Therapeutic drug monitoring of darunavir levels in pregnancy

Emma Wainwright and Fabian Chen, The Florey Clinic, Royal Berkshire Hospital, Reading, UK.

Summary

• Case note audit of therapeutic drug monitoring (TDM) in pregnant women taking darunavir/ritonavir in 2017 and 2018
• 9 pregnancies with darunavir as part of the regimen; 8 of these had a TDM performed (1 pregnancy had 2 TDMs performed and 1 pregnancy did not have a TDM)
• Only 1 TDM reported as inadequate for wild type virus and 3 inadequate for resistant virus
• All pregnancies with a TDM reported as inadequate for either wild type or resistant virus had undetectable viral loads

Introduction

There are numerous physiological changes in pregnancy which can affect drug absorption, distribution, metabolism and elimination. Therefore drug levels and levels of active drug can be very different in pregnancy compared to the non-pregnant state.

A number of studies have suggested lower levels of protease inhibitors in pregnancy. However, protease inhibitors are highly protein-bound and the fraction of protein-bound drug decreases in pregnancy (thereby increasing the levels of active drug). Crauwels et al. (1) studied 16 pregnant women living with HIV who were taking darunavir/ritonavir 800/100 od. They found that the area under the curve (AUC) for 24 hours for total darunavir was 35% lower in the third trimester compared to postpartum but that unbound (active) darunavir levels were only 20% lower. The levels in pregnancy exceeded the minimum concentration needed for wild type virus in all but one case (and this one case reported non-adherence). 100% of the 14 subjects who remained in the study at the end of pregnancy were fully suppressed in the 3rd trimester. All babies were HIV negative. Zorilla et al. (2) studied 14 pregnant women living with HIV who were taking darunavir/ritonavir 600/100 bd. They found that the AUC for 12 hours for total darunavir was 17% lower in the third trimester compared to postpartum but that unbound darunavir was only 7% lower. 90% (9 of 10) women had full viral suppression in the 3rd trimester. All babies were HIV negative.

BHIVA guidelines (3) recommend considering therapeutic drug monitoring (TDM) in the third trimester and recommends considering twice daily darunavir dosing if initiating darunavir in pregnancy or if there is known resistance.

Aim

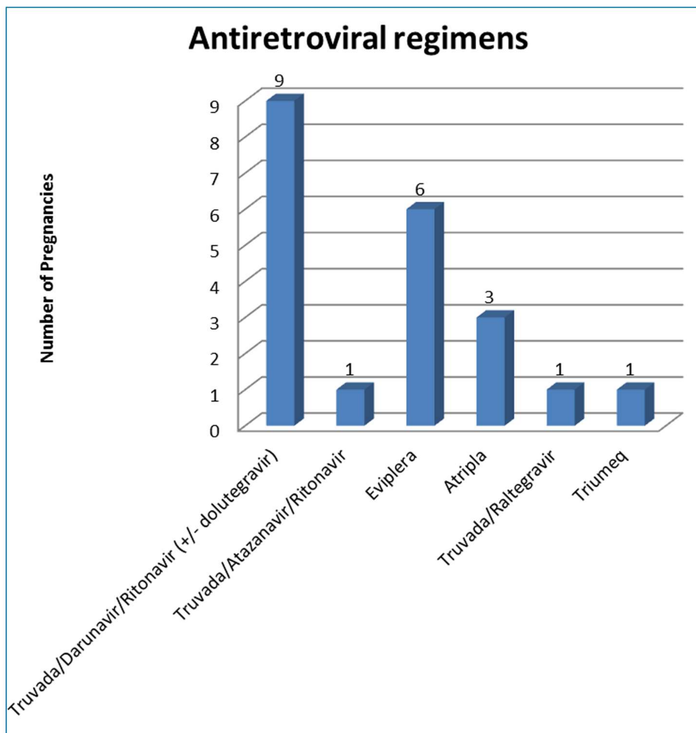
This audit aimed to find out if our clinic was undertaking TDM for darunavir as per BHIVA guidance, to assess whether there were many women with inadequate darunavir levels and to record what action was taken.

Methods

We conducted a notes audit of all pregnancies on our antenatal multi-disciplinary team clinic database between January 2017 and June 2018.

Results

There were 21 pregnancies in this time period in 20 women living with HIV-1. The mean age of women at the time of delivery was 33 years (range 24 to 44 years).

