The Whole is Greater than the Sum of the Parts, Combination Use as CABENUVA in Treating HIV: Meta-Analysis from Clinical Datasets

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Abstract: CABENUVA is a 2-drug co-packaged product for the treatment of HIV-1 infection in adults to replace current antiretroviral therapy. The development of more effective and convenient medication can improve the lives of HIV patients. This article mainly focuses on the drug profile, clinical trial and comparative analysis of CABENUVA with other newly approved HIV-1 drugs. There have been several HIV-1 drugs approved since 2018, but the route of administration of them is still oral. The appearance of CABENUVA indicates the possibility of introducing and developing injection HIV medications.

1 INTRODUCTION

1.1 Introduction of HIV-1

HIV is a type of retrovirus that infects cells of the human immune system and causes the spread of diseases in the human body by destroying the body's T-lymphocytes, thereby blocking cellular and humoral immune processes. That causes the immune system to become paralyzed, thus creating the environment for AIDS. Because HIV mutates so rapidly, it is difficult to produce a specific vaccine. The fact that is no effective treatment for the disease made it a great threat to human health.

The Joint United Nations Programme on HIV/AIDS estimates that in 2019, 38 million people worldwide will be living with HIV, 1.7 million will be newly infected and 690,000 will die from HIV disease. Compared with their estimation in 2010, the overall HIV incidence in 2019 has decreased by 23% and mortality by 37%. However, age stratification shows a 52% reduction in new infections among children, and only a 13% reduction among adults. With mortality declining but HIV incidence and population continuing to grow, the total number of people living with HIV in 2019 is 24% higher than in 2010. (De Cock, 2021)

In the nearly 40 years since the discovery of HIV, great progress has been made in developing effective treatments. However, a vaccine that prevents HIV infection remains elusive. Most licensed vaccines protect through the induction of antibodies. In the case of HIV, the antibodies induced by the vaccine must be able to protect the human immune system against the effects of the multiple variants of HIV that are prevalent worldwide, known as broadly neutralizing antibodies. Recent advances in the identification and characterization of such antibodies, as well as progress in the design of candidate antibodies to stimulate cellular immunity and the results of recent clinical trials, are driving efforts to develop an HIV vaccine that can eradicate the virus once and for all. (Koff, 2016)

However, the development of an HIV vaccine has not been successful, the number of people living with HIV is still huge and continues to grow, and the need for HIV suppressant drugs gets stronger every day.

Antiretroviral therapy (ART), is the treatment of HIV with a combination of several antiviral drugs. Although ART is effective in suppressing the onset of HIV, it is time-consuming and has serious side effects. There is an urgent need to find new and easier ways to cure HIV infection or suppress the onset of AIDS.

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1.2 CABENUVA

CABENUVA is a 2-drug co-packaged product for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace current antiretroviral therapy in patients who are virologically stable and suppressed. (Surve, 2020) CABENUVA kept HIV-1 viral load at a suppressed level.

CABENUVA is the world's first complete and long-acting HIV treatment regimen, administered by intramuscular injection (IM) once a month. The approval of the drug marks a major milestone that will revolutionize HIV treatment by shifting from oral administration 365 days a day throughout the year to monthly injections for only 12 days of treatment throughout the year. CABENUVA (Cabotegravir and Rilpivirine), developed by ViiV Healthcare is also the latest drug currently approved by the FDA for the treatment of AIDS, with approval scheduled on January 20, 2021.

CABENUVA, an easier and more effective treatment, is a huge improvement of the quality of life for people with HIV. Simplified regimens for the treatment of HIV-1 infection may increase patient satisfaction and facilitate adherence. (Surve, 2020)

2 DRUG PROFILES

2.1 Highly Active Antiretroviral Therapy

In 1996, the Chinese-American scientist D.Y. Ho proposed the highly active antiretroviral therapy (HAART), in which three or more antiretroviral drugs are used in combination to treat AIDS. The HAART combines protease inhibitors with a variety of antiviral drugs, resulting in effective control of AIDS. The application of this therapy reduces the drug resistance caused by unitary medication, maximizes the inhibition of viral replication, and restores some or even all of the body's immune function. Eventually, it slows the progression of the disease, prolongs the patient's life , and improves their quality of life. CABENUVA (Cabotegravir and Rilpivirine) also uses the principle of highly active antiretroviral therapy to achieve better HIV suppression through a combination of drugs.

