To dose-adjust or not to dose-adjust: lamivudine dose in kidney impairment

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Objectives: To assess the risk of adverse diagnoses and laboratory abnormalities associated with a 300 or 150 mg daily dose of lamivudine (3TC) initiated by people with HIV (PWH) with an estimated glomerular filtration rate (eGFR) between at least 30 and 49 ml/min per 1.73 m^2 or less.

Design: Longitudinal study based on electronic health records of 539 PWH with eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort.

Methods: Common unintended effects of 3TC were evaluated as composite outcomes. We estimated the incidence (univariate Poisson regression) and association between dose and incident composite outcomes (multivariate Poisson regression) among PWH without the relevant diagnoses or laboratory abnormalities at 3TC initiation.

Results: PWH initiating 150 mg 3TC had higher HIV RNA, lower eGFR, and more comorbidities than those initiating 300 mg 3TC. The prevalence of relevant diagnoses and laboratory abnormalities was similar in both groups. The most common lab abnormality was low hemoglobin. There was no statistically significant difference in incident adverse diagnoses/severe lab abnormalities with 300 mg versus 150 mg [incidence rate ratio (IRR): 1.51; 95% confidence interval (CI) 0.59–3.92). However, a statistically significant association was observed when gastrointestinal symptoms/moderate lab abnormalities were included in the outcome (IRR: 3.07, 95% CI 1.12–8.40).

Conclusion: As 3TC is a well tolerated drug with a wide therapeutic window, dose adjustment may be unnecessary among PWH with eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less. Clinical judgement is key when weighing the risks and benefits of 3TC dose adjustment for PWH experiencing gastrointestinal symptoms or moderate lab abnormalities.

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Introduction

Lamivudine (3TC) is a cytosine dideoxynucleoside analogue with potent in-vitro activity against HIV demonstrated through the inhibition of reverse transcriptase [1–3]. Early-phase clinical trials of 3TC monotherapy demonstrated potent antiretroviral activity as well as a positive safety profile; mild headache, insomnia, and

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abdominal symptoms were the most commonly reported adverse events [4,5]. In a late-phase clinical trial, participants randomized to 600 mg total daily 3TC reported more gastrointestinal symptoms and headache than participants randomized to 300 mg daily but these differences were not statistically significant [6]. Dose-ranging studies of 3TC have evaluated doses between 0.25 and 20 mg/kg in asymptomatic people with HIV (PWH) with normal kidney function and demonstrated that following oral administration, 3TC was rapidly absorbed with a mean absolute bioavailability of 82%; approximately 70% of the 3TC was renally excreted unchanged [7].

The pharmacokinetics of 3TC have previously been evaluated in individuals with both normal and impaired kidney function [8]. In one study, 16 PWH with creatinine clearance (CrCl) ranging from less than 10 ml/min to at least 60 ml/min were administered a single 300 mg dose of 3TC, which was well tolerated regardless of kidney function [9]. This study demonstrated higher peak serum concentrations, longer half-lives, and larger areas under the concentration–time curves in individuals with CrCl less than 40 ml/min. Renal clearance of 3TC was shown to be linearly correlated with creatinine clearance, suggesting the need for dose adjustment in PWH with decreased creatinine clearance, in both this study [9] and another single-dose study of 3TC among individuals without HIV infection with CrCl 82–117, 25–49, or 13–19 ml/min [10]. Using a population pharmacokinetic analysis, Bouazza *et al.* [11] analyzed the 3TC plasma concentrations of 244 PWH with a range of renal function on 3TC (CrCl <30 to >90 ml/min). Consistent with the single-dose studies described above, they reported that 3TC clearance increased with creatinine clearance and suggested dose adjustments in PWH with CrCl 90 ml/min or less.

On the basis of the absorption, distribution, metabolism, and excretion (ADME) characteristics of 3TC, current guidelines state that dose adjustment should be considered in individuals with renal insufficiency (CrCl <50 ml/min) [12]. Renal impairment and chronic kidney disease are common comorbidities in PWH [13] and 3TC is commonly used by PWH. Given the availability of 3TC as a single agent in multiple dosing and multiple fixed-dose combination formulations, a real-world population-level assessment of 3TC's safety profile, when prescribed to PWH with decreased CrCl, will provide insight into the clinical management of these individuals. This study aimed to estimate the incidence rate and the association between 3TC dose and the incidence of adverse diagnoses and laboratory abnormalities, considered as two composite outcomes, among PWH with a baseline estimated glomerular filtration rate (eGFR) between at least 30 and 49 ml/min per 1.73 m^2 or less.

