# Phase 4 DEFINE Switch Study to Manage InSTI-related Weight Gain: Metabolic and Biomarker Analysis

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## Introduction

- InSTI-based ARV therapies have been associated with greater weight gain compared to NNRTI or boosted PI regimens, and these weight effects disproportionately impact Black and Hispanic individuals and women living with HIV-1[1-5]
- The underlying mechanisms of InSTI-related weight gain and the potential impact of switching ARV classes on weight gain are unclear and under investigation
- The 48-week DEFINE trial is the first prospective, randomized trial designed to investigate the impact of switching from an InSTI-based regimen to a PI-based regimen to mitigate or reverse InSTI-related weight gain
- The previously reported DEFINE primary analysis showed no significant difference in the least squares mean percent change in body weight from baseline to Week 24 between individuals who switched to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) and those who continued their InSTI + TAF/FTC regimen (0.63 [95% CI: −0.44, 1.70] and −0.24 [95% CI: −1.35, 0.87], respectively; $p = 0.2394$)[7,8]
- Analyses of metabolic and biomarker data at baseline and Week 24 from DEFINE are reported here

## Objective

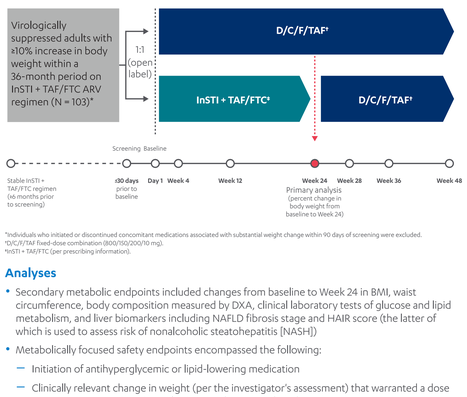
- To evaluate metabolic parameters and biomarkers at baseline and 24 weeks after switching to D/C/F/TAF or continuing InSTI + TAF/FTC among individuals with InSTI-related weight gain

## Methods

### Study Design

- DEFINE (ClinicalTrials.gov Identifier: NCT04442737) is a randomized, prospective, 48-week, active-controlled, open-label, multicenter, phase 4 trial being conducted in the United States that assesses a switch to D/C/F/TAF versus continued InSTI + TAF/FTC among individuals who had ≥10% weight gain while on an InSTI + TAF/FTC ARV regimen (**Figure 1**)
- Participants were maintained on a TAF/FTC regimen pre- and post-randomization to isolate the impact of an InSTI to PI switch
- Strategies were implemented to ensure a diverse study population representative of women and Black individuals living with HIV-1[9]

**Figure 1.** DEFINE study design




*Individuals who initiated or discontinued concomitant medications associated with substantial weight change within 90 days of screening were excluded.
†D/C/F/TAF fixed-dose combination (800/150/200/10 mg).
‡InSTI + TAF/FTC (per prescribing information).

### Analyses

- Secondary metabolic endpoints included changes from baseline to Week 24 in BMI, waist circumference, body composition measured by DXA, clinical laboratory tests of glucose and lipid metabolism, and liver biomarkers including NAFLD fibrosis stage and HAIR score (the latter of which is used to assess risk of nonalcoholic steatohepatitis [NASH])
- Metabolically focused safety endpoints encompassed the following:
  - Initiation of antihyperglycemic or lipid-lowering medication
  - Clinically relevant change in weight (per the investigator's assessment) that warranted a dose reduction or discontinuation of antihyperglycemic or lipid-lowering medication
  - Grade 2 to 4 hyperglycemia or lipid abnormality AE of interest
- DXA data were assessed in a completer analysis set of participants who had completed study assessments at both baseline and Week 24
- All other outcomes were assessed in the ITT set of participants who had been randomized and received ≥1 dose of the study drug
- Metabolic and biomarker data are reported using descriptive statistics

## Results

### Study Population

- A total of 103 adults were randomized to switch to D/C/F/TAF (n = 53) or to continue InSTI + TAF/FTC (n = 50); overall, 30% were female, 61% were Black/African American, and the median BMI was 32.7 kg/m$^2$ (**Table 1**)
- Greater than 90% of participants remained enrolled in the study at Week 24

