Metabolic and Liver Outcomes Through Week 48 Following Switch to Dolutegravir/Lamivudine in Older, ART-Experienced Adults: The Phase 3b EYEWITNESS Study

P154

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Key Takeaways

- **EYEWITNESS enrolled 205 adults aging with HIV, most with substantial multimorbidity and many at elevated cardiometabolic risk**
- **After switching from BIC/FTC/TAF to DTG/3TC, weight, body composition, lipid and glycemic measures, and blood pressure remained broadly stable through Week 48**
- **Among participants with baseline steatosis or fibrosis, most improved in CAP-defined steatosis grade or LSM-defined fibrosis stage, respectively, through Week 48**
- **Findings from EYEWITNESS expand the evidence base supporting DTG/3TC use in aging people with HIV, where metabolic and liver health are increasingly important considerations when optimizing ART**

Plain Language Summary

- As the population living with HIV ages, weight gain, fatty liver disease, high cholesterol, hypertension, and diabetes become more important considerations when choosing an HIV medicine, including when switching from one medicine to another
- This study assessed these health measures in adults aging with HIV, the majority of whom had several other health conditions, who switched from the 3-drug regimen bictegravir/emtricitabine/tenofovir alafenamide to the 2-drug regimen dolutegravir/lamivudine
- Weight, body fat, cholesterol, blood sugar, and blood pressure generally remained stable through 48 weeks. Most people who started the study with liver fat or scarring had an improvement after switching to dolutegravir/lamivudine

Introduction

- In people aging with HIV, rising prevalence of cardiometabolic disease and steatotic liver disease underscores the importance of understanding metabolic and liver outcomes with maintenance antiretroviral therapy (ART)[1-3]
- Weight and metabolic changes have been reported with integrase strand transfer inhibitor– and tenofovir alafenamide–based ART,[3,4] but metabolic and liver outcomes after treatment simplification are less understood, particularly in older adults with multimorbidity
- Switch to dolutegravir/lamivudine (DTG/3TC) was associated with less weight gain, lower odds of >5% weight gain, and lower frequency of liver steatosis vs switch to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in adults with virologic suppression through 96 weeks in the randomized PASO-DOBLE study[5-8]
- The EYEWITNESS study assessed changes in weight, body composition, hepatic steatosis and fibrosis, lipids, glycemic parameters, and blood pressure through Week 48 after switch from BIC/FTC/TAF to DTG/3TC in older adults with virologic suppression, the majority of whom had multimorbidity

Methods

- EYEWITNESS was a phase 3b, international, multi-center, single-arm study of older adults aged ≥50 years with virologic suppression (HIV-1 RNA <50 c/mL) on BIC/FTC/TAF for ≥6 months before screening who switched to DTG/3TC; enrollment targets were prespecified to recruit participants with cardiovascular risk, comorbidity burden, and other traditionally underrepresented populations
- This prespecified analysis focuses on metabolic and liver outcomes through Week 48; primary virologic efficacy outcomes will be reported separately
- Exploratory outcomes assessed changes from baseline to Week 48 for the following parameters:
  - Weight and body composition (dual-energy x-ray absorptiometry [DXA])
  - Hepatic steatosis (controlled attenuation parameter [CAP]) and fibrosis (liver stiffness measurement [LSM]) by transient elastography; an improvement or worsening was considered a change of ≥1 steatosis grade or fibrosis stage
  - Lipids, regardless of fasting status and use of lipid-lowering therapy
  - Insulin resistance (using homeostatic model assessment for insulin resistance [HOMA-IR])
  - Systolic and diastolic blood pressure
- Adverse events (AEs) of special interest included hypertension and diabetes mellitus

Results

Baseline Demographics and Characteristics

- 205 participants switched from BIC/FTC/TAF to DTG/3TC with a median (range) age of 61 (50, 83) years; 42% (87/205) were female sex at birth and 33% (68/205) identified as Black or African American
- Most of the study population had multimorbidity at baseline (67% had >3 comorbidities); many had elevated cardiometabolic risk (44% had a 10-year cardiovascular disease risk score of ≥20%); and 37% and 30% of participants, respectively, had a body mass index category of overweight and obesity (Table 1)

Table 1. Baseline Metabolic, Liver, and Comorbidity Characteristics of the Study Population