Methods

Study design and population

Prospectively captured, routine clinical data from the electronic health records (EHR) of 103 369 PWH in the Unite States (85 clinics in 19 states and one United States territory) were utilized; the PWH are part of the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort database. The OPERA database obtains annual institutional review board (IRB) approval from Advarra IRB, including a waiver of informed consent and authorization for the use of protected health information. The study population included PWH who were aged 13 years or older, were prescribed 3TC for the first time between 17 November 1995 and 31 December 2018 and had a CKD-EPI eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less at 3TC initiation. First exposure to 3TC was defined as a total daily adjusted dose of 150 mg (150 mg once daily) or a full dose of 300 mg (150 mg twice daily or 300 mg once daily) after inclusion in the OPERA database. Each person contributed person-time from 3TC initiation until occurrence of an outcome of interest or one of the following censoring events: 3TC discontinuation because of any cause, defined as a gap of at least 45 days, change in total daily dose of 3TC, first out-of-range eGFR during follow-up (i.e. <30 and >49 ml/min per 1.73 m^2), loss to follow-up (i.e. any 12-month period in which no clinical contact is made), death, or study end (i.e. 31 March 2019).

Study outcomes

Composite outcomes of interest were defined by diagnoses and laboratory abnormalities, selected in collaboration with the Food and Drug Administration, and based on documented unintended effects of 3TC. Diagnosis codes were used in conjunction with text searches of the diagnosis field of the EHR. Composite Outcome 1 included specific diagnoses of interest (lactic acidosis; paraesthesia; peripheral neuropathy; pancreatitis; rhabdomyolysis; anemia; neutropenia; thrombocytopenia; nausea) and severe laboratory abnormalities (DAIDS grade 3+; Table 1). Composite Outcome 2 included the same specific diagnoses of interest as Composite Outcome 1, in addition to diagnoses of gastrointestinal symptoms (hyperlactatemia; nausea; vomiting; abdominal pain), and moderate/severe laboratory abnormalities (DAIDS grade 2+; Table 1). An outcome was considered present at the first incident event listed during follow-up.

Statistical analysis

The 12-month baseline period preceding 3TC initiation was used to describe demographic and clinical characteristics; medians with interquartile ranges (IQR) and proportions were used for continuous and categorical variables, respectively. Statistical comparisons by 3TC total daily dose (150 versus 300 mg) were performed using Pearson's chi-square for categorical variables and

Table 1. Composite outcomes definitions.

	Composite Outcome 1	Composite Outcome 2
Diagnoses	Lactic acidosis; paresthesia; peripheral neuropathy; pancreatitis; rhabdomyolysis; anemia; neutropenia; thrombocytopenia; nausea	
Laboratory abnormalities[a]		
Neutrophils	<600 cells/μl	<800 cells/μl
Hemoglobin	<8.5 g/dl in women; <9 g/dl in men	<9.5 g/dl in women; <10 g/dl in men
Platelets	<50 000 cells/μl	<100 000 cells/μl
Alanine aminotransferase	≥5 × ULN	≥2.5 × ULN
Aspartate transaminase	≥5 × ULN	≥2.5 × ULN
Total bilirubin	>2.6 × ULN	>1.6 × ULN
Lactate	>2.0 × ULN + pH <7.3	>2.0 × ULN + pH ≥7.3
Creatinine kinase	>10 × ULN	>6 × ULN
Red blood count[b]	Not included	$<4.10 \times 10^{12}$/l in women; $<4.52 \times 10^{12}$/l in men
Mean corpuscular volume[b]	Not included	>96
Gastrointestinal symptoms diagnosis	Not included	Hyperlactatemia; nausea; vomiting; abdominal pain

ULN, upper limit of normal.
[a]Composite Outcome 1: Division of AIDS (DAIDS) grade 3+ (i.e. severe abnormality); composite outcome 2: DAIDS grade 2+ (i.e. moderate or severe abnormality).
[b]Not graded by DAIDS.

