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TEACHING FILES (GRAND ROUNDS)

HYPERBILIRUBINEMIA IN A CHILD ON ANTI-RETROVIRAL THERAPY

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Clinical Problem:
A 20 years old HIV infected girl on anti-retroviral therapy (ART) since the age of 12 years presented with jaundice for 3 months. There was no fever. She was initially on stavudine (d4T), lamivudine (3TC) and efavirenz (EFV) till the age of 17 years and was subsequently shifted to abacavir (ABC), lamivudine (3TC) and lopinavir/ritonavir (LPV/r) in view of virological failure. In view of high pill burden and undetectable viral load, LPV/r was omitted and Atazanavir/ritonavir (ATZ/r) (300/100 mg) was started 3 months ago and ABC and 3TC were continued. Subsequently, the girl developed jaundice. Her total bilirubin 3 months ago was 3.8 mg/dL with a direct bilirubin of 1.98 mg/dL. Currently, her total bilirubin was 2.8 mg/dL with a direct bilirubin of 0.78 mg/dL. Her liver transaminases, serum lactate and lipid levels were normal. Hepatitis B and Hepatitis C Elisa was negative.

What is the cause of the jaundice and how to manage the jaundice?

Discussion:
Liver function test (LFT) abnormalities are frequently identified in HIV patients. The common causes of jaundice in these patients are drug-induced hyperbilirubinemia, alcoholic liver disease, opportunistic infections and neoplasms.[1] ATZ is a protease inhibitor. It has favorable pharmacokinetics that enables once-daily dosing which helps in reducing pill burden. It also has a better lipid profile as compared to other protease inhibitors.[2] It is also safe to use during pregnancy but neonatal hyperbilirubinemia should be monitored.[3] The common side effects associated with ATZ are headache, nausea, jaundice, insomnia and fever. Atazanavir competitively inhibits UDP glucuronosyltransferase (UGT1A1) – a microsomal enzyme responsible for bilirubin conjugation in the hepatocytes. This results in unconjugated hyperbilirubinemia which is not associated with hepatic injury.[4] ATZ induced hyperbilirubinemia is more common in the presence of UGT1A1*28 allele. The frequency of this allele is more in Indians, Caucasians and African Americans than the rest of the world.[4] Bilirubin levels start to rise within a week of initiating ATZ. Commonly the bilirubin levels in the serum are markedly elevated for lengthy periods and the levels fluctuate with time. In one cohort study comprising of 1150 HIV infected patients, the cumulative incidence of grade 3 and 4 hyperbilirubinemia (equal to >2.5 and >5 times the upper limit of normal, respectively) was markedly higher among ATZ-exposed patients, occurring in 30% after 1 year of exposure, 73% after 5 years, and 84% after 8 years, compared with 1%, 4%, and 7%, respectively, among those not exposed to ATZ.[5] However this side effect does not appear to degrade liver functions, quality of life or adherence; hence did not affect clinical outcomes.[5,6] It is important to counsel patient beforehand regarding the safety and long term benefit of this drug to improve adherence. Increasing bilirubin concentration has been seen with higher plasma ATZ concentration, hence patients on the ritonavir-boosted ATZ regimen may benefit with removing ritonavir.[7] This should be considered only when the HIV viral load is undetectable and there is clinically evident jaundice.

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