Cabotegravir/rilpivirine in pregnancy: early insights from clinical practice

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Objective: To describe early experience with the use of cabotegravir/rilpivirine (CAB/RPV) in pregnancy and make recommendations based on these observations.

Design: This is a case series.

Setting: This took place at a multidisciplinary HIV clinic based at an academic centre in Ottawa, Canada.

Participants: Women who received CAB/RPV during pregnancy and carried their child through to delivery are described.

Methods: The first seven such women were enrolled and their clinical course is described.

Main outcome measure(s): The primary outcome was a description of the experience and clinical effectiveness of CAB/RPV when used through pregnancy.

Results: Initially, CAB/RPV was discontinued after pregnancy was confirmed and oral antiretroviral therapy was initiated instead. With evolving information on the safety and pharmacokinetics of cabotegravir and rilpivirine and advancing clinical experience, CAB/RPV given every 2 months was continued through pregnancy and oral antiretroviral therapy was added at 34–36 weeks gestation up until delivery to address the potential for subtherapeutic levels of cabotegravir and/or rilpivirine. In one individual where oral therapy was not an option, CAB/RPV was administered monthly from 20 weeks' gestation. All women maintained an undetectable viral load at the time of delivery.

Conclusions: With the challenges and potential risks associated with interrupting CAB/RPV before or during pregnancy, we have established an approach to address this. Maintaining CAB/RPV q monthly or supplementing CAB/RPV q2 months with oral therapy starting at 34–36 weeks' gestation until delivery are potential approaches that allow CAB/RPV to be administered uninterrupted during pregnancy.

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Introduction

Cabotegravir/rilpivirine (CAB/RPV) is the first approved complete long-acting injectable antiretroviral regimen, representing a major advance in the management of HIV infection. It is recommended in major international guidelines as an option for a switch in therapy when virologic suppression has been achieved [1–4]. With limited safety and efficacy data, it is currently not recommended in pregnancy nor in women actively trying to become pregnant [1–4]. This recommendation is based, at least in part, on the anticipated reduction in drug concentrations during the third trimester of pregnancy, particularly for rilpivirine, where decreased exposure has been shown to be clinically significant with oral formulations [5,6].

CAB/RPV use during pregnancy could be very valuable, particularly in cases where oral therapy is poorly tolerated or adherence to oral therapy is challenging. For patients treated with CAB/RPV who become pregnant, clinicians and patients are confronted with the need to address the risks and benefits of transition to a treatment for which there is more established evidence, and recommended within treatment guideline, but which may counterintuitively increase the risk of breakthrough viremia and negative pregnancy outcome. This is not a theoretical concern. Cases have already been reported in which patients with adherence challenges were switched from effective CAB/RPV back to an oral regimen in anticipation of conception. Following the treatment change, loss of viral control and emergent resistance to RPV occurred, preventing retreatment with long-acting injectable therapy [7].

Methods

Here we describe the management of the first seven patients in our academic center-based multidisciplinary clinic who received CAB/RPV during a pregnancy up to delivery and provide suggestions on the management of pregnant women who wish to remain on CAB/RPV during their pregnancy.

Results

CAB/RPV was approved by Health Canada in March 2020 and available in pharmacies for prescription in September 2020. In 2022, our first patient who became pregnant while on treatment with CAB/RPV was a 38-year-old Burmese woman with well managed HIV infection for over 11 years. She had been receiving every 2 monthly CAB/RPV for approximately 4 months when pregnancy was detected at approximately 15 weeks' gestation. After an extensive discussion with the patient and her partner, a decision was made to discontinue CAB/RPV and begin bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) at 16 weeks' gestation. She went on to have an uncomplicated delivery of a healthy infant. The second and third women, both of whom started CAB/RPV before they were known to be pregnant, were approached in a similar fashion. They received their last doses of CAB/RPV at 18 and 12 weeks' gestation respectively and began BIC/TAF/FTC at 24 and 21 weeks' gestation.

As challenges arose with interrupting and reinitiating CAB/RPV, and as more information became available on the safety and pharmacokinetics of CAB/RPV in pregnancy, a different approach was taken. In the fourth, fifth and seventh women, q2 monthly CAB/RPV was continued uninterrupted throughout and following pregnancy, and supplementary antiretroviral therapy (specifically BIC/TAF/FTC) was prescribed during the final 4–6 weeks of pregnancy.

In the sixth woman, in whom a switch to or addition of oral therapy was not a viable option due to pill intolerance, CBV/RPV was prescribed q monthly starting at 25 weeks' gestation, the goal of which was to optimize the drug levels of rilpivirine and cabotegravir during the late second and third trimesters.

