COMPASSIONATE USE OF LONG-ACTING (LA) CABOTEGRAVIR (CAB) AND RILPIVIRINE (RPV) FOR PATIENTS IN NEED OF PARENTERAL ANTIRETROVIRAL THERAPY

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PEB0263

Introduction

- Cabotegravir (CAB) and rilpivirine (RPV) are a novel 2-drug long-acting (LA) therapeutic regimen for the maintenance of HIV-1 virologic suppression[1,2]
  - Phase 3 studies in adults with HIV-1 demonstrated non-inferiority of IM CAB + RPV LA every 4 weeks (Q4W) to daily oral standard of care at 48 weeks (ATLAS[1] [NCT02951052] and FLAIR[2] [NCT02938520])
  - CAB + RPV LA dosed Q8W (ATLAS-2M [NCT03299049]) was non-inferior to Q4W dosing[3]
- An inherent responsibility of drug development is allowing early access to medications in late-stage development to patients in need of life-sustaining therapies before regulatory approval
- The present analysis aims to examine efficacy and safety in adult patients with HIV-1 infection who were provided access to CAB + RPV LA through a compassionate use (CU) program

Methods

- Physicians could request CU under an expanded access program, supported by both ViiV Healthcare and Janssen
  - Each request was separately reviewed and approved by a committee of senior physicians at both companies
- Key criteria for granting requests included need for parenteral therapy, advanced disease, absence of key mutations associated with resistance to CAB or RPV, and established retention in care
- A 1-month oral lead-in (OLI) phase consisting of CAB (30 mg daily) + RPV (25 mg daily) was recommended for most patients but this could be omitted when underlying clinical conditions prevented the use of oral medication
- All patients received a loading dose of CAB (600 mg) + RPV (900 mg) LA followed by Q4W maintenance dosing of CAB 400 mg + RPV 600 mg LA
- Data were obtained from standardized CU applications and quarterly clinical updates from treating physicians, with the data extracted and compiled by the lead CU physician
  - Data extracted included viral load (VL), CD4+ cell count, resistance profile, number of injections, and tolerability, including injection site reactions (ISRs), if reported by the treating physician
  - Local physicians were accountable for the monitoring of patient safety, including timely reporting of pregnancies and adverse events (AEs) and serious AEs (SAEs) leading to withdrawal to GSK/ViiV and Janssen

Results

- Available efficacy and safety data for 35 patients from 10 countries who received CAB + RPV LA are presented from the start of the program in February 2016
  - The geographical distribution of patients is as follows: 12 patients from the United Kingdom; 11 from the United States; 2 each from Belgium, Canada, Netherlands, and Switzerland; and 1 each from Portugal, Italy, South Korea, and Spain
    - 12 patients from France received CU but are not included in the present analysis
- Patient demographics and clinical characteristics at start of CU are shown in Table 1
  - CU requests primarily involved patients with chronic poor adherence due to psychological conditions

Efficacy

- 28/35 (80%) patients entered the CU program (10 without OLI) with detectable viremia (median [range] CD4+ cell count, 61.5 [3-691] cells/mm^3), and at the time of this analysis, 16/28 (57%, 4/10 without OLI) achieved virologic suppression (<50 c/mL) with CAB + RPV LA
  - Median (range) duration of follow-up was 11 months (1-47; Figure 1)
  - Median (IQR) time to virologic suppression as reflected in the quarterly clinical updates was 6 months (1-31)
- 7/35 patients had virologic suppression at initiation of oral CAB + RPV
  - 1/7 (patient no. 9) withdrew from the program and was suppressed on a different regimen
  - 6/7 maintained suppression on CAB + RPV LA at their last physician visit
- At the last follow-up, 22 (63%) patients were virologically suppressed on CAB + RPV LA (<50 c/mL)
  - 2/13 (15%) patients (patient nos. 30 and 32) had not received injections until the last follow-up; hence, data are unavailable
  - 3/13 (23%) patients (patient nos. 25, 26, and 29) started the program within the last 4 months; hence, adequate duration for full viral suppression was not yet achieved
  - 5/13 (38%) patients (Table 2) withdrew from the program, 2 of whom (patient nos. 9 and 35) became suppressed (<50 c/mL) on other drugs after stopping CAB + RPV LA

Incomplete Virologic Responses Leading to Withdrawal

- 5 (14%) patients had incomplete virologic responses and stopped CAB + RPV LA treatment (Table 2)
  - 4 patients had NNRTI resistance-associated mutations at failure and 2 had INI resistance-associated mutations

Table 1. Patient Demographics and Clinical Characteristics at Start of CU Program

Characteristic	N=35
Female, n (%)	20 (57)*
Perinatally infected, n (%)	11 (31)
Age, median (range), y	36 (20-67)
BMI, median (range), kg/m^2	21 (16-38)
AIDS diagnosis, n (%)	23 (66)
No. of regimens before CU, median (range)	4 (1-10)
Detectable viremia, n (%)	28 (80)
CD4+ cell count, median (range), cells/mm^3	100 (3-918)
Initiation of injections without OLI, n (%)	12 (34)
Primary reason for CU request, n	
Psychological†	15
Physical challenges‡	8
Malabsorption	6
Dysphagia	3
Limited cognitive skills	3