2.2 Cabotegravir and Rilpivirine

The first part is a separate analysis of Cabotegravir and Rilpivirine. The analysis illustrates Rilpivirine, a long-term active, non-nucleoside reverse transcriptase inhibitor; and Cabotegravir, a long-term active HIV-1 integrase strand transfer inhibitor.

The target of Rilpivirine is NNRTIs, and the target of Cabotegravir is HIV integrase. Rilpivirine (TMC278) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that vigorously represses wild-type and NNRTI-resistant HIV-1. activity. NNRTIs work by binding to and blocking HIV reverse transcriptase, an HIV enzyme. Cabotegravir (GSK744, GSK1265744) is an HIV integrase inhibitor that is effective within a broad range of HIV subtypes and inhibits the chain transfer reaction catalyzed by HIV-1 integrase with an IC50 of 3 nM.

The following two figures (Figure1 and Figure2) will show each chemical structure formula of two important components of CABENUVA.

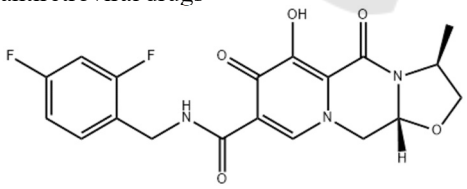

Figure 1: Chemical structure of Cabotegravir.

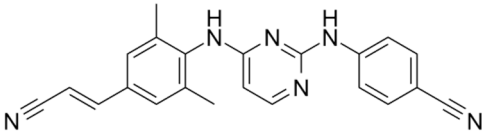

Figure 2: Chemical structure of Rilpivirine.

2.3 Pharmacokinetics and Treatment Satisfaction

In terms of PHARMACOKINETICS, the research team of the University of Nebraska's Medical Center confirmed that during therapy, Cabotegravir and Rilpivirine concentrations in plasma were similar to those reported during oral therapy (Figure 3). Both drugs from the first trough at week 8 to the trough at week 48 showed a cumulative accumulation of approximately 2.3-fold, close to steady-state drug concentrations. The geometric mean plasma concentrations of Cabotegravir and Rilpivirine at week 48 (2.84 micrograms per milliliter and 90.3 nanograms per milliliter, respectively) were each 17 and 7.5 times their respective protein-adjusted concentrations, respectively, required for 90% viral suppression, similar to the results obtained after monthly dosing in the phase 2 study. (Swindells, 2020)

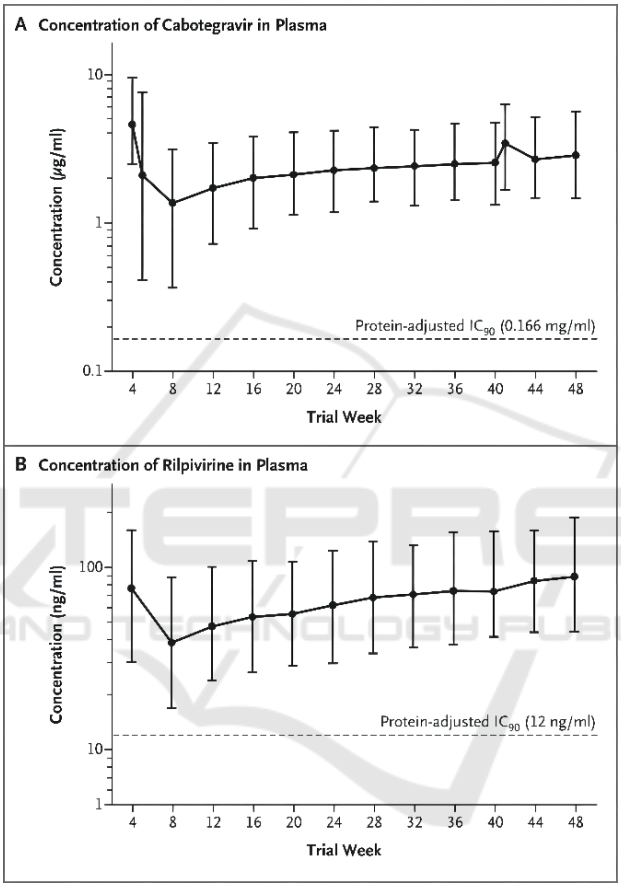

Figure 3: Plasma Concentration–Time Profiles.

