An Approach to Improve Diversity and Inclusion in Clinical Trials: The DEFINE Trial (D/C/F/TAF Evaluated As a Fixed-dose Combination Regimen in Participants Switching From an Integrase Inhibitor Who Have Experienced Rapid Weight Gain)

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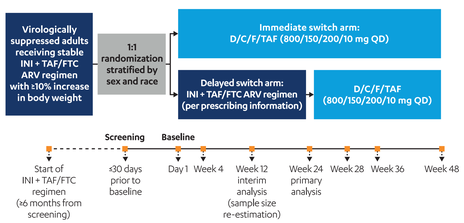
INTRODUCTION

- Black/African Americans, and particularly Black/African American women, are disproportionately affected by human immunodeficiency virus (HIV) compared to other races, and yet are often underrepresented in HIV clinical trials in the United States[1,2]
- Weight gain following initiation of integrase inhibitor (INI)–based regimens has been observed in people living with HIV and also appears to disproportionately affect women and Black/African American patients[3]
- Currently, it is unknown whether weight gain can be attenuated or reversed by switching off an INI-based regimen[3]
- The purpose of this presentation is to highlight the unique design of DEFINE, a trial currently in progress, as an approach to improve diversity and inclusion in clinical trials and to address this current data gap
- Specific efforts for diverse enrollment were particularly important when studying the question of antiretroviral (ARV)-related weight gain given the current understanding that different patient populations are impacted more than others

METHODS

- DEFINE is an ongoing, prospective, randomized, open-label, 48-week, phase 4 study evaluating the tolerability of switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) compared to continuing an INI + tenofovir alafenamide/emtricitabine (TAF/FTC) regimen in virologically suppressed adults living with HIV who have experienced rapid and significant weight gain, defined as ≥10% increase within a 12-month time period (**Figure 1**)
- To ensure representation of a diverse population in this trial, specific actions with regard to site selection and enrollment requirements were implemented
- Unique aspects of the DEFINE trial highlighted in this presentation include:
  - Incorporation of ability to enroll a diverse population as a main consideration in site selection
  - Use of an interactive web-based response system (IWRS) to monitor diversity demographics and "force" diverse enrollment
  - Development of an adaptive study design
  - Evaluation of changes in weight and metabolic outcomes when switching from an INI-based regimen to a boosted protease inhibitor (bPI)–based regimen; DEFINE is the first prospective study to include such assessments

Figure 1. Study design of the DEFINE trial



QD, once daily.

Study Site Selection

Identification of potential study sites	Electronic site feasibility questionnaire	Site assessment visit	Final site selection
• Expanded site selection to include sites not previously involved in Janssen clinical trials • Prioritized ability to enroll a diverse population over previous clinical trial experience with Janssen	• Questions related to sex and race were incorporated into the electronic site feasibility questionnaire (eFQ; **Figure 2**)	• Site assessment visits (SAVs) were conducted on-site or via telephone • SAVs included open conversations about diversity, similar to questions in the eFQ, to ensure consistent responses and understanding of requirements	• Final sites were selected and geographic location was considered with respect to diversity, target population, and obesity rates

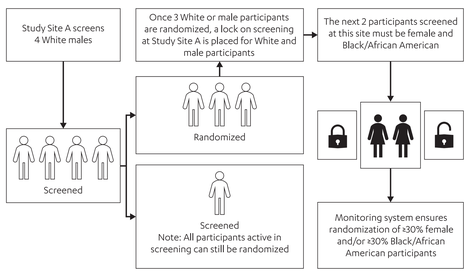
Figure 2. Electronic site feasibility questionnaire

Questions focused on sex or race
What percentage of participants who would switch off an INI to a bPI due to weight gain meet the following: • Female _____% • Black/African American _____%
Would you be willing to participate in this study if there was a requirement to enroll 1 female participant for every 2 male participants?
Would you be willing to participate in this study if there was a requirement to enroll 1 Black/African American participant for every 2 non-Black/African American participants?

