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Biktarvy® (BIC/FTC/TAF) Effect on Glucose or Insulin

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and changes in glucose or insulin levels.

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Summary

Background

Traditional risk factors contributing to the development of insulin resistance and diabetes mellitus include abdominal obesity, physical inactivity, genetics, and older age. HIV-associated diabetes risk factors include peripheral lipoatrophy, increased liver or muscle fat, decreased testosterone levels, HCV co-infection, and the use of select ARVs. Both types of risk factors contribute to a 2% to 14% prevalence of diabetes mellitus in PWH.[1,2]

Prospective Studies on the Effects of BIC/FTC/TAF on Glucose or Insulin Levels

In four phase 3 studies with ARV-naïve or VS participants, ≥2% experienced Grade 3 or 4 glycosuria and/or fasting hyperglycemia (BIC/FTC/TAF: 1–3%; comparators: 1–4%).[3-7] Treatment-emergent diabetes occurred in 1% to 2% of ARV-naïve participants, with no statistically significant differences in median fasting glucose changes between arms.[8]

A phase 3b study of switching to CAB + RPV vs continuing BIC/FTC/TAF found similar rates of metabolic syndrome and insulin resistance in both treatment arms at Month 12.[9,10]

In the EBONY study, VS participants who switched to BIC/FTC/TAF did not have statistically significant changes from baseline in mean blood glucose levels through Week 48.[11]

In the real-world SCOLTA study, there was an increase in mean blood glucose values among TE participants without diabetes and no statistically significant differences in mean blood glucose changes or new-onset diabetes rates between BIC and DTG groups.[12,13]

Retrospective Studies on the Effects of BIC/FTC/TAF on Glucose or Insulin Levels

In a real-world study of PWH who started or switched to BIC/FTC/TAF, 18.4% had prediabetes at baseline, of whom 8.1% developed diabetes. Among the 880 participants without prediabetes at baseline, 11.7% and 1.3% developed prediabetes and diabetes, respectively.[14]

An observational study in Taiwan showed a statistically significant increase in HbA1c from 5.31% at baseline of 0.12% at Week 96 in VS PWH after switching to BIC/FTC/TAF.[15]

In the METABIC study, among patients who switched to BIC/FTC/TAF, from baseline to Month 12, the increase in mean blood glucose levels and decrease in the mean TyG ratio were not statistically significant.[16]

Another observational analysis found that changes from baseline in insulin and HOMA-IR were similar between groups starting on BIC/FTC/TAF or DTG/ABC/3TC.[17]

Prospective Studies on the Effects of BIC/FTC/TAF on Glucose or Insulin Levels

Gilead Clinical Data

In four phase 3 studies that included ARV-naïve or VS participants, Grade 3 or 4 glycosuria and/or fasting hyperglycemia were reported in ≥2% of participants overall (BIC/FTC/TAF, 1–3%; comparators, 1–4%).[3-7] Among ARV-naïve participants, treatment-emergent diabetes occurred in 1% to 2% of all participants through Week 144. The difference in median fasting glucose changes was not statistically significant between BIC/FTC/TAF and DTG/ABC/3TC (P=0.64) or DTG + FTC/TAF (P=0.96).[8]

SOLAR: Phase 3b, Noninferiority Study

A randomized, noninferiority study compared safety and efficacy outcomes between VS participants who switched to long-acting CAB + RPV regimen administered monthly or every 2 months (n=454) and those who continued daily BIC/FTC/TAF (n=227).[9,10] At baseline, in the long-acting CAB + RPV and BIC/FTC/TAF arms, baseline characteristics included the following: the overall median age was 37 years; 17% and 18%, respectively, were female; 69% and 70% were White; 38% and 34% were overweight; 21% and 23% were obese; 17% in each arm had metabolic syndrome; and 42% and 43% had insulin resistance.[9]
At Month 12, the rates of participants with metabolic syndrome or insulin resistance were similar between treatment arms among the overall study population and among females.[9,10]

EBONY: Single-Arm, Open-Label, Pilot Study[11]

The EBONY study evaluated the efficacy and tolerability of switching from EFV/FTC/TDF to BIC/FTC/TAF in VS participants (N=214). At baseline, the mean glucose level was 90 mg/dL, the median age was 53 years, 84.6% were male, 87.4% were White, and the mean BMI was 25.3 kg/m^2. Mean (SD) glucose changes from baseline were not statistically significant: Week 24, +0.7 (22) mg/dL (n=202; P=0.929); Week 48, +0.9 (20) mg/dL (n=178; P=0.534).

Real-World Data From SCOLTA

Participants enrolled in SCOLTA, a prospective, observational, multicenter project, were included in a study on the metabolic and hepatic safety of BIC/FTC/TAF in PWH. Participants who started or switched to BIC/FTC/TAF were HBV-negative, and had baseline and 6-month data were included in the analysis (N=539). The participants' mean age was 48 years, 74% were male, 87.9% were White, 16.1% were ARV-naïve, and the mean BMI was 25.4 kg/m^2. From baseline to 6 months, weight increased by 1.4 (95% CI: 0.4–2.2) kg among ARV-naïve participants, and the mean blood glucose increased by 2.2 (95% CI: 0.5–4) mg/dL among TE participants without diabetes.[12]