As assessed by HIVTSQs: after 44 weeks, participants in the long-term active treatment group showed a substantial promotion in treatment satisfaction compared to those in the oral treatment group. The adjusted mean score for the long-term active treatment group was 5.68 points (95% CI, 4.37 to 6.98) higher than that of the oral treatment group. This difference met the threshold of a minimal clinically important difference according to a distribution-based approach. In a within-group comparison conducted at week 48 in the long-term active treatment group, 97% of participants who responded to the questionnaire and 86% of participants in the intention-to-treat exposed population chose injectable therapy over daily oral therapy as their preferred HIV treatment. (Swindells, 2020)

Eventually, Nebraska's research team concluded the comparative trial of long-term active Cabotegravir and Rilpivirine with oral induction therapy for HIV-1 infection. The conclusion is that monthly injections were non-inferior to standard oral therapy for maintaining HIV-1 suppression. Injection-related adverse events were familiar but infrequently led to medication withdrawal. (Swindells, 2020)

3 STUDY RESULTS

3.1 Pharmacology Property

CABENUVA was proved very effective to treat single-cycle HIV-1 infections and HIV-1 mutants with site-directed mutations (Elvitegravir-resistant integrase mutants, raltegravir-resistant integrase mutants, and raltegravir-resistant integrase mutants). When using it for dolutegravir-resistant integrase mutants and raltegravir-resistant integrase mutants, the medication was less effective. The EC50 value was shown below in Table.1.

Table 1: CABENUVA EC50 value of HIV mutants.

Mutants	EC50 (nmol/L)
92UG029, NL4-3, LAI, MJ4, 92UG001, MVP5180-91	1.3-2.0
Y143C, T97A+Y143C	1.2
E92Q+N155H	5.9
E138K+G140S+Q148R	*15*
E92Q+Y143C	2.4
E92Q+NQ155H	12
G140A+Q148R	11

Participants were randomly allocated to IM cabotegravir 800 mg after 14 days of receiving 30 mg oral cabotegravir once a day, followed by three 200 mg SC doses, three 200 mg IM doses, or three One 400 mg IM doses every four weeks, or a second cabotegravir 800 mg IM treatment after 12 weeks. At month 3 (1200 mg) and month 4, those in the 200 and 400 mg IM cohorts received IM doses of long-acting rilpivirine (900 or 600 mg). For all four regimens, treatment-related plasma cabotegravir concentrations (mean > 4 PA-IC90) were seen 3 days after injection and lasted until the conclusion of the dosing interval. The cabotegravir 800 and then 400 mg IM regimens showed accumulation until the fourth month, whereas the other regimens appeared to be stable after three months.

The pharmacokinetic characteristics of the two medications have low to moderate inter-subject variability (cabotegravir AUC CV percent is 23-52 percent, and ripavirine AUC CV percent is 34-35 percent). At week 8, 4 weeks following the first IM loading dosage (primary trough concentration), the cumulative geometric mean (95 percent CI) plasma concentrations for CAB (1.31 to 1.46) and RPV (38.05 to 41.80) were 1.38 g/mL (1.31 to 1.46) and 39.88 ng/mL (38.05 to 41.80), respectively. The geometric mean (95 percent confidence interval) plasma concentration of CAB was 2.97 g/mL (2.85 to 3.10) at week 48, whereas the RPV was 86.42 ng/mL. (82.87 to 90.14).