Wilcoxon rank-sum test for continuous variables. The prevalence of Composite 1 and 2 events within 12 months before 3TC initiation was described overall and by type of event (Composite 1: diagnoses, severe laboratory abnormalities; Composite 2: diagnoses, moderate/severe laboratory abnormalities, gastrointestinal symptoms).

Analyses of incident Composite Outcomes 1 or 2 were performed in a study population further restricted to PWH without any of the respective prevalent events. Univariate Poisson regression was employed to estimate incidence rates of each composite outcome among PWH. To evaluate the association between 3TC total daily dose and incidence of the composite outcomes, multivariate Poisson regression was employed to estimate incident rate ratios (IRR); the models were adjusted for drug/alcohol abuse and baseline hemoglobin level. Parsimony in the covariate selection was imposed by small sample sizes. Analyses of incident Composite Outcome 1 were repeated in a sensitivity analysis, such that person-time was not censored when eGFR decreased below 30 or increased above 49 ml/min per 1.73 m^2.

Results

A total of 539 PWH in the OPERA cohort database met all eligibility criteria and were included in the study population, representing 0.5% of all PWH in OPERA. Of those, 103 (19%) initiated 3TC with an adjusted daily dose of 150 mg and 436 (81%) initiated 3TC with a full daily dose of 300 mg. Compared with individuals on the full dose, those on the adjusted dose were more likely to be women and African American (Table 2). They were also generally sicker, with higher viral loads, higher veterans aging cohort study mortality (VACS) index values [14] and lower eGFRs; they also had a higher likelihood of several comorbid conditions including diabetes and substance abuse (Table 2).

Composite Outcome 1: diagnoses and severe laboratory abnormalities

Diagnoses and severe lab abnormalities included in Composite Outcome 1 were common within the 12 months prior to 3TC initiation but did not differ between the two groups (35% among adjusted dose and 28% among full dose recipients; $P = 0.19$; Table 3). The most common diagnoses were anemia (19% for 150 mg and 13% for 300 mg) and peripheral neuropathy (6% for both). Individuals initiating 3TC at the adjusted dose were more likely to have preexisting severe lab abnormalities than those initiating a full dose ($P < 0.01$). The most common severe lab abnormality, low hemoglobin, differed by group (17% for 150 mg and 6% for 300 mg); all other severe lab abnormalities were reported by less than 5% of the study population and did not differ by group (Table 3).

Out of 67 PWH initiating 150 mg of 3TC without any prevalent diagnoses and severe lab abnormalities from Composite Outcome 1, only five experienced Composite Outcome 1 over 40 person-years of follow-up (incidence rate: 12.6 per 100 person-years, 95% CI: 5.2–30.2; Fig. 1). Out of 312 PWH initiating 300 mg of 3TC without pre-existing Composite Outcome 1 conditions, 29 experienced conditions from Composite Outcome 1 over 148 person-years of follow-up (incidence rate: 19.6 per 100 person-years, 95% CI: 13.6–28.2; Fig. 1). After adjusting for drug/alcohol abuse and baseline hemoglobin, there was no statistically significant difference in the incidence rate of Composite Outcome 1 with the full dose compared with the adjusted dose (IRR: 1.51, 95% CI: 0.59–3.92; Fig. 1).

Table 2. Baseline demographic and clinical characteristics of people with HIV with estimated glomerular filtration rate at least 30 and 49 ml/min per 1.73 m^2 or less at 3TC initiation.

