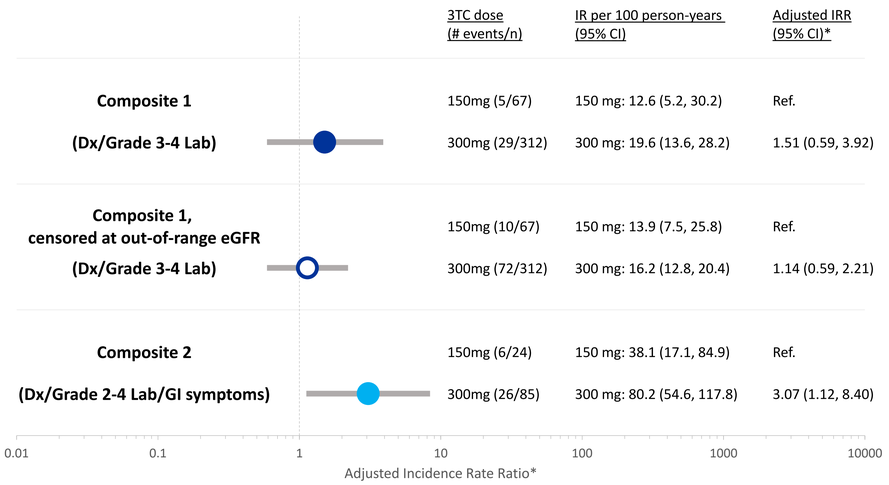


Figure 2. Incidence rates and rate ratios for unintended events by 3TC dose, excluding PLWH with prevalent events



* Adjusted for drug/alcohol abuse and hemoglobin level

Discussion

- Dose adjustment more frequently prescribed to women, African Americans, and sicker PLWH (Table 2)
  - Suggests that physicians weighed the risks and benefit 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
- Unintended 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 3TC 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
- 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/1.73m^2:
  - 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

1. Petersen N, et al. Prevalence of impaired renal function in virologically suppressed people living with HIV compared with controls: the Copenhagen Comorbidity in HIV Infection (COCOMO) study*. HIV Medicine 2019.
2. Mocroft A, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010.
3. Wyatt CM, et al. Chronic kidney disease in HIV infection: an urban epidemic. AIDS 2007.

Acknowledgements

This research would not be possible without the generosity of people living with HIV and their OPERA caregivers. Additionally, we are grateful for the following individuals: Robin Beckerman (SAS programming), Jeff Briney (QA), Ted Ising (Database Arch & Mgmt), Bernie Stooks (Database Mgmt), Judy Johnson (Med Terminology Classification), Rodney Mood (Site Support)

Support

This research was sponsored by:
ViiV Healthcare

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