**Table 1.** Baseline demographics and characteristics (ITT set)

| Parameter | Treatment arm | | Total (N = 103) |
|---|---|---|---|
| | D/C/F/TAF (n = 53) | InSTI + TAF/FTC (n = 50) | |
| Age, y, median (range) | 42.0 (22, 73) | 49.0 (22, 69) | 45.0 (22, 73) |
| Female sex, n (%) | 16 (30) | 15 (30) | 31 (30) |
| Race, n (%)* | | | |
| Black/African American | 33 (62) | 30 (60) | 63 (61) |
| White | 19 (36) | 19 (38) | 38 (37) |
| Hispanic or Latino ethnicity, n (%) | 6 (11) | 10 (20) | 16 (16) |
| BMI, kg/m$^2$, median (range) | 31.4 (22, 61) | 34.7 (22, 58) | 32.7 (22, 61) |
| Body weight, kg, median (range) | 94.5 (69, 188) | 102.9 (70, 188) | 100.2 (69, 188) |
| Percent weight gained on current regimen at baseline, median (range)† | 12.8 (−4, 56) | 15.7 (−15, 86) | 14.2 (−15, 86) |
| Type of InSTI regimen at baseline, n (%)‡ | | | |
| EVG/c/TAF/FTC | 5 (9) | 7 (14) | 12 (12) |
| DTG + TAF/FTC | 4 (8) | 4 (8) | 8 (8) |
| BIC/TAF/FTC | 44 (83) | 39 (78) | 83 (81) |
| Taking antihypertensive, antihyperglycemic, or lipid-lowering agents, n (%) | 23 (43) | 33 (66) | 56 (54) |
| Baseline CD4+, cells/mm$^3$, median (range) | 696.0 (205, 1543) | 622.5 (153, 2059) | 680.0 (153, 2059) |

*One participant in the D/C/F/TAF arm with race classified as "other" and 1 participant in the InSTI + TAF/FTC arm with race classified as "multiple" are not shown in the table. These participants are included in the denominators used to calculate the percentages shown in the table; thus, percentages do not sum to 100%.
†Missing data for 1 participant in the D/C/F/TAF arm.
‡Percentages may not sum to 100% due to rounding.

### Clinical Measurements

- At baseline, the median (IQR) BMI was 31.4 (27.6, 39.0) kg/m$^2$ in the D/C/F/TAF arm and 34.7 (30.8, 40.1) kg/m$^2$ in the InSTI + TAF/FTC arm; at Week 24, these values were 30.9 (28.0, 37.6) kg/m$^2$ and 35.2 (30.0, 40.7) kg/m$^2$, respectively
- At baseline, the median (IQR) waist circumference was 102.1 (94.0, 116.8) cm in the D/C/F/TAF arm and 112.8 (106.7, 122.4) cm in the InSTI + TAF/FTC arm; at Week 24, these values were 101.6 (96.5, 113.0) cm and 114.5 (104.1, 125.7) cm, respectively
- At Week 24, the majority of participants in both treatment arms remained classified as obese (≥30 kg/m$^2$; **Figure 2**) and were in the same waist circumference category (**Figure 3**)

**Figure 2.** BMI category at baseline and Week 24 (ITT set)

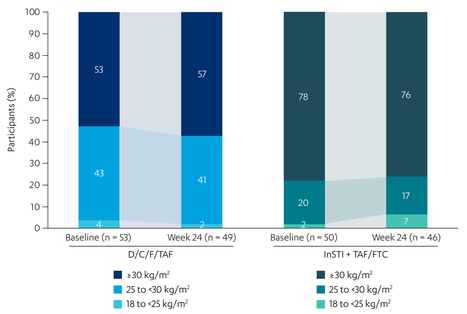
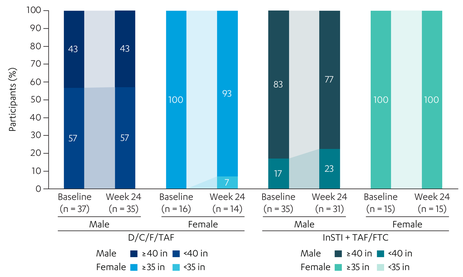