Characteristic	3TC daily dose: 150 mg ($N = 103$)	3TC daily dose: 300 mg ($N = 436$)
Age (years), median (IQR)	54 (48–61)	54 (47–61)
Female sex [*n* (%)]	40 (39)	119 (27)
African American race [*n* (%)]	67 (65)	202 (46)
Hispanic ethnicity [*n* (%)]	11 (11)	55 (13)
Log10 HIV viral load, median (IQR)	2.1 (1.3–4.5)	1.7 (1.3–2.9)
Calendar year of HIV diagnosis, median (IQR)	2004 (1996–2009)	2004 (1996–2010)
Calendar year at baseline (3TC initiation), median (IQR)	2013 (2011–2015)	2014 (2011–2015)
Previous ART experience		
ART-naive [*n* (%)]	12 (12)	49 (11)
ART-experienced [*n* (%)]	88 (85)	358 (82)
No known experience, no HIV VL [*n* (%)]	3 (3)	29 (7)
Prior emtricitabine exposure [*n* (%)]	53 (52)	225 (52)
Prior tenofovir disoproxil fumarate exposure [*n* (%)]	51 (50)	227 (52)
Co-prescription of antiretrovirals[a]		
Requiring dose adjustment[b] [*n* (%)]	41 (40)	154 (35)
Known to inhibit tubular secretion of creatinine[c] [*n* (%)]	74 (72)	332 (76)
eGFR (ml/min per 1.73 m^2)		
Median (IQR)	40 (36–46)	43 (38–47)
>40 to ≤49 [*n* (%)]	51 (50)	288 (66)
≥30 to ≤40 [*n* (%)]	52 (51)	148 (34)
Low hemoglobin (<8.5 g/dl in women or <9 g/dl in men) [*n* (%)]	17 (17)	28 (6)
VACS mortality index,[14] median (IQR)	47 (32–70)	36 (24–54)
Comorbid conditions		
Diabetes (diagnosis, prescription or labs) [*n* (%)]	33 (32)	98 (23)
Hypertension [*n* (%)]	68 (66)	246 (56)
Cardiovascular disease [*n* (%)]	30 (29)	92 (21)
Hepatitis B [*n* (%)]	11 (11)	27 (6)
Hepatitis C [*n* (%)]	20 (19)	74 (17)
Liver diseases (other than viral hepatitis) [*n* (%)]	9 (9)	44 (10)
Substance abuse (drug and alcohol) [*n* (%)]	28 (27)	79 (18)

3TC, lamivudine; ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PWH, people with HIV; VACS, Veterans Aging Cohort Study; VL, viral load.
[a]Categories are not mutually exclusive
[b]There were no differences between the 3TC daily dose groups with respect to tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC), atazanavir (ATV), ritonavir-boosted lopinavir (LPV/r), stavudine (d4T), didanosine (ddI), zalcitabine (ddC), zidovudine/azidothymidine, or maraviroc use.
[c]There were no differences between groups with respect to cobicistat, rilpivirine (RPV) or darunavir (DRV); dolutegravir (DTG) was prescribed more often (39%; $P = 0.0028$) and ritonavir was prescribed less often (38%; $P = 0.0100$) among PWH receiving a 3TC daily dose of 300 mg than among PWH prescribed a 3TC daily dose of 150 mg (23 and 52%, respectively).

Table 3. Prevalence of Composite 1 and Composite 2 outcomes within 12 months before or at 3TC initiation.

Outcome [*n* (%)]	3TC daily dose: 150 mg ($N = 103$)	3TC daily dose: 300 mg ($N = 436$)	*P* value
Composite Outcome 1[a]	36 (35)	124 (28)	0.19
Diagnoses of interest[b]	27 (26)	92 (21)	0.26
Severe laboratory abnormalities (DAIDS grade 3+)[c]	24 (23)	57 (13)	0.01
Composite Outcome 2[a]	79 (77)	351 (81)	0.39
Diagnoses of interest[d]	27 (26)	90 (21)	0.22
Moderate/severe laboratory abnormalities (DAIDS grade 2+)[e]	77 (75)	333 (76)	0.73
Diagnoses of gastrointestinal symptoms[f]	12 (12)	22 (5)	0.01

3TC, lamivudine; DAIDS, Division of AIDS (within the US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases).
[a]Sub-categories are not mutually exclusive.
[b]Lactic acidosis; paraesthesia; peripheral neuropathy; pancreatitis; rhabdomyolysis; anemia; neutropenia; thrombocytopenia; or nausea within 3 months of baseline.
[c]Neutrophils less than 600 cells/μl; hemoglobin (<8.5 g/dl in women; <9 g/dl in men); platelets less than 50 000 cells/μl ; ALT at least 5 × ULN; AST at least 5 × ULN; total bilirubin greater than 2.6 × ULN; lactate greater than 2.0 × ULN + pH less than 7.3; or creatinine kinase greater than 10 × ULN.
[d]Lactic acidosis; paraesthesia; peripheral neuropathy; pancreatitis; rhabdomyolysis; anemia; neutropenia; or thrombocytopenia.
[e]Neutrophils less than 800 cells/μl; hemoglobin (<9.5 g/dl in women; <10 g/dl in men); platelets <100 000 cells/μl; ALT at least 2.5 × ULN; AST ≥2.5 × ULN; total bilirubin greater than 1.6 × ULN; lactate greater than 2.0 × ULN with pH at least 7.3; creatinine kinase greater than 6 × ULN; red blood count (RBC, not graded by DAIDS: $<4.52 \times 10^{12}$/l in adult men, $<4.10 \times 10^{12}$/l in adult women); or mean corpuscular volume (MCV) greater than 96 (not graded by DAIDS).
[f]Hyperlactatemia; nausea; vomiting; or abdominal pain.

