Outcomes for Participants During Long-Term Follow-Up After Discontinuation of Cabotegravir + Rilpivirine Long-Acting in the Phase 3/3b Clinical Trials

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Disclosure

- Paula Teichner is an employee of ViiV Healthcare and stockholder of GlaxoSmithKline

Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) dosed monthly or every 2 months is the first complete long-acting (LA) regimen recommended by treatment guidelines[1,2] for the maintenance of HIV-1 virologic suppression
- Regulatory approval of CAB + RPV LA was supported by data from three Phase 3 clinical studies, ATLAS,[3] FLAIR,[4,5] and ATLAS-2M,[6] each of which demonstrated that the LA maintenance regimen was well tolerated and effective
- As CAB + RPV LA provides a novel treatment option with drug concentrations that persist for prolonged periods even after discontinuation, safety and efficacy following a switch to alternative antiretroviral (ARV) therapy was assessed during a long-term follow-up period in each study
- Here, we describe results for participants who discontinued CAB + RPV LA and elected to enter 12-month long-term follow-up across the ATLAS, FLAIR, and ATLAS-2M studies

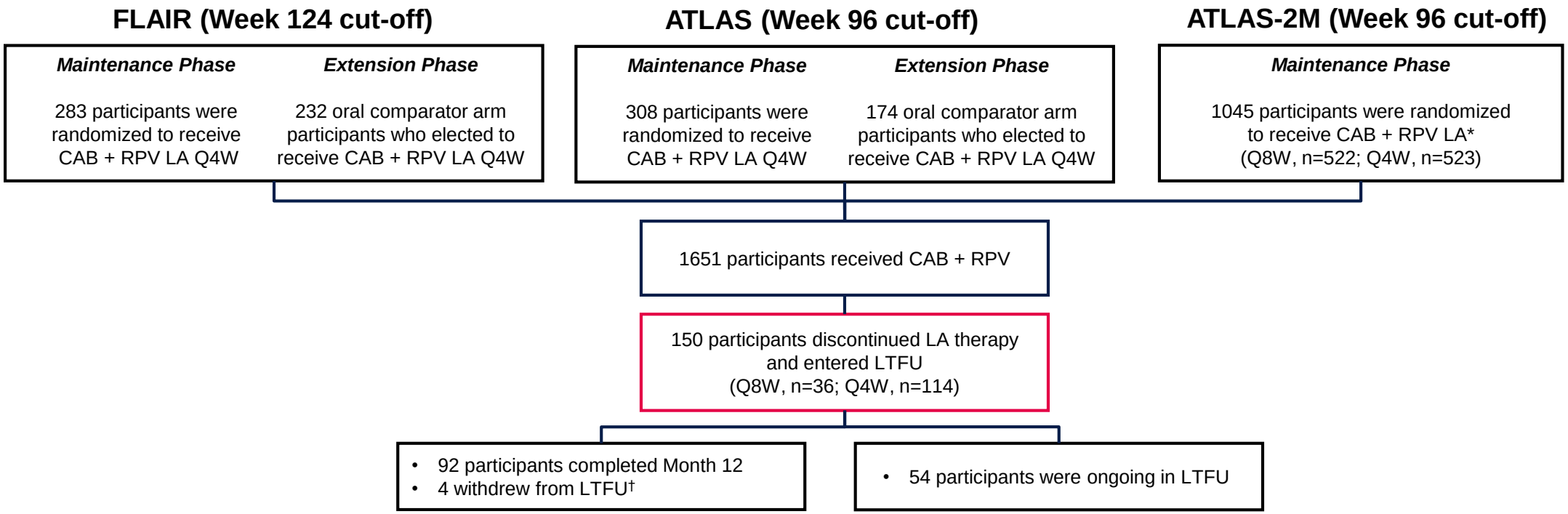
1. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/15/virologic-failure. Accessed July 25, 2021.
2. Saag MS, et al. *JAMA*. 2020;324(16):1651–1669. 3. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123. 4. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135. 5. Orkin C, et al. *Lancet HIV*. 2021;8(4):e185–e196. 6. Overton ET, et al. *Lancet*. 2021;396(10267):1994–2005.

Methods

- All participants exposed to at least 1 dose of CAB + RPV LA, with either every 4 (Q4W) or 8 weeks (Q8W) dosing, who discontinued treatment and elected to enter 52 weeks of long-term follow-up were included in this analysis from:
  - ATLAS and ATLAS-2M through 96 weeks and FLAIR through 124 weeks of exposure*
- Evaluations during long-term follow-up for this analysis included:
  - Participant demographics for those entering long-term follow-up
  - Reason(s) for discontinuation of LA therapy
  - Clinical outcomes, including safety and tolerability, of subsequent daily oral ARV therapy

*Includes participants with up to 144 weeks of CAB + RPV exposure.
ARV, antiretroviral; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

Participants Entering Long-Term Follow-Up



- In total, 150 participants (9%) discontinued LA therapy and entered long-term follow-up, including:
  - 36 participants who received the Q8W regimen and 114 who received the Q4W regimen
  - 138 participants randomized to LA therapy at the start of the Maintenance Phase and 12 Switch/Extension Phase participants