FLAIR (N = 566) and ATLAS (N = 618) trials were conducted in HIV-1 infected adults to demonstrate its non-inferior antiviral efficacy. The distinction is that FLAIR enrolls ART-naive patients, while ATLAS select ART-experienced patients who were stable on an ARV regimen. (Clinical Review Report)

The trials were divided into 3 stages. First of all, the induction phase (FLAIR only) controls their plasma HIV-1 RNA. Then in the maintenance phase, the patients were randomly grouped in half to remain on oral CART or switch to the CAB + RPV regimen. Patients in the FLAIR studies continued their therapy during the induction phase, whereas those in the ATLAS trials continued to utilize their existing ARV regimen. The latter group takes oral CAB + RPV (30 mg/25 mg, one tablet each) once a day for at least four weeks, then injects the first dosage of CAB + RPV (600 mg/900 mg) within two hours of the final oral dose, then injects CAB + RPV (400 mg/600 mg) every four weeks after that. Patients in the CAB + RPV group continued their IM dose as normal throughout the "extension phase," and those moving from the CART group to CAB + RPV followed the same treatment regimen.

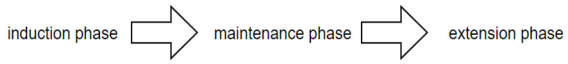

Figure 4: Trial process.

HIV-1 immunotherapeutic vaccines, systemic immunomodulators, acetaminophen (if acute viral hepatitis is present), chronic use of systemic glucocorticoids, HCV therapy, certain antibiotics, consistent administration of medications that lower the concentration of any study drug component, and other exploratory agents, ARV drugs (not otherwise specified), cytotoxic chemotherapy, or radiation therapy were not allowed at any time during the study.

Over 90% of the patients in both trials were continuing through or completed the maintenance phase. However. 22% of patients in FLAIR and 12% patients in ATLAS were considered screening failures since lack of efficacy (5%), AE or withdraw

from the trials (approximately 5% to 7% after entering the long-term follow-up phase).

The results existed at week 48 as the virologic responses became significant, which is the standard time frame used in the HIV-1 trial and is consistent with the shortest analysis duration recommended by the FDA for virological endpoints. The trial is ongoing and the planned duration is 120 to 148 weeks.

In FLAIR, virologic failure was reported in 2.1 percent and 2.5 percent of patients in the CAB + RPV and CART groups, respectively, with HIV-1 RNA levels of 50 copies/mL or above at week 48. In CART, 1.6 percent of patients in the CAB + RPV group and 1.0 percent in the CART group. In FLAIR, CAB + RPV and CART scored 94 percent and 93 percent, respectively, while in ATLAS, CAB + RPV and CART scored 93 percent and 95 percent, respectively. At week 48, HIV-1 RNA was less than 50 copies/mL. In FLAIR and ATLAS, treatment differences were 0.4 percent (95 percent CI, 3.7 to 4.5) and 3.0 percent, respectively. It shows that there isn't much of a difference between CAB+RPV and CART effectiveness. The 96-week results confirm the 48-week findings, indicating that long-acting cabotegravir and rilpivirine are non-inferior to maintaining a standard care regimen in individuals with HIV-1 for viral suppression maintenance. These findings suggest the long-acting cabotegravir and rilpivirine as a treatment choice for virally suppressed people with HIV-1 over a nearly 2-year period.

3.2 AE and Model Health-Related Quality of Life

In both studies, the CAB + RPV group had higher AEs than those in the CART group in the process of the maintenance. In ATLAS and FLAIR, more than 90% of patients in the CAB + RPV group had at least one AE across trials, whereas in ATLAS and FLAIR, the overall prevalence of AEs in the CART group was 71 percent and 80 percent, respectively. Most of AEs were classified as grade 1 or 2. The revealed higher occurrence of AEs was due in part to a variety of ISRs caused by the monthly IM injections. Another trial suggests that the observed AE profile with CAB + RPV LA treatment was identical to that in the CAR arm, omitting ISRs, and is consistent with the previously oral therapy. Despite the fact that ISRs are widespread (they account for 25% of all injections), the majority of them are moderate (99 percent grade 1 or 2). Throughout the trial, the overall incidence of ISRs rapidly declined from 70% at week 4 to 16% at week 48, and the length of ISRs was brief (median 3 days). These findings show that the initial high rate of ISRs was due to the introduction of a novel treatment administration method (IM injection), with a lower rate over time as participants got more comfortable with the injection process.