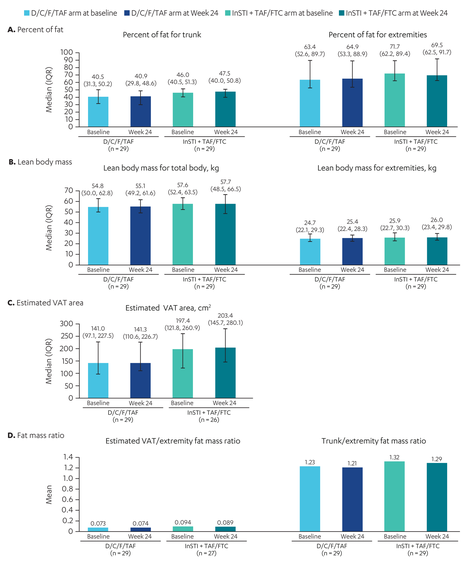

**Figure 3.** Waist circumference category at baseline and Week 24, stratified by sex (ITT set)




### Body Composition

- There were small numerical changes between baseline and Week 24 in body composition as measured by DXA (**Figure 4**)
- Lean body mass was preserved among participants in both treatment arms
- From baseline to Week 24, the ratios of estimated VAT/extremity fat mass and trunk/extremity fat mass remained largely unchanged (within ±5%) in both treatment arms

**Figure 4.** Body composition measurements by DXA (completer analysis set)




### Glucose Metabolism

- Changes in glucose and HbA1c values were minimal over 24 weeks; however, there were decreases in insulin and HOMA-IR values in the InSTI + TAF/FTC arm (**Table 2**)
- Between baseline and Week 24, 0 participants in the D/C/F/TAF arm and 2/50 (4%) participants in the InSTI + TAF/FTC arm started antihyperglycemic medication
- No participants in either arm had a clinically relevant change in weight that warranted a dose reduction or discontinuation of antihyperglycemic medication
- Over 24 weeks, 1/50 (2%) participants in the InSTI + TAF/FTC arm had a grade 2 to 4 hyperglycemia AE of interest; it was considered unrelated to the study drug

### Lipid Metabolism

- Numerically greater lipid elevations were observed in the D/C/F/TAF arm compared with the InSTI + TAF/FTC arm over 24 weeks (**Table 2**)
- Between baseline and Week 24, 8/53 (15%) participants in the D/C/F/TAF arm and 17/50 (34%) participants in the InSTI + TAF/FTC arm were taking lipid-lowering medication; among these, 2 participants in each treatment arm started lipid-lowering medication post-baseline
- No participants in either arm had a clinically relevant change in weight that warranted a dose reduction or discontinuation of lipid-lowering medication
- Over 24 weeks, 3/53 (6%) participants in the D/C/F/TAF arm and 1/50 (2%) participants in the InSTI + TAF/FTC arm had a grade 2 to 4 lipid abnormality event of interest; none were considered related to the study drug

**Table 2.** Summary of key glucose and lipid metabolism parameters (ITT set)

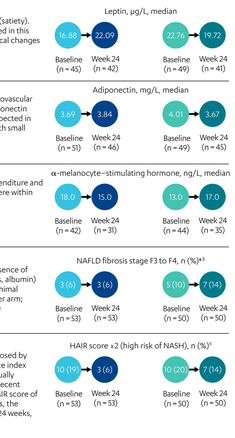
| Parameter, median | Central laboratory (Labcorp) reference range | D/C/F/TAF | | InSTI + TAF/FTC | |
|---|---|---|---|---|---|
| | | Baseline | Week 24 | Baseline | Week 24 |
| Fasting glucose, mg/dL | 70-110 | 95.5 (n = 51) | 94.6 (n = 44) | 100.9 (n = 50) | 97.3 (n = 42) |
| Insulin, µIU/mL | 1.9-23.0 | 10.9 (n = 53) | 11.7 (n = 47) | 12.7 (n = 50) | 9.9 (n = 45) |
| HOMA-IR | <2.5* | 2.6 (n = 53) | 2.8 (n = 47) | 3.4 (n = 50) | 2.3 (n = 43) |
| HbA1c, % | <6.5 | 5.5 (n = 53) | 5.4 (n = 46) | 5.5 (n = 50) | 5.5 (n = 44) |
| Fasting total cholesterol, mg/dL | <200 | 184.8 (n = 51) | 211.1 (n = 44) | 185.6 (n = 48) | 187.2 (n = 42) |
| Fasting LDL, mg/dL | <130 | 107.9 (n = 51) | 133.0 (n = 43) | 111.0 (n = 48) | 109.0 (n = 42) |
| Fasting HDL, mg/dL | 40-60 | 44.9 (n = 51) | 46.0 (n = 43) | 48.3 (n = 48) | 46.8 (n = 42) |
| Fasting triglycerides, mg/dL | <150 | 93.9 (n = 51) | 119.6 (n = 43) | 94.8 (n = 48) | 119.6 (n = 42) |