*Includes 391 participants who transitioned from the ATLAS study with prior CAB + RPV exposure (comprising 253 participants who were initially randomized to CAB + RPV LA in the Maintenance Phase and 138 participants initially randomized to the oral comparator arm who elected to receive CAB + RPV LA in the Extension Phase).
†Includes lost to follow-up (n=2) and withdrawal by participant (participant relocated, n=1; burden of procedures, n=1).
CAB, cabotegravir; LA, long-acting; LTFU, long-term follow-up; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Baseline Characteristics for Participants Entering Long-Term Follow-Up

Parameter	Participants entering LTFU (n=150)
Age, median (range) years	38 (19–65)
Age ≥50 years, n (%)	34 (23)
Female (sex at birth), n (%)	44 (29)
Female (self-reported gender), n (%)	45 (30)
Race, n (%)	
White	105 (70)
Black or African American	29 (19)
Other	16 (11)
Body mass index, median (IQR) kg/m^2	24.9 (22.2–29.0)
Q4W regimen, n (%)	114 (76)
Q8W regimen, n (%)	36 (24)
Duration of CAB + RPV LA therapy prior to discontinuation, median (range), weeks	36.7 (0.9–144.0)
Time to start subsequent oral ARV therapy, median (IQR), weeks	4.1 (4.0–6.1)

- The median (range) duration of CAB + RPV LA exposure prior to participants entering long-term follow-up was 36.7 (0.9–144.0) weeks, with 38% (n=57/150) entering long-term follow-up after 1 year of LA therapy

ARV, antiretroviral; CAB, cabotegravir; IQR, interquartile range; LA, long-acting; LTFU, long-term follow-up; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Reasons for Entering Long-Term Follow-Up Across the Phase 3 Program

Reason for discontinuation from Maintenance/Extension Phase, n (%)	Participants entering LTFU (n=150*)
AE	60 (40)
Participant withdrawal	35 (23)†
Lack of efficacy	27 (18)
Insufficient viral load response	8
CVF¶	19
Physician decision	10 (7)‡
Protocol deviation	10 (7)§
Protocol-specific withdrawal criterion met	3 (2)‖
Missing	5 (3)

*Four of these participants discontinued in the LTFU phase (lost to follow-up, n=2; withdrawal by participant, n=2). †Most common reasons (≥5 participants) included burden of procedures (n=5), frequency of visits (n=9), intolerability of injections (n=13), participant relocation (n=6), and other (n=17). ‡Included resistance to RPV (n=1), pulmonary tuberculosis (n=1), pregnancy (n=4), overall status including elevated cardiovascular risk (n=1), requirement for long-term anticoagulant (n=1), and other (n=2). §Included non-compliance with protocol procedures (n=3), non-compliance with study treatment (n=1), pregnancy (n=2), and prohibited medication use (n=5). ‖Included pregnancy (n=2) and participant meeting defined liver chemistry stopping criteria (n=1). *Participants may have more than one sub-reason for withdrawal.*

- The most common reasons for entering long-term follow-up included discontinuation due to AEs, participant withdrawal, and lack of efficacy
- Overall, 1% (n=19/1651) of participants met the CVF criterion¶ and entered long-term follow-up through up to 124 weeks of exposure across the Phase 3 program#

¶Two consecutive HIV-1 RNA ≥200 copies/mL. #Includes participants with up to 144 weeks of CAB + RPV exposure.
AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; LTFU, long-term follow-up; RPV, rilpivirine.