HRQoL can be a valuable data for us to evaluate the patients' prognosis. In that case, HIVTSQ, PIN, ACCEPT, HAT-QoL, NRS, and SF-12 are used to evaluate a variety of characteristics of HRQoL, such as acceptance of an injectable regimen and issues that may arise as a result of it. In ATLAS, the HIVTSQs and PIN results were statistically significant in favor of the CAB + RPV group, but this was not the case in FLAIR (after adjusting for multiplicity). The other measurements revealed that CAB + RPV had a numerical advantage in terms of patients' HRQoL. None of these analyses were multiplicity-adjusted, except the total score of HIVTSQs and PIN, hence the results should be regarded with care. (Clinical Review Report)

4 PHARMACOECONOMIC RESULT

Pharmacoeconomic research of CABENUVA has been made by ViiV and CADTH using the Markov cohort state transition model to discover its cost and QALY to evaluate the value of this drug as a treatment to HIV, especially comparing with oral ART administration. The result was shown below in Figure 5.

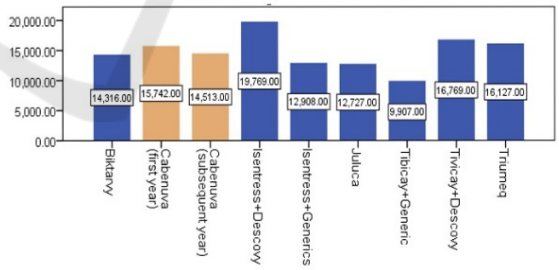

Figure 5: Annual Cost comparison between HIV treatments.

In comparison to combined oral ART, CAB+RPV has lower overall costs and less total QALYs, as indicated in the figure, indicating that it is not cost-effective. The overall estimated cost of CAB + RPV during the patient's lifetime is $647,491, whereas the total estimated cost of oral contraceptives ART is $646,865. The two comparisons generated similar life years (CAB + RPV = 24.33; oral contraceptives ART = 24.21) and QALY (18.05 and 17.96). The major cause of the discrepancies in predicted QALYs was

found by CADTH as adherence. The sponsor model projected no drop in adherence among CAB + RPV users, but increased adherence (measured as treatment disruptions) in the oral ART method (decline in adherence = 8.12 percent). (Pharmacoeconomic Review Report, 2020)

Over and above what is already being done, there is a need and potential for community pharmacists to be used in major global health sectors. Pharmacists may use their prescription knowledge to fill gaps in care that fit with significant global health activities and programs, from workforce development to drug administration. It took decades for pharmacists in high-income nations to move from product-centered to patient-centered services with public health consequences. It will take time for pharmacists in low- and middle-income nations to make the transition. These encouraging results highlight the strategic necessity of enlisting the help of community pharmacists in the Cabenuva administration. This would be especially advantageous in many communities where HIV services for extremely vulnerable groups are endangered by anti-gay legislation. Cabenuva administration at community pharmacies provides feasible, discreet, and cost-effective choices for patients and donor agencies supporting ART programs in such scenarios. Finally, authorities should ensure that pharmacists in their communities have the resources they need to properly support the administration of Cabenuva and other potential public-health medications. The aforementioned measures would complement the many efforts being undertaken to achieve UNAIDS' goal of ending the AIDS pandemic by 2030 by attaining 95 percent diagnosis and 95 percent antiretroviral treatment (ART) among all people living with HIV (PLHIV). 95% on antiretroviral therapy (ART) among diagnosed, and 95% virally suppressed (VS) among treated. (Rasaq Kayode O, 2021)

The initiator created a queuing Markov state transition model and a decision tree process hybrid model. To represent the possibility of treatment failure and/or interruption, the sponsor modelled three ART lines and one remedial therapy line. The cohort in this model migrated to the sponsor's health condition, which was determined by the treatment line, viral load, and CD4+ T cell count. Patients may develop ADE, treatment-related AEs, or cardiovascular illness in these conditions. The transition between health condition in each monthly cycle is determined by the cohort's viral status and CD4+ T cell count, and the patient can reach the absorptive state of death at any time throughout the model cycle.