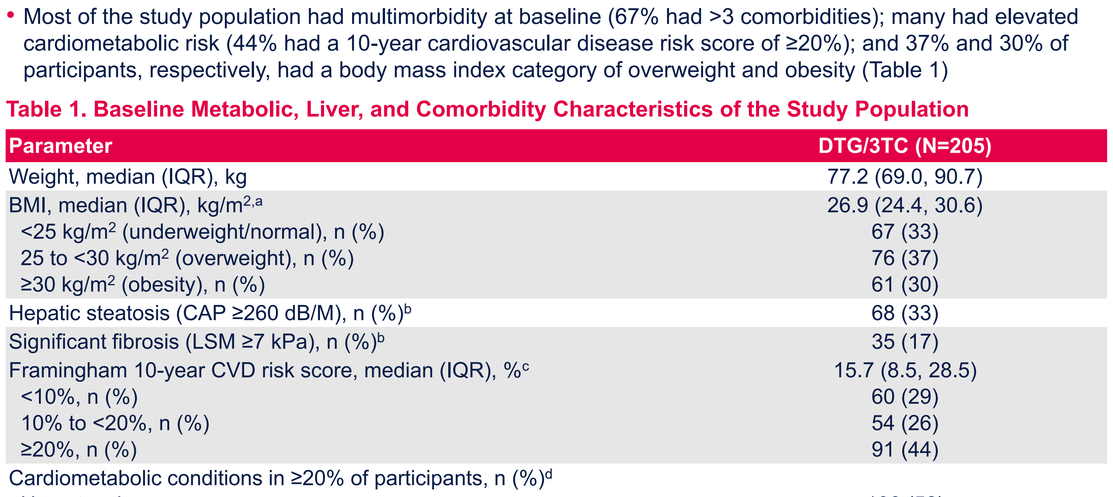
Parameter	DTG/3TC (N=205)
Weight, median (IQR), kg	77.2 (69.0, 90.7)
BMI, median (IQR), kg/m^2[,a]	26.9 (24.4, 30.6)
<25 kg/m^2 (underweight/normal), n (%)	67 (33)
25 to <30 kg/m^2 (overweight), n (%)	76 (37)
≥30 kg/m^2 (obesity), n (%)	61 (30)
Hepatic steatosis (CAP ≥260 dB/M), n (%)[b]	68 (33)
Significant fibrosis (LSM ≥7 kPa), n (%)[b]	35 (17)
Framingham 10-year CVD risk score, median (IQR), %[c]	15.7 (8.5, 28.5)
<10%, n (%)	60 (29)
10% to <20%, n (%)	54 (26)
≥20%, n (%)	91 (44)
Cardiometabolic conditions in ≥20% of participants, n (%)[d]	
Hypertension	106 (52)
Hyperlipidemia	56 (27)
Diabetes mellitus	45 (22)
Dyslipidemia	42 (20)
>3 comorbidities, n (%)	137 (67)
>5 non-ART concomitant medications, n (%)	85 (41)

BMI, body mass index; CVD, cardiovascular disease; IQR, interquartile range. [a]1 participant with missing data. [b]Assessed using transient elastography; categories are non-invasive estimates and do not reflect histologic grades. [c]Calculation not performed for participants who indicated current or past myocardial infarction (n=10); however, these participants were included in highest risk category. [d]Includes cardiac, vascular, and metabolism and nutrition disorders. Additional conditions in ≥5% of participants included vitamin D deficiency (17% [n=35]), hypercholesterolemia (16% [n=32]), obesity (11% [n=23]), impaired glucose tolerance (7% [n=15]), coronary artery disease (5% [n=11]), and hepatic steatosis (5% [n=11]).

Weight Change and Body Composition

- Weight was stable through Week 48 (median change, -0.2 kg [interquartile range, -2.7, 2.2]) after switching from BIC/FTC/TAF to DTG/3TC (Figure 1A)
- Weight changes of >10% were infrequent through Week 48: 2% (4/179) of participants had >10% weight gain and 2% (4/179) had >10% weight loss (Figure 1B)

Figure 1. (A) Median Change From Baseline in Weight and (B) Proportions of Participants With >5% or >10% Weight Change at Weeks 24 and 48



Dashed line in panel A indicates baseline weight. BL, baseline; IQR, interquartile range.