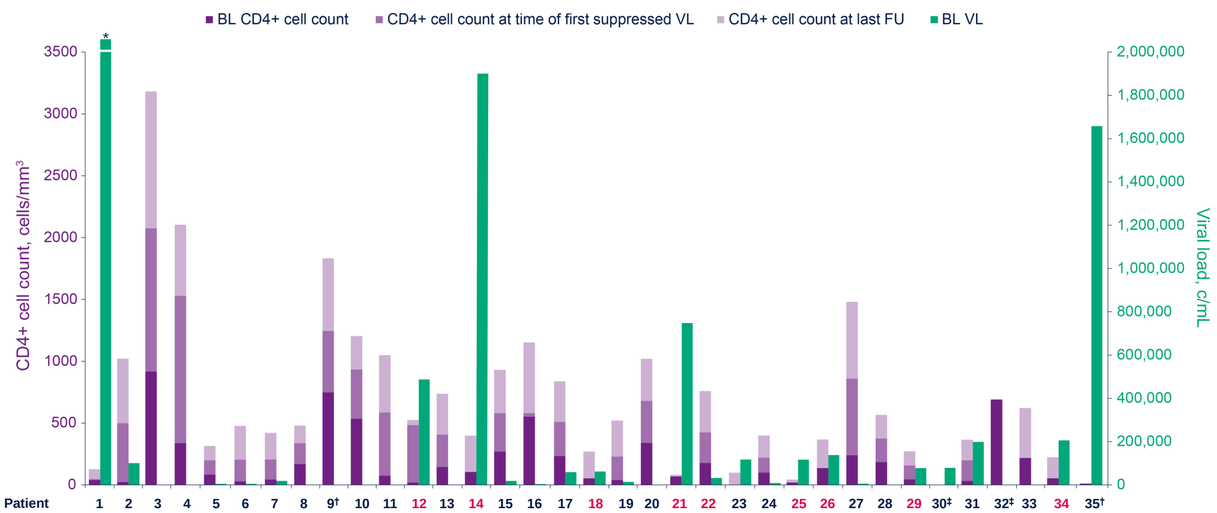
*1 patient is a transgender male who was female at birth, †Includes issues with swallowing pills, pill fatigue, chronic poor oral adherence, and stigma. ‡Includes issues such as chronic diarrhea, incarcerated ventral hernia, severe mucositis, pancreatic insufficiency, intractable vomiting, and dumping syndrome.

Table 2. Incomplete Virologic Responses Leading to Withdrawal

Patient description and reason for CU	• Patient no. 9 • 62 y, female • Extensive small bowel resection	• Patient no. 18 • 34 y, female • History of non-adherence due to trauma	• Patient no. 22 • 48 y, obese female • Non-adherence (cognitive impairment)	• Patient no. 34 • 39 y, female • Pill phobia	• Patient no. 35 • 24 y, female • Poor adherence (cognitive impairment)
VL at CU start	<40 c/mL	61,600 c/mL	32,000 c/mL	205,000 c/mL	1,639,794 c/mL
VL at failure	• VL blip (55 c/mL) with no change in adherence; repeat VL <40 c/mL	Not available	799 c/mL	186,972 c/mL	66,000 c/mL
Mutations at CU start		RT: M184V, K219E, E138G	RT: K238K/R, E138G		RT: K103N
Mutations at VF	IN: G118G/R	RT: E138E/K	RT: E138G, M230L; IN: Q148R, N155H	RT: K101E, Y181Y/C	RT: Y181C, K219N
Treatment regimen	• Discontinued CAB + RPV LA and changed to double-dosed DRV/r + TAF/FTC	• No OLI, LA dosing initiated with detectable viremia	• No OLI • VL <50 c/mL 4 wk after first injection and remained <50 c/mL for up to 5 mo	• Virologic suppression after 4-wk OLI • VF after first maintenance injection	• VL 512,000 c/mL after 4-wk OLI • VF after second injection
Outcome	• Tolerating new regimen (DRV/r + TAF/FTC) with no concerns or issues	• On day of scheduled dose, trough PK for CAB 6500 ng/mL; trough PK for RPV, 94.2 ng/mL • Final regimen: DRV/c + CAB + RPV LA	• Treatment failure with morbid obesity (BMI increase from 35 to 43 kg/m^2 since start of CU) • Switch to DRV/r/TAF/FTC	• Withdrawn from CU program and restarted DRV/r + TDF/FTC • Still struggling with adherence issues	• Withdrawn from CU program and started on oral DRV/c/ TAF/FTC
Most recent VL and CD4+ cell count*	• Last VL obtained 2 wk after starting DRV/r + TAF/FTC was <40 c/mL	• VL, 13,300 c/mL • CD4+ cell count, 220 cells/mm^3	VL, 1170 c/mL	• VL, 18,000 c/mL • CD4+ cell count, 170 cells/mm^3	• Last VL obtained was 41 c/mL after starting DRV/c/TAF/FTC

*Most recent as of June 2020.