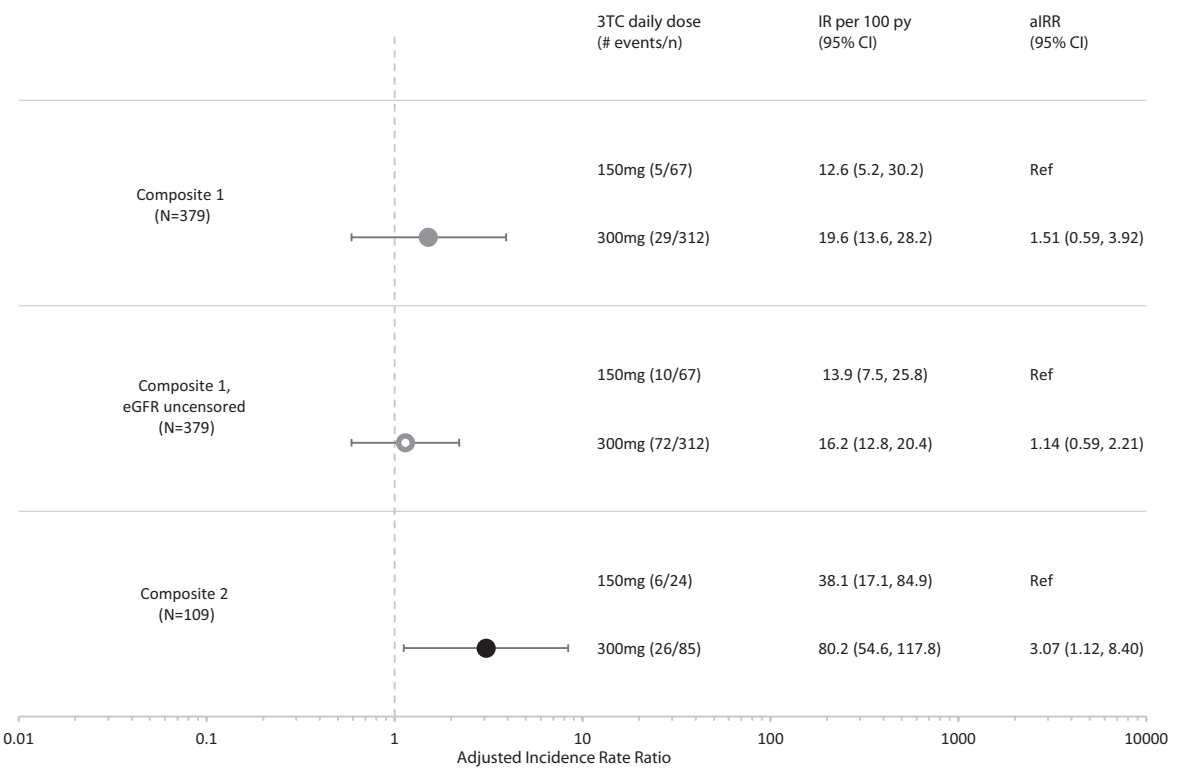

Fig. 1. Adjusted incidence rate ratio[a] for the association between 3TC daily dose (300 vs. 150 mg) and composite outcomes[b] among people with HIV with kidney impairment. 3TC, lamivudine; aIRR, adjusted incidence rate ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; IR, incidence rate; *n*, number; PWH, people with HIV; Ref, reference group. [a]Adjusted incidence rate ratios from a Poisson regression adjusted for drug/alcohol abuse and baseline hemoglobin level. [b]Composite 1 includes select diagnoses (lactic acidosis, paresthesia, peripheral neuropathy, pancreatitis, rhabdomyolysis, anemia, neutropenia, thrombocytopenia, nausea) and/or grade 3–4 laboratory abnormalities (neutrophils, hemoglobin, platelets, ALT, AST, total bilirubin, lactate + pH, creatinine); for eGFR uncensored, person-time is not censored at the first eGFR greater than 49 ml/min per 1.73 m^2 or less than 30 ml/min per 1.73 m^2. Composite Outcome 2 includes select diagnoses (same as Composite 1), and/or grade 2-4 laboratory abnormalities (same as Composite 1), and/or gastrointestinal symptoms (hyperlactatemia, nausea, vomiting, abdominal pain).