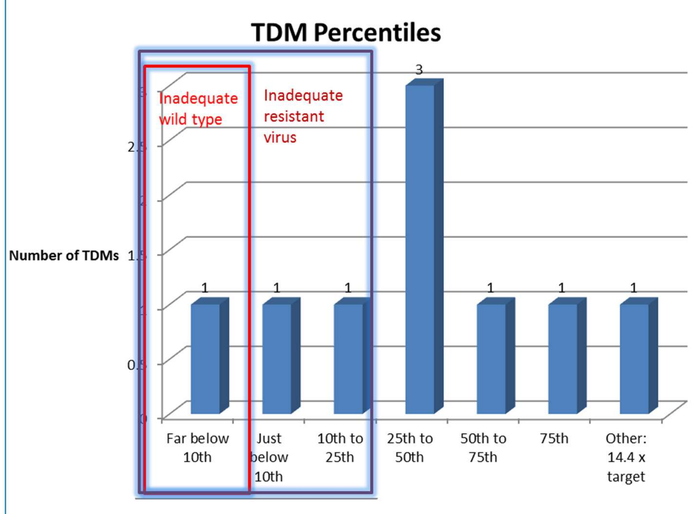


•There were 9 pregnancies with darunavir as part of their regimen (43% of pregnancies). All of these were on once daily darunavir initially. All of these were on darunavir/ritonavir rather than darunavir/cobicistat.

•5 of the 9 (56%) started darunavir during pregnancy and 4 (44%) conceived on it.

•8 of the 9 pregnancies had a TDM performed (89% of darunavir-pregnancies). The one patient who did not have a TDM performed had switched to darunavir 1 week before delivery due to a detectable viral load therefore there was no time for a TDM. 1 patient had 2 TDMs performed in 1 pregnancy.

•7 of the 9 TDMs (78%) were performed in the 3rd trimester.



•1 of the 9 TDMs (11%) was reported as inadequate for wild type virus.

•3 of the 9 TDMs (33%) were reported as inadequate for resistant virus.

•For all of the cases with levels inadequate for wild type or resistant virus the HIV viral load at the time of the TDM was undetectable (even for the TDM with levels far below the 10th percentile).

•In the 2 patients with results below the 10th percentile their darunavir regimen was changed to 600mg twice daily plus ritonavir 100mg twice daily. In neither case was the TDM repeated after the switch. These 2 cases had started darunavir in pregnancy rather than conceiving on it.

•1 woman had a detectable viral load at the time of the TDM (1820cp/ml) and in the last measurement before delivery (633 cp/ml). Her TDM measurement had been between 50th and 75th percentile. For 1 pregnancy the last viral load measurement was unknown (delivery was at another hospital). For the 7 other darunavir-pregnancies the last viral load was undetectable.

•The baby's outcome for the darunavir-pregnancies:

HIV status of baby for those on darunavir	Number
Negative so far	4
Not recorded in sexual health notes	4
Not delivered yet	1

•All pregnancies and babies are discussed in our antenatal MDT and there have been no babies with a positive HIV test in this time period.
•Other notes of interest:
2 pregnancies with dolutegravir as part of the regimen: 1 started dolutegravir just 1 week before delivery and there were no reported congenital abnormalities; 1 conceived on dolutegravir but terminated the pregnancy in the first trimester.

Conclusions

•A high proportion (9 of 21; 43%) of the pregnancies in this time period were taking darunavir/ritonavir as part of their regimen.
•All of these were taking once daily darunavir rather than twice daily.
•Most TDMs (8 of 9) showed levels of darunavir that were predicted to be adequate for wild type virus.
•Those with levels predicted to be inadequate for wild type or resistant virus had undetectable viral loads.
•Despite the fact that all pregnant women and babies are discussed in our antenatal MDT the HIV status of the babies was not always clearly recorded in the sexual health notes and this has now been addressed by ensuring that the HIV status of the baby is always recorded in the sexual health notes before the patient is removed from our antenatal MDT list.

References

1. Pharmacokinetics of once-daily darunavir/ritonavir in HIV-1-infected pregnant women. Crauwels HM, Kakuda TN, Ryan B, Zorrilla C, Osiyemi OO, Yasin S, Brown K, Verboven P, Hillewaert V, Baugh B. HIV Med. 2016 Oct;17(9):643-52.
2. Total and unbound darunavir pharmacokinetics in pregnant women infected with HIV-1: results of a study of darunavir/ritonavir 600/100 mg administered twice daily. Zorrilla CD, Wright R, Osiyemi OO, Yasin S, Baugh B, Brown K, Coate B, Verboven P, Mrus J, Falcon R, Kakuda TN. HIV Med. 2014 Jan;15(1):50-6.
3. https://www.bhiva.org/guidelines