Figure 1. Patient-Level Data for Change in Viral Load and CD4+ Cell Count



Patient	1	2	3	4	5	6	7	8	9†	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30‡	31	32‡	33	34	35†
VL at last FU	<40	<20	<20	<20	<20	<20	<50	<20	<40	<20	<20	262	<20	86	<30	<30	<20	13,300	<40	<40	133	1170	<50	<40	26,703	70	<20	<20	97	—	<20	—	<20	18,000	41
Injection visits, n	47	23	27	31	8	22	19	21	15	22	18	21	15	15	8	14	11	9	11	10	6	11	4	7	4	4	5	6	2	0	2	1	7	2	2
Prior regimens, n	3	5	3	1	5	10	4	5	3	2	2	4	5	7	1	2	10	7	9	2	8	5	5	4	3	4	4	3	4	2	6	3	7	8	8

FU, follow-up; VL, viral load. Patient numbers shown in red text were not virologically suppressed at the last visit. *VL = 10,000,000. †Patients suppressed on other drugs after discontinuation of CAB + RPV LA. ‡Data unavailable at last FU.

Safety (As Reflected and Extracted From Quarterly Updates)

- The most common AE was ISRs, with the most common being pain (31%; n=11) and nodule formation (9%; n=3); however, not all quarterly updates commented on AEs or ISRs
- No patients stopped CAB + RPV LA treatment because of ISRs
- 3 deaths occurred that were not related to treatment
- 5 patients reported SAEs, 1 of which was treatment related; all continued CAB + RPV LA treatment (Table 3)

Table 3. Summary of SAEs

SAE	Description
Incarcerated hernia	• History of inguinal hernia; worsened during treatment; led to hospitalization/surgery • SAE not related to treatment and patient recovered
Cryptococcal meningitis/IRIS	• AIDS and history of cryptococcal meningitis and atypical mycobacterial infection • Hospitalized 85 days after starting CU; evaluated by treating physician as IRIS • SAE not related to treatment
Loss of consciousness	• Past medical history of loss of consciousness, pneumonia, and herpes zoster • Episode of loss of consciousness 30 days after receiving the first loading dose and 2 days after the first maintenance dose of CAB + RPV LA • SAE possibly related to treatment; patient recovered
Right inguinal abscess	• History of grade 3 vaginal, anal, and vulva intraepithelial neoplasia; developed severe grade 3 groin abscess • SAE not related to treatment and patient recovered
Right nasal (nares) vestibulitis	• Significant history of diabetes mellitus • Developed grade 2 nasal vestibulitis on CU; treated with amoxicillin + clavulanate potassium; CAB + RPV LA continued with no change • SAE not related to treatment and patient recovered

IRIS, immune reconstitution inflammatory syndrome.

Case Narrative: On-Treatment Pregnancy (Patient No. 21)

- A 22-year-old female patient (BMI, 40 kg/m^2) with perinatally acquired HIV infection and a history of chronic oral non-adherence since childhood was approved for CU and received OLI followed by LA therapy
- She had an unplanned pregnancy while receiving LA therapy and, after informed consent, opted to continue CAB + RPV LA
  - Prophylactic low-molecular-weight heparin during pregnancy was prescribed
- Detectable viremia was observed despite timely injections
- After VL increase from 333 to 1500 c/mL, genotypic resistance results showed wild-type virus
  - Oral DRV/c + TAF/FTC was added and subsequent VLs improved (ranging from 113-183 c/mL) although not undetectable despite detectable plasma DRV levels
- She had a late miscarriage at 23 weeks + 1 day with maternal results negative for congenital infections and COVID-19
- The patient continues CU of CAB + RPV LA with DRV/c + TAF/FTC as of June 2020 but DRV therapeutic drug monitoring level was zero, suggesting oral non-adherence; most recent VL was 133 c/mL

Conclusions

- Among patients having severe adherence challenges with oral therapy for various psychological reasons or issues related to malabsorption or other GI pathology, most achieved or maintained virologic suppression on CAB + RPV LA Q4W
  - CAB + RPV LA was used successfully to treat a cohort of perinatally infected individuals (30% of this cohort), with 82% achieving or maintaining virologic suppression in this compassionate use setting
- CAB + RPV LA Q4W was generally well tolerated in the majority of individuals
  - Of the few SAEs that were reported, 1 was considered possibly related to treatment
- Overall, CAB + RPV LA CU access has been a valuable treatment option for individuals with co-morbidities or other issues preventing enteral administration of antiretroviral drugs

Acknowledgments: This study was funded by ViiV Healthcare. The authors would like to acknowledge Annie Cameron and Charles Maurer from GSK for their involvement in this program. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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Data have been updated since the abstract was submitted.

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