Of importance, all seven women had an undetectable viral load at the time of delivery. In two of these women (#5 and 6), drug levels were available late in the third trimester (7 and 5 weeks after the last bimonthly injection respectively). Levels of both cabotegravir and rilpivirine were below the target C_{min} in one, and in the target range in the other (see Table 1).

Discussion

Being able to use CAB/RPV as a safe and effective option during and throughout pregnancy would be an important advance in the management of this population. The safety of CAB in pregnancy has been established through studies of CAB as preexposure prophylaxis [9,10]. More recently, studies of the pharmacokinetics of CAB throughout pregnancy suggest that levels of CAB, even when administered q2 monthly, remain in a range which provides adequate virologic activity [11,12].

The safety of rilpivirine during pregnancy is well established and first trimester exposure to RPV is not associated with an increased risk of congenital abnormalities [13]. As summarized in the DHHS guidelines, RPV plasma concentrations after oral dosing are decreased by approximately 20% to 50% during pregnancy [1]

Table 1. Characteristics of women receiving CAB/RPV through pregnancy

	Country of birth	Age (years)	GTPAL	First dose of CAB/ RPV	ART prior to CAB/RPV	GA at last dose of CAB/ RPV (weeks)	Interruption of CAB/RPV schedule	CAB/RPV regimen in pregnancy	GA at first dose of oral therapy (weeks)	Oral therapy initiated in pregnancy	Drug levels		
											CAB[a]	RPV[b]	GA (weeks)
1	Burma	42	G3T0P0A0L2	5 weeks pre conception	EVG/COBI/FTC/ TAF	7	Y	q2m	14	BIC/FTC/TAF			
2	Ukraine	38	G4T3P0A0L3	13 weeks gestation	BIC/FTC/ TAF	18	Y	q2m	24	BIC/FTC/TAF			
3	Liberia	47	G4T3P0A0L3	54 weeks pre conception	BIC/FTC/ TAF	12	Y	q2m	21	BIC/FTC/TAF			
4	Cameroon	44	G5T3P0A1L3	7 weeks pre conception	DTG/TDF/ 3TC	32	N	q2m	36	BIC/FTC/TAF	857	45	40
5	Nigeria	30	G2T1P0A0L1	120 weeks pre conception	EVG/COBI/FTC/ TAF	39	N	q2m	35	BIC/FTC/TAF	2619	74	36
6	Cote d'Ivoire	25	G1T0P0A0L0	25 weeks gestation	BIC/FTC/ TAF	37	N	q1m	N/A	N/A			
7	Democratic Republic of Congo	37	G6T5P0A0L5	7 weeks gestation	BIC/FTC/ TAF	31	N	q2m	35	BIC/FTC/TAF			

GA, gestational age.
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide.
EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
DTG/TDF/3TC, dolutegravir/tenofovir disoproxil fumarate/lamivudine.
[a]Cabotegravir target range: 1600–4000 ng/ml.
[b]Rilpivirine target range: 68–133 ng/ml.

As for the clinical experience of intramuscular CAB/RPV administered during pregnancy, there have been a few individual cases published [14–16] and a case series of 23 presented in abstract form [17]. While the reported experiences are informative and generally encouraging, the numbers are small and the heterogeneity too great to make any conclusions or to translate these observations into clinical practice.

With a great desire for guidance in the use of CAB/RPV during pregnancy, our experience suggests an appropriate approach to the use of CAB/RPV in pregnancy would be: in the exceptional circumstance when a woman is unwilling or unable to take oral therapy, CAB/RPV can be administered monthly starting before 28 weeks' gestation as a means of improving the pharmacokinetics of rilpivirine, or if oral therapy is an option, CAB/RPV can be continued every 2 months through pregnancy and oral therapy (i.e. supplementation with an effective single tablet regimen) can be prescribed beginning at week 34–36 gestation.

In the face of incomplete data, a bias for risk aversion has the potential to compromise long-term maintenance of HIV suppression with safe and convenient therapy. When CAB/RPV has been initiated in a patient who becomes pregnant, the reasons for use of long-acting injectable therapy and the potential risk of incomplete adherence to oral treatment needs to be considered alongside the growing evidence of safety in this population. Ongoing experience from our center and others, including that from the antiretroviral pregnancy registry will help inform optimal use of CAB/RPV during pregnancy [8].

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Conflicts of interest

There are no conflicts of interest.

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