*Reference range not per central laboratory but based on recommended HOMA-IR cutoff value.[10,11]

### Biomarkers and Liver Function Scores

- Changes were minimal in leptin, adiponectin, and α-melanocyte–stimulating hormone levels in both treatment arms from baseline to Week 24 (**Figure 5**)
- Minimal changes were seen in NAFLD fibrosis score through Week 24; however, the percent of participants at high risk of NASH as determined by HAIR score decreased in both arms (**Figure 5**)

**Figure 5.** Summary of key biomarkers and liver function scores (ITT set)




*Reference range per Quest Diagnostics.
†Reference range per central laboratory (Labcorp).
‡NAFLD fibrosis stage is based on NAFLD score; scores <−1.455 were classified as stage F0 to F2; scores of −1.455 to 0.675 were classified as indeterminate, and scores >0.675 were classified as stage F3 to F4.
§Participants missing data: D/C/F/TAF at baseline, 4 (8%); D/C/F/TAF at Week 24, 14 (26%); InSTI + TAF/FTC at baseline, 6 (12%); InSTI + TAF/FTC at Week 24, 9 (18%).
¶Participants missing data: D/C/F/TAF at baseline, 2 (4%); D/C/F/TAF at Week 24, 9 (17%); InSTI + TAF/FTC at baseline, 2 (4%); InSTI + TAF/FTC at Week 24, 8 (16%).

## Key Findings at 24 Weeks

- Changes in secondary metabolic endpoints mostly paralleled the findings of the primary endpoint
- No clinically meaningful changes in BMI or waist circumference were observed
- There were small numerical changes between baseline and Week 24 in body composition as measured by DXA
- Changes in glucose and lipid metabolism parameters over time were minimal
- Limited changes in leptin, adiponectin, α-melanocyte–stimulating hormone, NAFLD fibrosis stage, and HAIR score were observed

## Conclusions

- In the first 24 weeks post–ARV switch, there were minimal changes in body weight in either treatment arm of this prospective, randomized clinical trial comparing metabolic outcomes of PI- versus InSTI-based therapy among individuals who had ≥10% weight gain while on an InSTI + TAF/FTC ARV regimen
- Secondary metabolic endpoints, including measures of BMI and waist circumference, body composition by DXA scan, and metabolic laboratory parameters, showed similarly small changes over this period
- Few participants began medications related to hyperglycemia or hyperlipidemia
- DEFINE is an ongoing, 48-week study, and extended observation following the switch from an InSTI-based regimen to a PI-based regimen may clarify whether this management strategy leads to any clinically meaningful improvements

### Abbreviations

AE, adverse event; ALT, alanine aminotransferase; ARV, antiretroviral; AST, aspartate aminotransferase; BIC/TAF/FTC, bictegravir/tenofovir alafenamide/emtricitabine; BMI, body mass index; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG + TAF/FTC, dolutegravir + tenofovir alafenamide/emtricitabine; DXA, dual-energy x-ray absorptiometry; EVG/c/TAF/FTC, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; HAIR, hypertension, alanine aminotransferase, and insulin resistance; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; InSTI, integrase strand transfer inhibitor; InSTI + TAF/FTC, integrase strand transfer inhibitor + tenofovir alafenamide/emtricitabine; IQR, interquartile range; ITT, intention-to-treat; IU, international unit; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF/FTC, tenofovir alafenamide/emtricitabine; VAT, visceral adipose tissue.

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