Managing HIV patients in general practice

There are many interactions between antiretroviral therapy and other drugs regularly prescribed by GPs, write Maria Jane Tempany and Fergus O’Kelly

IN IRELAND WE ARE CURRENTLY PART OF a global epidemic of HIV/AIDS. In the world of general practice, this condition is often feared, mainly because of a lack of awareness regarding its management. Yes, all HIV patients are (or at least should be) seen in specialist centres, but they still present to their GPs with anything ranging from simple infections to psychiatric issues.

The drug treatment for HIV, highly active antiretroviral therapy (HAART), although highly effective at suppressing this virus, has been shown to interact with many other medications. As aptly stated in the US government’s antiretroviral treatment guidelines, the list of interactions involving antiretroviral drugs is “extensive and constantly expanding”. We feel that this is an area in which GPs need to be educated in order to avoid or adjust doses appropriately when prescribing drugs that may interact with these vital medications.

HIV/AIDS first came to light in the early 1980s when young gay men and intravenous drug users (IVDUs) throughout America started to get rare, opportunistic illnesses, including Kaposi’s sarcoma (previously a rare, benign cancer occurring primarily in older people) and pneumocystis carinii pneumonia (now renamed pneumocystis jiroveci). From the early 80s right through to the present day, the global understanding and treatment, and one would like to hope acceptance, of HIV has excelled beyond belief.

We have moved from a time when president Reagan refused to advocate safer sex and condom use, choosing instead to press for a ban on HIV positive immigrants entering America to an era where awareness campaigns and HAART reign. Because of all these advances, many patients taking HIV drugs can now expect to live into their 70s – an advancement inconceivable prior to HAART.

Why is HIV such an important issue? Well, its prevalence alone answers this question. According to the WHO in 2009, there were 33.3 million adults and children living with HIV throughout the world and 1.8 million AIDS-related deaths in that year alone. HIV is thought to have peaked globally in 1999, with the incidence of newly diagnosed HIV cases falling by 19% since then, according to the 2010 UNAIDS report.

However, while the incidence of HIV has declined globally, it has more than doubled here in Ireland since 1999, from 190 new cases reported then, to 395 in 2009. Here in Ireland we now have 5,637 people reported as having HIV, 1,038 as having AIDS and a total of 414 having died from AIDS.

An important issue to address is that in high-income nations, HIV infection was historically concentrated principally among injecting drug users and homosexuals. While these groups are still at high risk, heterosexual intercourse accounts for a growing proportion of cases. In the US, a quarter of people diagnosed with AIDS in 2008 were female and three quarters of these women were infected as a result of heterosexual sex.

In our south inner-city practice we decided to do an audit of our HIV patients. Forty-six patients were coded as having HIV using the practice coding system, Socrates. On further investigation, 10 of these patients were found to have died, leaving 36 current attenders. We looked at the following parameters for each of the patients: age, sex, GMS/private, whether they are attending an infectious disease specialist, whether they have co-existent hepatitis C, whether they are on methadone, whether their most recent CD4 count is above 200 and whether they are on HAART and, if so, what agents they are on.

This is largely a GMS patient-based practice, therefore unsurprisingly 92% were GMS patients; 58% of these patients were over 40 years old, supporting the fact that patients with HIV are now living into their 60s and 70s, as previously noted. Fifty-eight per cent were male and 42% female; 86% were found to be currently attending an infectious disease specialist, whether they have co-existant hepatitis C, whether they are on methadone, whether their most recent CD4 count is above 200 and whether they are on HAART and, if so, what agents they are on.

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We have mentioned HAART quite a few times up to now, but what exactly is highly active antiretroviral drug treatment? A combination of different classes of antiretroviral (ARV) drugs are administered and the use of a combination of drugs aims to reduce the rate at which resistance develops, making treatment more effective in the long-term. It
Classes of drugs that interact with antiretroviral medications