Among those without pre-existing Composite Outcome 1, there was no difference detected between groups in the proportion of PWH who discontinued 3TC (150 mg: 24%, 300 mg: 18%) or changed their 3TC dose (150 mg: 10%, 300 mg: 8%). The most common reasons for censoring were changes in eGFR to more than 49 ml/min per 1.73 m^2 or less than 30 ml/min per 1.73 m^2 (Table 4).

In a sensitivity analysis that did not censor person-time at the first out-of-range eGFR, there was no difference in the incidence of Composite Outcome 1 between the adjusted dose (incidence rate: 13.9 per 100 person-years, 95% CI: 7.5–25.8) and full dose groups (incidence rate: 16.2 per 100 person-years, 95% CI: 12.8–20.4) (Fig. 1). After adjusting for drug/alcohol abuse and baseline hemoglobin, there was no statistically significant difference in the incidence of the Composite Outcome 1 with the full dose compared with the adjusted dose (IRR: 1.14, 95% CI: 0.59–2.21; Fig. 1); results were attenuated toward the null from the main analysis.

Table 4. Censoring events during follow-up.

Censoring event [*n* (%)]	PWH without pre-existing Composite 1			PWH without pre-existing Composite 2		
	3TC daily dose: 150 mg (*n* = 67)	3TC daily dose: 300 mg (*n* = 312)	*P* value	3TC daily dose: 150 mg (*n* = 24)	3TC daily dose: 300 mg (*n* = 85)	*P* value
eGFR >49 ml/min per 1.73 m^2	31 (46)	176 (56)	0.10	7 (29)	47 (55)	0.03
3TC discontinuation	16 (24)	57 (18)	0.46	12 (50)	15 (18)	<0.01
eGFR <30 ml/min per 1.73m^2	9 (13)	35 (11)	0.60	2 (8)	11 (13)	0.59
Change in 3TC dose	7 (10)	24 (8)	0.46	2 (8)	7 (8)	0.95
Loss-to-follow-up/death/study end	4 (6)	20 (6)	0.94	1 (4)	6 (7)	0.68

3TC, lamivudine; eGFR, estimated glomerular filtration rate; PWH, people with HIV.

Composite Outcome 2: diagnoses, gastrointestinal symptoms, and moderate/severe laboratory abnormalities

Diagnoses, moderate/severe lab abnormalities, and gastrointestinal symptoms included in Composite Outcome 2 were very common within the 12 months prior to 3TC initiation among PWH initiating 150 mg (77%) and 300 mg (81%), with no difference between the groups ($P = 0.39$). There was no difference in the prevalence of preexisting moderate/severe lab abnormalities ($P = 0.73$) between PWH initiating the adjusted or full daily dose of 3TC (Table 3). Only moderate/severe reduction in hemoglobin level was significantly more prevalent among PWH who initiated the adjusted dose of 3TC compared with the full dose (25% for 150 mg and 12% for 300 mg; $P < 0.01$); all other individual moderate/severe lab abnormalities were similar between the two groups. Diagnoses of gastrointestinal symptoms (i.e. hyperlactatemia; nausea; vomiting; abdominal pain) were also significantly more common prior to 3TC initiation among PWH receiving the adjusted dose than the full dose of 3TC ($P = 0.01$), primarily because of the prevalence of abdominal pain within 3 months of 3TC initiation (Table 3).

After excluding all individuals with preexisting diagnoses, moderate/severe laboratory abnormalities, or gastrointestinal symptoms included in Composite Outcome 2, 24 (23%) individuals remained in the 150 mg group and 85 (20%) remained in the 300 mg group; no statistically significant difference was detected in the incidence of Composite Outcome 2 between the two groups over 16 person-years of follow-up on 150 mg (incidence rate: 38.1 per 100 person-years, 95% CI: 17.1–84.9) and 32 person-years of follow-up on 300 mg (incidence rate: 80.2 per 100 person-years, 95% CI: 54.6–117.8 for 300 mg) (Fig. 1). After adjusting for baseline substance abuse and hemoglobin, the full 3TC dose was associated with an incidence rate of Composite Outcome 2 three times that of the adjusted dose group (IRR: 3.07, 95% CI: 1.12–8.40; Fig. 1).