Participants who started on or switched to a BIC- or DTG-based ARV regimen were included in a separate cohort analysis that evaluated changes from baseline to Month 12 in blood

glucose levels (N=2272). Excluding 111 participants with diabetes at baseline, there was no difference in the change in mean blood glucose level between PWH receiving BIC (n=571) and those receiving DTG (n=1176, *P*=0.56). The difference in the changes in mean blood glucose levels between the TE (n=1265) and ARV-naïve (n=378) groups was not statistically significant (*P*=0.11). Mean blood glucose levels decreased in PWH with baseline blood glucose >100 mg/dL: -8 mg/dL in TE participants receiving BIC vs -5.4 mg/dL in those receiving DTG (*P*=0.33) and -12.9 mg/dL in ARV-naïve participants receiving BIC vs -22.1 mg/dL in those receiving DTG (*P*=0.06). There was no difference in the rate of new-onset diabetes between the BIC and DTG groups: 1.4% vs 1.2%, respectively (*P*=0.63).[13]

Retrospective Studies on the Effects of BIC/FTC/TAF on Glucose or Insulin Levels

Study of New-Onset Diabetes in PWH[14]

A real-world study described the prevalence and incidence of prediabetes and diabetes in PWH (N=1078) who started or switched to BIC/FTC/TAF from June 2018 to July 2021. At baseline, the median participant age was 48 years, 85% were male, and 33% were ARV-naïve.

Among participants with no prediabetes at baseline (n=880), 11.7% developed prediabetes and 1.3% developed diabetes. Sixteen participants with prediabetes at baseline (n=198) developed diabetes. The median time to diabetes development was 47.7 weeks with a maximum follow-up time of 113 weeks.

Observational Study in Taiwan[15]

A retrospective study evaluated changes in glycemic parameters over 96 weeks in VS PWH who switched to BIC/FTC/TAF between October 2019 and May 2021 (N=889). At baseline, the mean patient age was 43.7 years, 97.2% were male, 30.6% were overweight, 23.4% were obese, 8.5% had diabetes, and 15.9% had prediabetes.

At Week 96, among the 813 patients without diabetes at the time of switching, HbA1c increased by +0.12% from 5.31% at baseline (n=789; *P*<0.0001). The HOMA-IR index increased nonsignificantly by +0.15 from a value of 2.48 at baseline (n=375; *P*=0.6565). Among the 141 patients with prediabetes and 672 without prediabetes at baseline, 15.6% (22/141) and 1% (7/672) of those who switched from EVG/COBI/FTC/TAF developed diabetes, respectively.

METABIC: Observational Study[16]

The METABIC study included PWH who switched from a TDF- or TAF-sparing ARV regimen to BIC/FTC/TAF between January 2019 and May 2022 (N=211). Changes in glucose and insulin resistance (based on the TyG ratio) at 6 and 12 months were secondary endpoints. At baseline, the median patient age was 55.3 years, 80.1% were male, 88.5% were Caucasian, 32.9% were overweight, 11.8% were obese, and 14.2% had diabetes.

The mean (95% CI) change in glucose levels was +1.3 (-2.2 to +5) mg/dL from baseline to 6 months (*P*=1) in the 189 patients with available data and +1.9 (-1.9 to +5.7) mg/dL at 12 months (*P*=0.716) in 141 patients. The mean (95% CI) TyG ratio changed from a baseline value of 4.7 (4.7–4.7; n=206) to -0.07 (-0.11 to -0.02; *P*<0.001; n=188) at 6 months, and to -0.03 (-0.08 to 0.01; *P*=0.229; n=139) at 12 months.

Observational Cohort Analysis[17]

A retrospective study evaluated the metabolic effects of treatment with BIC/FTC/TAF (n=73) or DTG/ABC/3TC (n=68) in ARV-naïve PWH. At baseline, mean age, proportion of males, proportion of White participants, mean BMI, mean glucose, mean insulin, and mean HOMA-IR index were similar between groups.

At Month 12, there were no statistically significant differences in mean change in glucose (+7.3 mg/dL vs +6.5 mg/dL; *P*=0.447), insulin levels (+4.2 mIU/L vs +3.8 mIU/L; *P*=0.195), or HOMA-IR indices (+0.71 vs +0.65; *P*=0.094) between the BIC/FTC/TAF and DTG/ABC/3TC arms, respectively. The increase in the number of individuals who had a HOMA-IR index >2.5 at Month 12 was not significantly different between treatment arms (*P*>0.05 for each arm).

Case Reports

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. Additionally, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include their retrospective design and publication bias.[18]

Three case reports describe adult patients with multiple comorbidities who initiated BIC/FTC/TAF and within 3 weeks to 4 months experienced increases in blood glucose levels and associated symptoms that required medical attention. Within 2 to 8 months of ARV treatment modification, 2/3 patients' HbA1c returned to baseline or within normal limits.[19]

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Abbreviations

3TC=lamivudine
ABC=abacavir
ARV=antiretroviral
CAB=cabotegravir
COBI=cobicistat
DTG=dolutegravir
EFV=efavirenz
EVG=elvitegravir
HOMA-IR=homeostatic model assessment of insulin resistance
INSTI=integrase strand-transfer inhibitor
PWH=people with HIV
RPV=rilpivirine
SCOLTA= Surveillance Cohort Long-Term Toxicity Antiretrovirals
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TyG=triglyceride-to-glucose
VS=virologically suppressed

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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