Consequently, due to the customized character of HIV-1 therapy, particularly in terms of the timing and reason for switching treatments, sponsors may have overstated the cost reductions associated with CAB + RPV. Cost reductions may or may not be obtained depending on the setting in which CAB + RPV is treated and if these expenses are shared by public healthcare payers. Patients were enthusiastic about the notion of a once-monthly injection, which is supposed to minimize stigma by giving HIV-1 patients greater privacy and discretion. Furthermore, patients thought that lowering pill load would increase adherence and, as a result, viral suppression. The experience of a patient on CAB + RPV, who experienced less side effects and the capacity to be more socially involved, was shared with one patient group. (Aschenbrenner, 2021)

5 COMPARATIVE ANALYSIS

5.1 Route of Administration

Besides Cabenuva, there are other newly FDA-approved HIV medications. Compared to other newly approved HIV drugs, Cabenuva has its advantages as well as its disadvantages, and the comparison will depend on several aspects including MOA, route of administration, indication. Although there is a large amount of new HIV medications since the beginning of this century. This article will mainly focus on the comparison between Cabenuva and other new HIV drugs since 2018.

Table 2. Route of administration and regimen of new medications

Name	Route of Administration	Regimen	Approved Time
Cabenuva	Injection	once a month	January 22, 2021
Trogarzo	Injection	every 2 weeks	March 6, 2018
Pifeltro	Oral	once daily	August 30, 2018

Dovato	Oral	once daily	April 8, 2019
Biktarvy	Oral	once daily	February 7, 2018
Symtuza	Oral	once daily	July 17, 2018
Delstrigo	Oral	once daily	August 30, 2018
Symfi	Oral	once daily	March 22, 2018
Cimduo	Oral	once daily	February 28, 2018

Table 2 shows the route of administration and frequency of newly approved HIV drugs since 2018. It can be concluded that the main route of administration is oral, and the patients should take medicine daily. Only Cabenuva and Trogarzo are administered via injection and the regimen is once a month and every 2 weeks, which reduces the impact on patients' daily life arising from taking medicines daily. Compared to the regimen of Trogazo, injection every 2 weeks, the regimen of Cabenuva is once a month through injection after the patients take the tablet for 28 days, which means only 12 days of treatment is required for an entire year. (Villaluz, 2021)

5.2 Indication and MOA

Table 3 shows the indication and MOA of these new medications. From Table 3, it can be concluded that Trogarzo, Pifeltro and Cimduo should be used in combination with other ARV. Dovato, Delstrigo and Symfi can only be applied in the treatment of HIV-1 in adults. Only Cabenuva and Biktarvy are indicated to be a complete regimen for all the patients. Considering the indication, long-acting effect, Cabenuva has its advantages to a large extent. Cabenuva can be applied to a wide range of patients and also can improve the lives of these patients. (Villaluz, 2021)

Table 3. Indication and MOA of New Medications

Name	Indication	MOA
Cabenuva	Long-acting regimen with the all HIV-1 patients	INSTI/NNRTI
Trogarzo	In combination with other ARV	Post-attachment Inhibitor
Pifeltro	In combination with other ARV	NNRTI
Dovato	Treatment of HIV-1 in adults	INSTI/NRTI
Biktarvy	Treatment of HIV-1 as a complete regimen	INSTI/NRTI
Symtuza	Treatment of HIV-1 in adults and pediatric patients	NNRTI/BOOSTER/NRTI
Delstrigo	Treatment of HIV-1 in adults	NNRTI/NRTI
Symfi	Treatment of HIV-1 in adults	NNRTI/NRTI
Cimduo	In combination with other ARV	NRTI

6 CONCLUSION

In conclusion, HIV is a dangerous disease that affects patients, and the daily life of them can be improved by accepting a wild range of treatments. Therefore, the development of more effective and convenient medication is important. Almost all the new HIV drugs approved since 2018 are administered orally

daily. However, there have been some drugs whose route of administration is injection such as Trogazo and Cabenuva. By reducing the frequency of medicine dosage, the life quality of HIV patients can be improved. Cabenuva, a newly approved HIV drug, is the first complete, long-acting HIV treatment regimen, administered by intramuscular injection once a month. This drug can make changes to the life of patients to a great extent compared to other HIV medications. Moreover, the development of Cabenuva indicates that it is possible to develop more long-acting HIV drugs, which set a new development trend not only focused on treatment efficiency but the life quality of patients.

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