- Total fat, trunk and limb fat, lean mass, and visceral adipose tissue remained stable, with minimal changes through Week 48 observed using DXA (Table 2)

Table 2. DXA Measures of Fat and Lean Mass Through Week 48

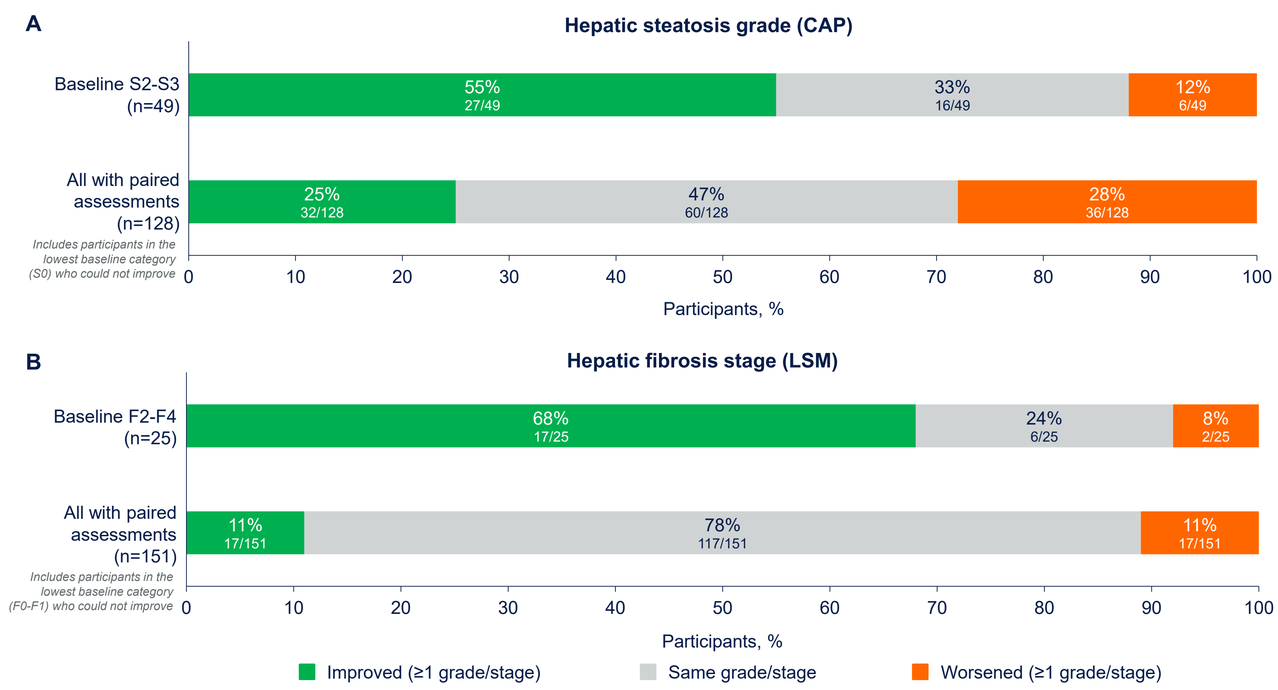
Parameter	Baseline, mean (SD)	Change from baseline, mean (SD)	n[a]
Total fat, kg	27.2 (9.8)	+0.2 (2.7)	132
Regional fat (trunk and limbs), kg	26.1 (9.7)	+0.2 (2.6)	132
Total lean mass, kg	48.8 (11.2)	-0.1 (1.8)	132
Regional lean mass (trunk and limbs), kg	45.5 (10.8)	-0.1 (1.7)	132
Estimated visceral adipose tissue volume, cm^3[,b]	1099.2 (753.7)	-3.6 (188.2)	127

[a]Indicates participants with change from baseline data at Week 48. Baseline sample sizes were available for 173 participants for all parameters except for estimated visceral adipose tissue volume (n=167). [b]DXA does not directly discriminate visceral from subcutaneous fat; thus, we used a score to calculate DXA-estimated visceral adipose tissue volume.