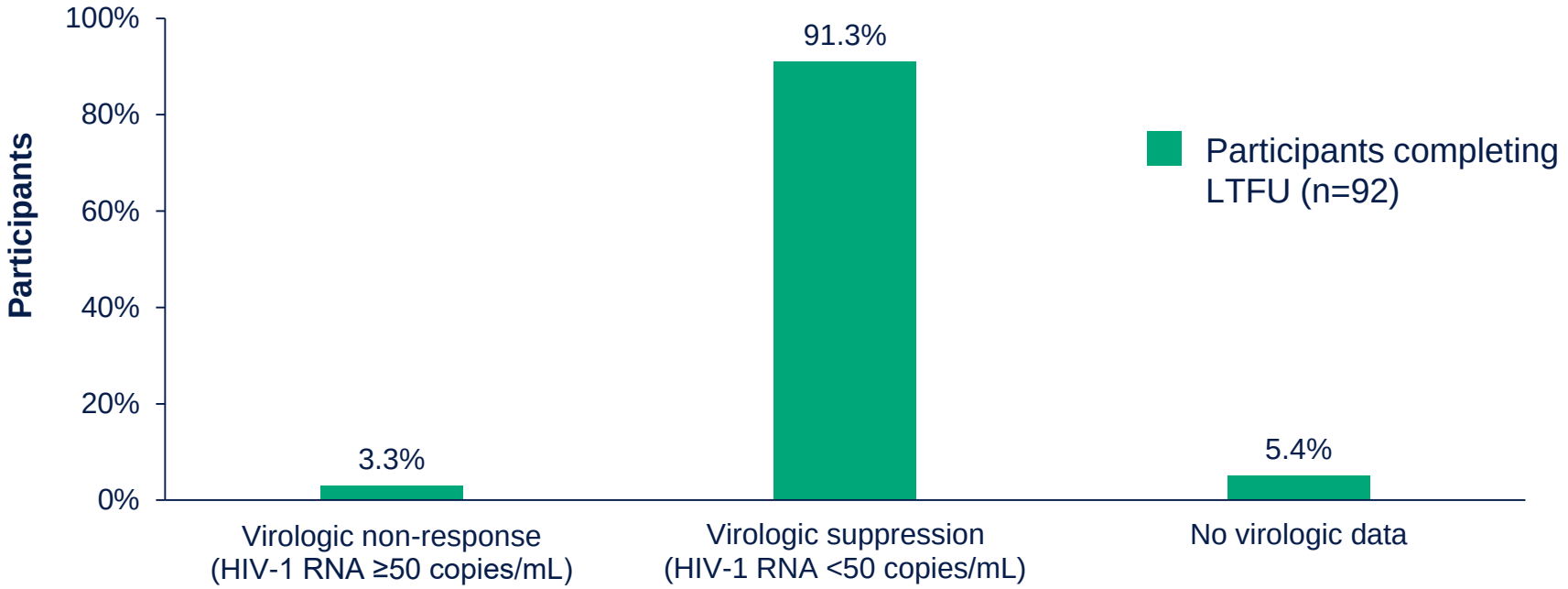
Initial ARV Regimens Taken by Participants During Long-Term Follow-Up

Regimen, n (%)	Participants entering LTFU (n=150)
INSTI-based	90 (60)
Dolutegravir	47 (31)
Bictegravir	20 (13)
Elvitegravir	13 (9)
Raltegravir	10 (7)
PI-based	31 (21)
Darunavir/cobicistat	12 (8)
Lopinavir/ritonavir	8 (5)*
Darunavir/ritonavir	6 (4)
Atazanavir/ritonavir	4 (3)
Atazanavir	1 (1)
NNRTI-based	29 (19)
Rilpivirine	13 (9)
Efavirenz	12 (8)
Doravirine	2 (1)
Nevirapine	1 (1)
Etravirine	1 (1)

- Participants primarily switched to INSTI-based regimens, with DTG most commonly utilized
- Overall, 82% of participants initiated an alternative ARV regimen within 8 weeks of CAB + RPV LA discontinuation (median [IQR], 4.1 [4.0–6.1] weeks)

*Includes one participant for which the booster used cannot be confirmed.
ARV, antiretroviral; CAB, cabotegravir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LA, long-acting; LTFU, long-term follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine.

Virologic Outcomes at Month 12 for Participants Completing Long-Term Follow-Up



- Of the 150 participants who entered long-term follow-up, 92 completed Month 12, four withdrew, and 54 were ongoing at the time of analysis
- At Month 12, 91% (n=84/92) of participants were virologically suppressed, including 88% (n=14/16)* of participants who entered long-term follow-up due to meeting the CVF criterion on LA therapy
  - The remaining three participants meeting the CVF criterion were missing Month 12 viral load data due to withdrawal during long-term follow-up

*Of those with viral load data at Month 12.
CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; LTFU, long-term follow-up; RPV, rilpivirine.

Safety During Long-Term Follow-Up on Subsequent Oral ARVs

Parameter, n (%)	Participants entering LTFU (n=150)
Any drug-related AEs	13 (9)
Grade ≥3	6 (4)
Drug-related AEs occurring in ≥1% of participants	
Diarrhea	3 (2)
Vomiting	2 (1)
Headache	2 (1)
AEs leading to withdrawal from LTFU	0
SAEs	17 (11)
Drug-related SAEs	3 (2)*

*Hodgkin's disease mixed cellularity (n=1), osteonecrosis (n=1), and myocardial infarction (n=1).

- In total, 13 (9%) participants reported drug-related AEs while on oral ARVs, with no AE-related discontinuations
- No new safety concerns were observed in participants who switched to oral ARVs (in the presence of declining CAB and RPV concentrations)

AE, adverse event; ARV, antiretroviral; CAB, cabotegravir; LTFU, long-term follow-up; RPV, rilpivirine; SAE, serious adverse event.

Conclusions

- Through to 144 weeks, approximately 9% of participants across the ATLAS, FLAIR, and ATLAS-2M studies discontinued CAB + RPV LA and entered long-term follow-up
  - The most common reasons for entering long-term follow-up included discontinuation due to AEs and participant withdrawal
- High rates of virologic suppression were observed on subsequent therapy, irrespective of the reason for entering long-term follow-up
- No efficacy or new safety concerns were observed in participants who switched to oral ARVs, regardless of the reason for switch, during the period of declining CAB and RPV concentrations
- CAB + RPV LA is a highly effective complete treatment regimen with durable efficacy, that can be simply and safely switched to an alternative ART regimen upon discontinuation

ARV, antiretroviral; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

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