- Other anti-HIV medications
- OI drugs (eg. voriconazole, clarithromycin)
- Antituberculosis drugs (rifampin, rifabutin)
- Antacids (eg. omeprazole, cimetidine)
- Cholesterol-lowering statins (eg. lovastatin, simvastatin)
- Recreational, street or party drugs
- Antidepressants (eg. fluoxetine, sertraline)
- Anticonvulsant drugs (eg. phenytoin, phenobarbital)
- Benzodiazepines (eg. alprazolam, midazolam, triazolam)
- Oral contraceptives containing oestrogen
- Erectile dysfunction drugs (eg. sildenafil, vardenafil)
- Methadone

is advised that HAART be initiated if the CD4 count is less than 350, if there is a history of an AIDS-defining illness, if the viral load is > 100,000 copies/ml or if the patient is pregnant.11

There are multiple ARV drugs and the currently recommended regimens typically include two NRTIs (nucleotide reverse transcriptase inhibitors) and either a boosted PI (protease inhibitor) or an NNRTI (non-nucleotide reverse transcriptase inhibitor).

Eighty-eight per cent of the HIV patients in our practice are currently taking HAART (29 of the 36 patients). Of these, 72% are taking two NRTIs and a boosted PI, 57% of these being on the tenofovir/emtricitabine+ritonavir-booted atazanavir combination. Fourteen per cent are taking two NRTIs and an NNRTI, seven per cent of these being on Atripla (efavirenz/tenofovir/emtricitabine), the one and only one-pill-a-day combination therapy initiated in 2008. The remaining 14% are on other combinations consisting of newer anti-HIV agents, including raltegravir (integrase inhibitor), etravirine (a new NNRTI) and maraviroc (CCR5 antagonist).

It is very important for GPs to be educated on the main interactions between HAART and other drugs that are regularly prescribed in general practice, in order to avoid certain drugs or adjust doses as appropriate. Before we can consider the drug interactions between HAART and other frequently prescribed drugs, we must first understand how the main classes of ARV drugs are metabolised. NRTIs undergo renal metabolism necessitating dose adjustment in renal insufficiency. While we are unlikely to be adjusting doses ourselves in general practice, it is important to be aware of our patients’ renal function for this consideration.

Main interactions

The main interactions between HAART and other drugs are:

- NNRTIs and PIs are CYP450 and P-glycoprotein substrates, therefore it is not uncommon to encounter interactions among them or with agents used to treat other conditions. Nevirapine induces, while efavirenz both inhibits and induces the enzyme. All approved PIs are metabolised by the CYP3A4 isoenzyme and are CYP3A4 inhibitors, therefore PIs slow the processing of other medications metabolised by the same isoenzyme, potentially allowing them to reach highly toxic concentrations.
- Probably the most important drug interaction to consider is that of methadone and HAART. As mentioned before, 50% of the HIV patients in the practice here are also on methadone, a long-acting narcotic analgesic metabolised via CYP3A4 and CYP2D6. Alarming, efavirenz and nevirapine significantly reduce methadone concentrations by 51-57%, by inducing CYP450 enzymes.12-13 In one study, 75% of patients beginning nevirapine or efavirenz therapy required an increase of approximately 20% in their methadone maintenance dose.13 It is important for us to keep this in mind as our HIV patients will often require additional methadone to counteract this interaction. Methadone-treated HIV-infected patients may also have signs and symptoms of withdrawal when they are taking ritonavir and other PIs. Despite the lack of CYP450 involvement with nucleoside analogue metabolism, some studies suggest that methadone taken alongside zidovudine can increase zidovudine levels by around 40%.14-15 Patients taking these concurrent medications should therefore be closely monitored for signs of zidovudine toxicity, eg. anaemia, myalgia, fatigue and headache.
- Aside from methadone, the complete list of interactions between HAART and other medications is endless, but a few categories of medications warrant particular attention either because they are commonly used by people with HIV or because their interactions are particularly frequent/significant. The vast majority are CYP450 substrates and are either risen to toxic levels by ARVs or reduce ARVs to sub-therapeutic levels.

Anticonvulsant therapy

In terms of anticonvulsant medications, clinicians should monitor anticonvulsant levels in patients taking concurrent HAART and anticonvulsant therapy. We should try to avoid prescribing carbamazepine, phenytoin and phenobarbital as they are all potent CYP450 inducers, thus rendering some PIs and NNRTIs ineffective. According to the New York State Department of Health Aids Institute, levetiracetam (Keppra) may be considered.