Hepatic Steatosis and Fibrosis

- Among participants with baseline steatosis (S2-S3), 55% (27/49) improved by ≥1 CAP-defined steatosis grade, whereas 33% (16/49) remained in the same grade and 12% (6/49) worsened through Week 48 (Figure 2A)
- Among participants with baseline fibrosis (F2-F4), 68% (17/25) improved by ≥1 LSM-defined fibrosis stage, whereas 24% (6/25) remained in the same stage and 8% (2/25) worsened through Week 48 (Figure 2B)

Figure 2. Proportions of Participants With Improvement, No Change, or Worsening in (A) CAP-Defined Steatosis Grade and (B) LSM-Defined Fibrosis Stage From Baseline to Week 48



Data from participants with paired baseline and Week 48 transient elastography assessments. Improved or worsened was defined as a change of ≥1 CAP-defined steatosis grade or LSM-defined fibrosis stage. Hepatic steatosis grades S2-S3 defined as CAP score ≥260 dB/m; hepatic fibrosis stages F2-F4 defined as LSM score ≥7 kPa. CAP- and LSM-defined categories are non-invasive estimates and do not reflect histologic grade or stage.

Lipids

- Lipids generally remained stable through Week 48, with small decreases in triglycerides and total cholesterol (Table 3)

Table 3. Fasting and Non-Fasting Lipids Through Week 48[a]

Parameter	Baseline, mean (SD)	Change from baseline, mean (SD)	n[b]
Triglycerides, mmol/L	1.42 (0.79)	-0.15 (0.64)	178
Total cholesterol, mmol/L	4.69 (1.15)	-0.02 (0.94)	178
LDL cholesterol, mmol/L	2.67 (0.97)	+0.02 (0.81)	177
HDL cholesterol, mmol/L	1.38 (0.41)	+0.02 (0.23)	178
Total cholesterol/HDL cholesterol ratio	3.59 (1.10)	-0.07 (0.85)	178

HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Lipids were assessed regardless of fasting status and use of lipid-lowering therapy. [b]Indicates participants with change from baseline data at Week 48. Baseline sample sizes were complete (N=205) for all parameters except for LDL cholesterol (n=204).

Insulin Resistance, Glycemic Parameters, and Blood Pressure

- Minimal changes in HOMA-IR, fasting glucose, and hemoglobin A1c were observed through Week 48; a slight decrease in blood pressure was observed (Table 4)

Table 4. Insulin Resistance, Glycemic Parameters, and Blood Pressure Through Week 48

Parameter	Baseline	Change from baseline	n[a]
HOMA-IR, geometric mean ratio (CV%)[b]	2.39 (91.77)	0.97 (90.08)	112
Fasting glucose, median (IQR), mmol/L	5.27 (4.83, 5.94)	-0.05 (-0.55, 0.50)	157
HbA1c, median (IQR), %	5.75 (5.50, 6.20)	0.00 (-0.20, 0.10)	155
Systolic blood pressure, mean (SD), mm Hg	132.3 (16.8)	-2.2 (17.3)	180
Diastolic blood pressure, mean (SD), mm Hg	80.9 (9.4)	-1.4 (9.9)	180

HbA1c, hemoglobin A1c; IQR, interquartile range. [a]Indicates participants with change from baseline data at Week 48. Baseline sample sizes were as follows: HOMA-IR, n=133; fasting glucose, n=189; HbA1c, n=188; systolic and diastolic blood pressure, N=205. [b]Based on $\log_e$-transformed data; baseline is the geometric mean and change from baseline is the geometric mean ratio. HOMA-IR summarized using fasting data only; participants with diabetes or who had taken anti-diabetic medication through screening were excluded (n=54). A higher HOMA-IR value indicates increased insulin resistance; a value <2 is generally considered normal.

AEs of Hypertension and Diabetes Mellitus

- No AEs of hypertension or diabetes mellitus were serious, considered related to DTG/3TC, or led to withdrawal
  - AEs of hypertension occurred in 4 of 205 (2%) participants and diabetes mellitus in 6 of 205 (3%) participants; most of these participants had pre-existing disease (3 new diagnoses overall)

Conclusions

- In this single-arm study of older adults with virologic suppression, many of whom had multimorbidity or cardiometabolic risk, metabolic and liver parameters remained broadly stable through Week 48 after switching from BIC/FTC/TAF to DTG/3TC
- Most participants with paired assessments and baseline steatosis (S2-S3) or fibrosis (F2-F4) improved in CAP-defined steatosis grade or LSM-defined fibrosis stage, respectively, by Week 48
- These findings provide important context for treatment optimization with DTG/3TC in older people with HIV and multimorbidity, for whom metabolic and liver health are important clinical considerations

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