Among PWH without pre-existing Composite 2, 3TC discontinuation occurred more frequently among those on the adjusted dose (50%) than those on the full dose (18%, $P < 0.1$). However, no difference was detected between groups in the frequency of 3TC dose changes (both 8%, Table 4).

Discussion

This study aimed to assess the risk of adverse diagnoses and laboratory abnormalities associated with the total daily dose of 3TC initiated by PWH with a baseline eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less. There was no statistically significant difference in the incidence of Composite Outcome 1 (i.e. specific diagnoses and severe lab abnormalities) by 3TC dose; findings were robust in a sensitivity analysis including person-time outside of the defined eGFR range. The risk of Composite Outcome 2 (additionally including gastrointestinal symptoms and moderate lab abnormalities) was increased among individuals who initiated 300 mg 3TC compared with 150 mg 3TC, possibly driven by gastrointestinal symptoms and moderate lab abnormalities.

This study included a total of 539 PWH, with 379 individuals without preexisting diagnoses and severe lab abnormalities, and 109 without preexisting diagnoses, moderate/severe lab abnormalities or gastrointestinal symptoms. It is one of a few studies to provide real-world evidence on the impact of 3TC dose adjustment for PWH who have an eGFR below 50 ml/min per 1.73 m^2 and is relatively consistent with prior studies, which enrolled a substantially smaller number of participants. In a cross-sectional study of 34 PWH with varying degrees of kidney impairment (i.e. CrCl values of >50, 30–49, 15–29, or <15 ml/min), 3TC was well tolerated and no adverse effects were reported, regardless of dose (100 to 300 mg daily) [15]. A case series of six PWH on chronic hemodialysis also evaluated 3TC dose. All PWH had previously used 3TC as part of a multitablet regimen prior to switching to a single-tablet regimen that included 3TC, abacavir, and dolutegravir; three of the PWH were on a full dose (300 mg) of 3TC and three received an adjusted dose (150 mg). Only one PWH (on 300 mg) self-reported an adverse event (nausea), over follow-up time that ranged from 5 to 18 months among the six PWH; the nausea resolved without drug discontinuation [16].

In the OPERA cohort, dose-adjusted (i.e. 150 mg) 3TC was more frequently prescribed to women, African Americans, and sicker PWH (higher viral load, lower eGFR, higher veterans aging cohort study index, higher likelihood of diabetes and substance abuse, low hemoglobin). Of note, prevalent gastrointestinal symptom diagnoses were more common in the overall population among PWH prescribed the adjusted dose than among those prescribed the full dose. Moreover, in the population without preexisting conditions included in Composite Outcome 2, those on the full 3TC dose were more likely to experience an improvement in eGFR to levels greater than 49 ml min per 1.73 m^2. These data suggest that prescribing physicians weighed the risks of prescribing a full dose (300 mg), including potential unintended events, against the potentially lower adherence [17] and effectiveness of the adjusted dose (150 mg) and channeled the sicker, most frail patients to the adjusted dose only available in multitablet regimens.

These findings could have an important impact for many, as single-tablet regimens are often preferred, and a fixed-dose of dolutegravir/tenofovir disoproxil fumarate/3TC

is being rolled out in low-income and middle-income countries worldwide [18]. One of the major strengths of this study is its applicability to PWH in the United States. The OPERA cohort database at the time of this study included routine clinical data from the EHR systems of 85 clinics across 19 states and 1 United States territory; the 103 369 PWH in the OPERA cohort represent approximately 9% of PWH in the United States and dependent areas [19]. The use of EHR in this large cohort allowed for access to extensive patient, clinical, and laboratory information that is reflective of real-world clinical care in the United States, where the 3TC dose-adjustment recommendation is not always followed among PWH with creatinine clearance CrCl less than 50 ml/min. The large OPERA cohort of over 100 000 PWH provided a unique opportunity to evaluate 3TC dosing among over 500 PWH with eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less who were first prescribed 3TC during the study period. Despite reduced sample sizes, the study's finding of no statistically significant difference between doses in terms of incident Composite Outcome 1 remained robust in sensitivity analysis; by not censoring at the first out-of-range eGFR, the total follow-up increased from 259 to 920 person-years and the median duration of follow-up increased from 3 to 13 months in the overall study population.