Antifungal medications

In terms of antifungal medications, the same institute also recommends that voriconazole (a potent antifungal used for treatment of invasive aspergillosis and serious fungal infections16) should not be prescribed for patients taking ritonavir (400mg q12h). Minimal interaction between fluconazole and ritonavir have been described, rendering it a suitable alternative.17

Respiratory medications

As we are well aware, HIV patients are more prone to TB infection secondary to their immunosuppression and rifampicin, part of standard first-line regimens for TB prophylaxis and treatment, is one of the most potent CYP450 inducers known, therefore causing significant reductions in PI levels. It is recommended (by the above named institute) to avoid rifampicin in all patients on PIs and to consider rifabutin with proper dose adjustment instead. From a GP front, we would all be alerting our respiratory physicians at this point!

Cardiac medications

As HAART proves to extend the lives of people with HIV,
hyperlipidaemia and its management in these patients is a growing concern. Dyslipidaemia occurs in approximately 70% of patients taking PIs, often requiring the use of HMG Co-A reductase inhibitors (statins) for treatment.18 Statins are also metabolised by CYP450, therefore their concentrations can be increased by PIs.

Lovastatin and simvastatin are contraindicated with all PIs as they can reach dangerously high levels potentially leading to rhabdomyolysis and kidney damage. Pravastatin is the safest drug during concurrent PI therapy. Atorvastatin can be used cautiously at lower doses (5-10mg) with careful titration and rosuvastatin can be used cautiously at lower doses (5mg) with careful titration.19,20

Oral contraceptives

The New York State Department of Health Aids Institute recommends that clinicians should use caution when prescribing oral contraceptives for patients receiving HAART because of variations in effect on ethinyl estradiol levels. NNRTIs and PIs may decrease hormone levels enough to cause unintentional pregnancy, therefore woman taking these drugs should use a back-up method of contraception.

A common feature among HIV patients is drug-seeking behaviour, given their history of IVDU depicting their addictive nature. In general practice, requests for benzodiazepines for anxiety/insomnia are not uncommon among this patient group. It is of the utmost importance for GPs to be aware that some drugs within this class may reach dangerously high concentrations when used with CYP450 inhibitors.

Midazolam and triazolam are contraindicated as they have the potential to cause fatal respiratory depression in combination with ritonavir, owing to the fact that they depend completely on CYP3A4 for clearance.21,22 Alprazolam depends only partially on CYP3A4 for clearance and, in one study, ritonavir was shown to produce only a small reduction in its clearance, therefore alprazolam and other BDZs can be used with caution if necessary in this patient group.

Antacids

Another important interaction worth bearing in mind is that medications which neutralise the acidity of gastric secretions can interfere with the absorption of drugs like atazanavir that require an acid environment. In December 2004, Bristol-Myers Squibb warned against the use of ritonavir-boosted atazanavir plus omeprazole after a study revealed a 76% reduction in atazanavir plasma concentrations when the drugs were co-administered.23

The effect is much greater with both PPIs and H2 blockers than with antacids such as Rolaid, Tums and Maalox. The former can alter gastric pH for 24 hours or longer while the latter typically exert their acid-neutralising effects for only a short time, making it possible to use them within one to two hours of acid-dependant drugs.24,25

Erectile dysfunction medications

A final important interaction is that of erectile dysfunction drugs with PIs, as sildenafil, vardenafil and tadalafil are extensively metabolised by CYP3A4. Studies have shown that sildenafil concentrations increased by more than four-fold when co-administered with ritonavir. Excessive plasma levels of these drugs may cause hypotension, dizziness, fainting, headaches, vision disturbances and priapism and therefore a lower starting dose should be adopted for patients receiving PIs.26

It is important to remember that this is not a complete summary of the medications that interact with HAART, but the table on page 51 does contain the most relevant interactions to us in general practice.

In conclusion, I hope we have highlighted the importance and prevalence of HIV in today’s society and the need for GPs to be aware of the interactions illustrated. We need to take it upon ourselves to monitor and adjust our HIV patients’ other medications accordingly, with a view to optimising the efficacy of their antiretroviral drugs and minimising the drastic consequences of sub-standard treatment.

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