The risks associated with stopping injectable ART in women who are trying to conceive: a case series

Harry Coleman[1], Julie Fox[1,2], Daniella Chilton[1]

Guy's and St Thomas' NHS Foundation Trust

Background:

Regulatory agencies have recently approved long-acting Cabotegravir/Rilpivirine (CAB/RPV) intramuscular injection, for treating HIV-1 infection in adults[1],[2],[3]. ATLAS and FLAIR, phase 3 randomised trials, established that switching to CAB/RPV was non-inferior to continuation of oral therapy[4],[5]. These studies excluded women who were pregnant, breastfeeding or planning to become pregnant.

Since pregnant women are nearly always excluded from phase 3 anti-retroviral therapy (ART) clinical trials, there is little trial data supporting ART use in pregnancy. Despite 1.5 million women living with HIV becoming pregnant each year[6], Zidovudine remains the only ART with a licence for use in pregnancy[7].

Within the ATLAS and FLAIR studies, 7 people had virological failure and of these 6 developed resistance mutations[8].

We describe two female patients with perinatally acquired HIV, and a history of poor adherence to ART who accessed long acting injectable (LAI) through the compassionate access programme. Both planned to conceive, therefore interrupted LAI and took oral therapy during LAI 'washout'. Both have subsequently developed NNRTI resistance, precluding CAB/RPV therapy.

Patient 1:

34 year old, on Darunavir/Ritonavir (DRV/r) commenced LAI (August 2019) following lead-in with oral Cabotegraivr/Rilpivirine and Darunavir/Ritonavir (July 2019).

At initiation and throughout LAI she maintained virological suppression (<20 copies/ml). She switched to Descovy (TAF/FTC) and Dolutegravir (DTG) (September 2020) to prepare for conception, including a 1 year 'washout'.

Due to psychological problems, she stopped her oral ART (August 2021). By November 2021 she had a VL of >50,000 copies/ml and a resistance test showed a new Y181C indicating intermediate Rilpivirine resistance.

Her last injectable was a year prior and she had a VL of <20 copies/ml in the intervening period. She had no previous NNRTI exposure.

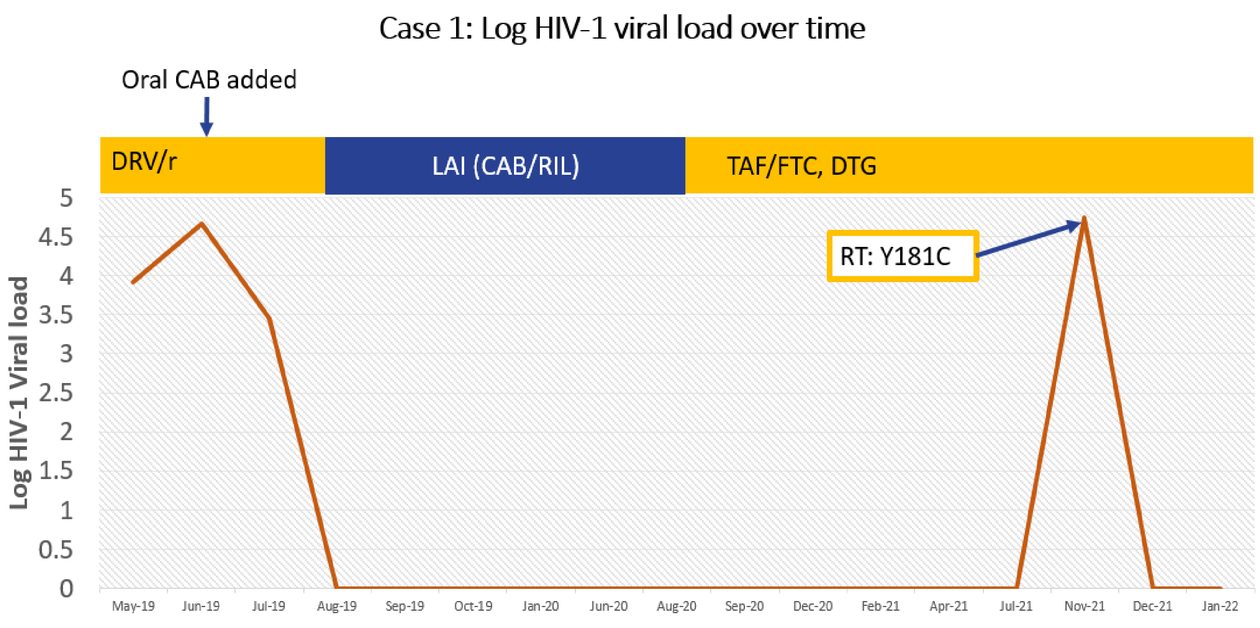
Patient 2:

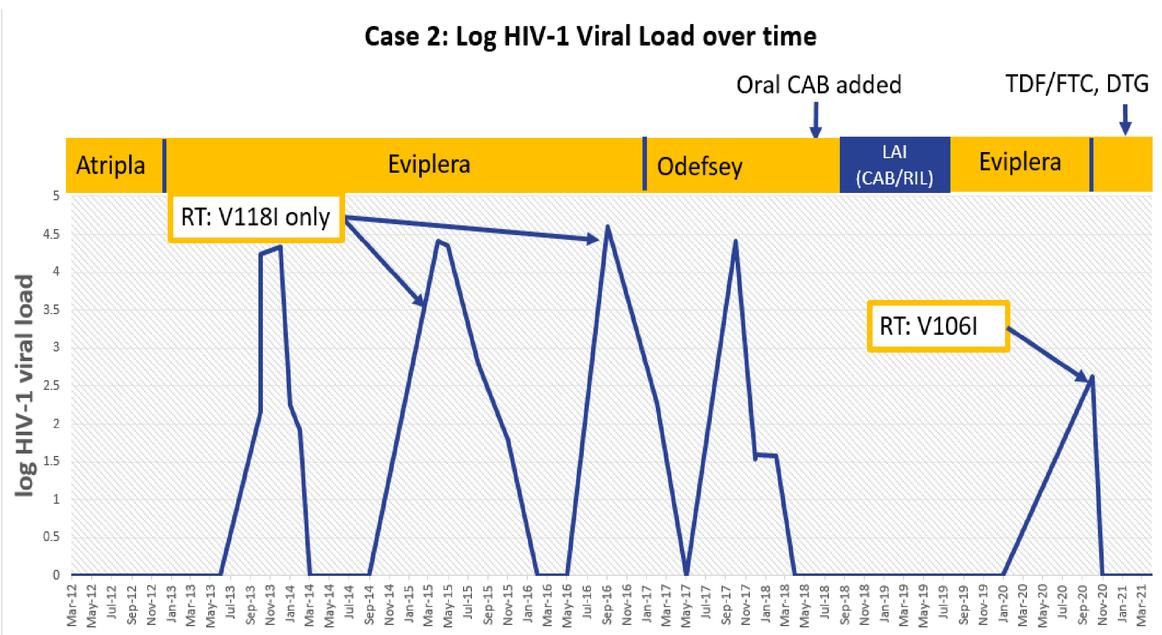
28 year old, on Odefsey, commenced LAI in June 2018 following lead-in with oral Cabotegravir and Odefsey. At initiation and throughout LAI she maintained virological suppression (<20 copies/ml).

She switched to Eviplera in July 2020 for a 'washout' period as she was planning conception. Virological rebound occurred at 3 months (VL 421 copies/ml) and the patient reported poor adherence to ART.

A genotype initially failed to amplify and she switched to Tenofovir/Emtricitibine and Dolutegravir. Virological control was achieved with intermittent adherence.

Subsequent resistance results (October 2020) have shown a new V106I indicating low-level Rilpivirine resistance.





Due to the lack of licenced drugs in pregnancy, switches are inevitable.

In these two patients who experienced significant stigma and psychological burden from oral ART, injectable treatment offered an excellent alternative and provided virological suppression.

Stopping injectable ART in people with known adherence issues can be problematic, as resistance in these two cases appears to have developed late and will limit future treatment options. The risk of new medications in pregnancy needs to be balanced with the risk of viraemia.

Drug companies and clinicians must report pregnancy outcomes to increase confidence and availability of ART during pregnancy.

[1] https://www.nice.org.uk/guidance/gid-ta10658/documents/final-appraisal-determination-document Date accessed: 1/1/2022
[2] https://www.ema.europa.eu/en/medicines/human/EPAR/vocabria Date accessed: 1/1/2022
[3] https://www.fda.gov/drugs/human-immunodeficiency-virus-hiv/fda-approves-cabenuva-and-vocabria-treatment-hiv-1-infection Date accessed: 1/1/2022
[4] Orkin C, Oka S, Philibert P, Brinson C, Bassa A, Gusev D, et. al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. Lancet HIV. 2021 Apr;8(4):e185-e196. doi: 10.1016/S2352-3018(20)30340-4. Erratum in: Lancet HIV. 2021 Dec;8(12):e734. PMID: 33794181.
[5] Swindells S, Lutz T, van Zyl L, Porteiro N, Stoll M, Mitha E, et al. Long-acting cabotegravir + rilpivirine for HIV-1 treatment: ATLAS week 96 results. AIDS. 2021 Jul 13. doi: 10.1097/QAD.0000000000003025. Epub ahead of print. PMID: 34261093.
[6] UNAIDS. The Gap Report 2014. Children and pregnant women living with HIV. Joint United Nations Programme on HIV and AIDS. http://www.unaids.org/sites/default/files/media_asset/09_ChildrenandpregnantwomenlivingwithHIV.pdf
[7] Bailey H, Zash R, Rasi V, Thorne C. HIV treatment in pregnancy. Lancet HIV. 2018 Aug;5(8):e457-e467. doi: 10.1016/S2352-3018(18)30059-6. Epub 2018 Jun 26. PMID: 29958853.
[8] Rizzardini G, Overton ET, Orkin C, Swindells S, Arasteh K, Górgolas Hernández-Mora M,. Long-Acting Injectable Cabotegravir + Rilpivirine for HIV Maintenance Therapy: Week 48 Pooled Analysis of Phase 3 ATLAS and FLAIR Trials. J Acquir Immune Defic Syndr. 2020 Dec 1;85(4):498-506. doi: 10.1097/QAI.0000000000002466. PMID: 33136751; PMCID: PMC7592884.