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Drug-drug interactions: it is not only CYP450's which matter

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The objectives of this review are:

- To highlight that although CYP450's are a major target for drug-drug interactions other mechanisms need to be considered.
- To appreciate that important interactions also occur due to a change in pH (gut) and inhibition of non P450 enzymes (eg UGTs).
- To discuss the increasing importance of understanding transporter based interactions in the gut, liver, kidney and blood brain barrier.
- To outline new data on clinically important drug-drug interactions between antiretrovirals and between antiretrovirals and other drugs.
- To discuss how to predict, manage and avoid drug-drug interactions including an outline of on-line resources available for this purpose.

Pharmacokinetic drug interaction studies performed during the drug development process, or post-licensing provide the substantive data base from which recommendations regarding the use of certain drug combinations are made. However given the sheer number of potential interactions extrapolation on the basis of potential mechanism of interaction is also important. Thus a foundational knowledge of drug disposition (enzymes, transporters involved etc) is essential so that *in vitro* data (is the drug a substrate; is the drug an inhibitor of a particular enzyme or transporter) can be used to underpin a clinical study or be the basis for an informed decision re the potential for an interaction. While the major focus in the HIV field has been on CYP450 enzymes (for the obvious reason that many of the drugs are extensively metabolised and/or are inducers/inhibitors) there is a growing awareness of the key role for other proteins – in particular UDP-glucuronyltransferases (UGTs) and transporters (ABC transporters such as P-pg, MRP1,2,7; SLCO transporters such as OATP1B1, OATP1B3, OATP1A2, OCT1,2, OAT1,2). This is a rapidly emerging field and one which is going to impact not only on our understanding of mechanisms of drug-drug interactions but also on seeing the bigger picture in relation to the role of pharmacogenetics in inter-individual variability.

Unexpected interactions will continue to emerge and will need to be managed.

Ultimately the key to management of patients on multiple drugs is clinical vigilance, access to adequate resources to help inform (eg web based resources), utility of therapeutic drug monitoring where available and close follow up of patients.

Recommended reading:

Dickinson L, Khoo S, **Back D**. Pharmacokinetics and drug-drug interactions of antiretrovirals: An update. Antiviral Res. 2009 Aug 7 (Epub ahead of print).

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