Antiretroviral drug-drug interactions in an era of polypharmacy

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One of the questions that I am frequently asked is 'are drug interactions still an important issue in the management of HIV+ patients in 2019'? Clearly, we have come a long way in recent years with the drugs/regimens available, our understanding of key clinical pharmacology issues and resources to aid in managing complex patients. Drug interactions really came to the fore following the Vancouver AIDS conference in July 1996; this heralded the protease inhibitor (PI) era. But with these exciting drugs came ritonavir boosting and an awareness that ritonavir not only boosted the antiretroviral drug but also potentially other co-medications that a patient may be taking. Alongside the boosted regimens there was the first generation of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and we soon learned that both efavirenz and nevirapine could also interact – not by increasing the exposure of a co-medication but by reducing the exposure as a result of induction of key drug disposition proteins. We have now moved on to the integrase era (certainly in the major international HIV treatment guidelines) and there are some important differences in relation to the extent of drug-drug interactions.

It is critical to recognize that not all antiretrovirals have the same interaction potential and we need to keep at the forefront of our minds that it is the presence of a booster in the regimen (with a PI or elvitegravir) or the use of efavirenz or nevirapine which leads to the greatest risk of interactions. On the other hand, the non-boosted integrase inhibitors, raltegravir,

dolutegravir and bictegravir have a much more limited interaction profile which is certainly encouraging as we move forward. However, they are not without some interactions. Similarly, the nucleoside reverse transcriptase inhibitors (NRTIs) have very few interactions – but not zero!

So what are some of the key mechanisms of drug-drug interactions? Many health care professionals will have heard of cytochrome P450 (CYP450) – this is a key family of enzymes that are involved in the breakdown of many, many drugs. The principle CYP enzyme is CYP3A4 and this metabolizes around 40% of all the drugs currently available. Ritonavir and cobicistat inhibit CYP3A4 – hence the boosting of PIs, whereas efavirenz can induce CYP3A4.¹ But there are other inhibitors (e.g., macrolide antibiotics, antifungal drugs) and inducers (e.g., rifampicin, older antiepileptics) which can give rise to clinically important interactions with different antiretrovirals. Another important enzyme is uridine glucuronyl transferase (UGT1A1) which is key to the breakdown of raltegravir, dolutegravir and bictegravir (partial); this can also be upregulated or inhibited. Also very important are transport proteins – shuttle pumps – that get drugs into and out of cells. Pumps such as P-glycoprotein (P-gp; present in the gastrointestinal tract), organic anion transporting protein (OATP1B1; present in the liver) or organic cation transporter (OCT2; present in the proximal tubule) are involved in a few, but important interactions.² There are other mechanisms. Particularly important are absorption interactions. This can involve changing the pH of the intestinal milieu impacting drugs that are pH sensitive. So the absorption of both atazanavir and rilpivirine is adversely affected by antacid drugs – particularly proton pump inhibitors. On the other hand the absorption of all the integrase inhibitors is reduced in the presence of cations (aluminum, magnesium, calcium or iron present in some

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antacids or supplements). It is important to know the specific guidance to deal with these situations.³

One of the key areas for drug interaction awareness is in patients with multiple comorbidities. In these patients we will be faced with polypharmacy, which is generally defined as ≥ 5 concomitant medications and is often unavoidable. In patients with HIV infection, polypharmacy usually refers to the drugs given in addition to antiretroviral therapy.⁴

Considering the potential negative consequences of polypharmacy, efforts should be made to i) reduce unnecessary co-medications and ii) ensure that health care professionals have the necessary understanding of drug-drug interactions. The Liverpool web resource www.hiv-druginteractions.org is now firmly established as a key tool to aid in managing interactions in patients. In addition, there are useful prescribing resources available on the site and the team are engaged in workshops at international HIV meetings and also at a local

country level. Look out for a drug interaction workshop at a location near you!

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