Interactive Web-based Response System

- The IWRS was built to monitor diversity demographics at each site
- Sites become locked from screening new participants if randomized participant demographics at that site drop below 30% female and/or 30% Black/African American (**Figure 3**)

Figure 3. Example of IWRS monitoring



Adaptive Study Design

- Aside from the aspects of this trial with regard to diversity and inclusion in clinical trials (DICT), the DEFINE trial contains the additional unique element of an adaptive trial design
- This innovative quantitative approach will allow:
  - Sample size re-estimation and ensure power at the interim analysis
  - Assessment of intercurrent events due to COVID-19
  - Longitudinal data analysis for the primary endpoint
- The adaptive study design is used to help address the uncertainty of treatment effect, variability, and statistical power, as this is the first prospective, randomized controlled trial switching patients off an INI to a bPI
- Related to DICT, the adaptive trial design will allow for feasibility assessment of subgroup analyses, including analyses by sex and race

Study Objectives and Outcomes of Interest

- DEFINE is the first randomized, prospective study to assess outcomes in participants switching from an INI to a bPI
- The primary objective of the study is to assess the percentage change in body weight at Week 24 from baseline when switching to D/C/F/TAF compared to continuing an INI + TAF/FTC regimen in virologically suppressed participants
- Additional key outcomes to be evaluated at Week 24 and Week 48 include:
  - Metabolic outcomes
    - Proportion of participants with >3% or >5% change in body weight
    - Change in body mass index and waist circumference
    - Change in body composition as measured by dual-energy x-ray absorptiometry (DEXA)
    - Change in fasting lipids, fasting glucose, blood pressure, and liver biomarkers
    - Change in concomitant medications of interest (antihypertensive, antihyperglycemic, and lipid-lowering agents)
  - Patient-reported outcomes (**Figure 4**)

Figure 4. Patient-reported outcomes evaluated in DEFINE

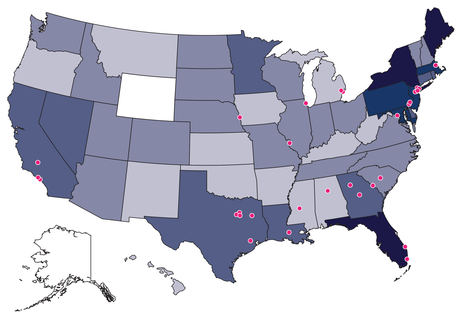
Burden of 20 common symptoms associated with HIV treatment or disease	**Concerns about body shape and focuses on the experience of "feeling fat"**
Eating-related concepts such as hunger, appetite, cravings, and satiety	**Change in overall status and participant satisfaction (fullness) after meals**

RESULTS

- In total, 52 potential study sites completed feasibility questionnaires
- Of the 52 sites, 9 (17%) were placed on hold or were declined due to expected low enrollment of either female or Black/African American participants
- A total of 30 sites were selected across 27 cities and 17 states in the United States (**Figure 5**)
- As of November 2020, 37% of screened participants were female and 44% were Black/African American, and projected enrollment timelines remain on track

Figure 5. DEFINE study sites across the United States

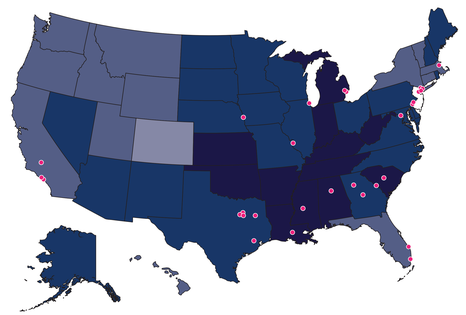
A. DEFINE study sites and prevalence of HIV among Black/African Americans



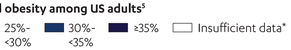
Rate of diagnosed HIV infection among Black/African Americans (per 100,000 population)[4]

*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

B. DEFINE study sites and obesity rates



Prevalence of self-reported obesity among US adults[5]



CONCLUSIONS

- **The clinical trial design and operational processes in the DEFINE study may be used as a model for future studies to ensure diversity among participants**
- **The study design, specifically fitting the primary endpoint in the framework of the estimation on the intended population, will help assess COVID-19 intercurrent events and missing data**
- **Importantly, this model demonstrates that enrolling a diverse population can be achieved without a compromise to enrollment timelines**
- **The DEFINE study will represent the first randomized controlled trial switching participants from an INI-based regimen to D/C/F/TAF, and results from this study will provide insight on managing patients who rapidly gain weight on an INI-based regimen**

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