This study is not without limitations. First, of the over 23 000 PWH in the OPERA database who had initiated 3TC (150 or 300 mg) for the first time between 17 November 1995 and 31 December 2018, only 539 (2%) had eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less and were eligible for this study; only 19% of those eligible PWH received an adjusted daily dose of 150 mg. In addition, many of the elements that constituted the composite outcomes (e.g. anemia, low hemoglobin) were present prior to 3TC initiation, limiting the number of PWH for whom incidence of the outcomes could be assessed after 3TC initiation. Therefore, the study's results may not be generalizable to all PWH with prevalent diagnoses and lab abnormalities. Moreover, small sample sizes and few events resulted in wide confidence intervals, and thus, to uncertainty around the study findings. These reduced sample sizes also required models to remain parsimonious and residual confounding is thus possible. However, results were robust to sensitivity analyses varying the adjustment set (data not shown). Second, Composite Outcome 2 included gastrointestinal symptoms in addition to specific diagnoses and moderate/severe lab abnormalities. As these gastrointestinal symptoms were identified through diagnoses only, more severe symptoms warranting documentation as a diagnosis in the EHR were more likely to be captured than milder symptoms noted only in the review of systems. In addition, most of these gastrointestinal symptoms were not attributed to 3TC use by the caregiver in the medical record during follow-up, resulting in uncertainty as to their association with the drug. Third, many diagnoses, lab abnormalities, and symptoms included in the composite outcomes were non-specific. Therefore, it is likely that some of them may have been unrelated to 3TC dosing but were rather associated with comorbid conditions. Fourth, symptoms, such as headache, fatigue, and malaise were not included as they were deemed too common and non-specific. However, such common symptoms are a major cause of dose adjustment and medication discontinuation. Finally, reasons for 3TC discontinuation were not detailed sufficiently in the EHRs to assess if they differed by 3TC dose. However, discontinuation and dose modification frequency did not differ significantly between dosing groups in the analysis of PWH without preexisting conditions included in Composite Outcome 1. In contrast, discontinuation of 3TC was more common with the adjusted than the full dose in the population used to assess incidence of Composite Outcome 2. This could have led to an overestimation of the risk associated with the full dose if 3TC was discontinued before events of interest were recorded in the EHR in the adjusted dose group only.

3TC is a well tolerated drug with a wide therapeutic index. Therefore, dose adjustment may be unnecessary among PWH with an eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less. Indeed, in this study, there was no statistically significant difference in the risk of severe events observed with the full compared with the adjusted 3TC dose. However, we observed a statistically significant increased risk of incident gastrointestinal symptoms and/or moderate lab abnormalities with the full compared with the adjusted 3TC dose among PWH with an eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less who were free of such diagnoses and lab abnormalities at baseline. Clinical judgement will be key in weighing the risks of unintended effects versus the benefits of fixed-dose combination regimens when considering 3TC dose adjustment in this population.

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L.B. conducted all the analyses. All authors have contributed to the interpretation of results, have critically reviewed and approved the manuscript, and have participated sufficiently in the work to take public responsibility for its content.

Conflicts of interest

K.M. has received research grants from Merck, Gilead Sciences, and Janssen; speaker honoraria from ViiV Healthcare, Merck, Gilead Sciences and Janssen; consultant fees from ViiV Healthcare, Gilead Sciences and Janssen; and advisory board participation of Epividian. L.B., J.S.F., and G.P.F. are employed by Epividian, Inc.; Epividian has been research funded by ViiV Healthcare, Merck & Co., Janssen Pharmaceutica, and Gilead Sciences. C.M.W. is a consultant for Epividian, Inc. V.V., A.R.T., M.S.S., and L.R. are employed by ViiV Healthcare and hold stocks and shares in GSK as part of their employment. R.H. has received research grants from Gilead, speaker honoraria and advisory boards from ViiV Healthcare, Merck, Gilead Sciences and Janssen, and advisory board participation of Epividian.

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