

Antiretroviral medications and HIV

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Background. Since 1996 the use of combination antiretroviral treatment including protease inhibitors has dramatically improved the prognosis for many people with HIV. However, antiretroviral medications are associated with significant side effects.

Objective. To outline some of the important side effects of antiretroviral medications and strategies for managing complications.

Discussion. Awareness of potential problems, careful prescribing behaviour and close monitoring can reduce the impact of many side effects of antiretroviral medication. Identification and management of side effects may also assist in improving adherence to treatment.

Combination antiretroviral treatment involving protease inhibitors were introduced in Australia for HIV infection in 1996. These treatments have dramatically changed the longer term prognosis for many people with HIV and the incidence of opportunistic infections and death associated with HIV has fallen sharply. However, antiretroviral medications used in the treatment of HIV are associated with multiple and sometimes debilitating side effects. The long term prognosis of people with HIV/AIDS is uncertain in part due to the unknown impact of long term toxicities and the development of resistance to these drugs. Many general practitioners in Australia provide care for people with HIV/AIDS and, although we may not be prescribing antiretroviral medications, it is important that we are all aware of the potential side effects. Safe careful prescribing behaviour and monitoring by clinicians can reduce the impact of many of these side effects. In most cases, the cure need not be worse than the disease.

Treatment regimens

There are three classes of approved antiretroviral medications available for people with HIV in Australia:

- nucleoside analogue reverse transcriptase inhibitors (NRTIs)
- non-nucleoside reverse transcriptase inhibitors (NNRTIs), and
- protease inhibitors (PIs) (Table 1).

When people commence treatment they usually start on a combination of three or four medications, usually from at least two of these three different classes of drugs. Treatment regimens will be developed for each individual based on their past exposure to these medications, dosing requirements, potential toxicities and comorbidities, and resistance testing if available.

Side effects

Side effects of antiretroviral medications may be:

- initial or 'start up' (eg, nausea, headache)
- persistent (eg, diarrhoea), or
- long term (eg, lipodystrophy).

Each medication has its own side effect profile and Gps need to be familiar with the potential side effects of each of the medications taken by their patients. People can be supported through many of the common short term initial side effects. However, some side effects can be life threatening and necessitate immediate cessation of the medication.

Diarrhoea

Diarrhoea is a common side effect of many HIV medications, as well as being a symptom of possible opportunistic infections. Didanosine and the protease inhibitors in particular can cause moderate to severe diarrhoea in from 5% (indinavir) to up to 32% (nelfinavir) of people. Malnutrition and serious weight loss can be the consequences of chronic intractable diarrhoea and may result in the need to cease some of these medications. Bulking agents and loperamide can be useful. Calcium supplements may alleviate nelfinavir associated diarrhoea. Often consultation with a dietician specialising in the management of people with HIV can be beneficial.

Nausea

Nausea is a common initial side effect of zidovudine (up to 30%). In 10% of people this can be severe, however, it may settle over time. Nausea may be controlled with domperidone (Motilium), prochlorperazine (Stemetil) or metoclopramide (Maxolon). Cold foods and drinks are less likely to exacerbate nausea.

Liver disease

Acute hepatitis can be a serious initial side effect of nevirapine. This medication should be started at a low dose and liver function should be closely monitored during initiation. Most antiretroviral medications can cause a significant rise in liver enzymes. This occurs in 13% of people taking stavudine and 9.5% of people taking didanosine, as well as with the protease inhibitors. It is important to monitor liver enzymes closely, usually three monthly, in all people on antiretroviral medications and especially in people with coexisting hepatitis C and/or B. It may be wise to advise cessation of alcohol consumption in people on antiretroviral medications with raised liver enzymes.

Pancreatitis

Severe life threatening pancreatitis is a significant side effect of didanosine. A rise in serum amylase occurs in 7% of people taking this drug for 12 months. It is important to have a baseline amylase measurement before treatment. A rise of 50% is considered significant. The risk is increased with concomitant use of hydroxyurea and didanosine. Didanosine should be ceased in any patient developing severe abdominal pain until the cause is determined.

Lactic acidosis

This rare side effect, due to mitochondrial toxicity caused by nucleoside analogues, may lead to organ failure, coma and death. Lactic acidemia is far more common and is often associated with mild constitutional symptoms, mild increases in concentration of liver enzymes, and peripheral lipoatrophy.

Peripheral neuropathy

Up to 20% of people taking didanosine, and up to 14% of people taking stavudine, may experience peripheral neuropathy. This can be distressing and may result in a need to cease these medications. Ritonavir may cause circumoral paraesthesia.

Mood disturbance

Up to 5% of people taking efavirenz can experience symptoms of depression and/or anxiety. Many people experience disturbing alterations in mental state during the first days on this medication although this is usually transient. Symptoms can include:

- impaired concentration
- somnolence
- vivid dreams, and
- mania.

This medication can also cause dizziness and is best taken just before bed. However, sleep disturbance is also not uncommon with efavirenz (up to 4%).

Lipodystrophy

The lipodystrophy syndrome involves:

- peripheral fat loss (especially in the face, limbs, and buttocks)
- central fat accumulation (especially visceral abdominal fat, breasts and as a 'buffalo hump' over the dorsocervical spine), and
- alteration of serum lipids and glucose.

This can be a very distressing side effect of protease inhibitors, occurring in up to 60% of people taking ritonavir for 12 months or more, 45% of people taking indinavir and 10% of people taking nelfinavir. It may also occur in regimens without protease inhibitors. Development of lipodystrophy may result in a need to stop this class of medication. There appears to be no benefit from dietary modification.

Hyperlipidaemia

This occurs especially with protease inhibitors (cholesterol > 7.77 occurs in 9% of people taking lopinavir) and efavirenz. Hypertriglyceridaemia (at levels > 16.9) occurs in up to 10% of people taking ritonavir. Monitoring of fasting lipid levels is important in people taking these medications. Diet, exercise and smoking cessation may result in some improvement as may the use of statins, although care is needed as there can be potential interactions between some statins and protease inhibitors. Use of these drugs should be discussed with the antiviral prescriber.

Diabetes and insulin resistance

Hyperglycaemia can be associated with protease inhibitors. Monitoring of blood glucose levels is important although it is unclear when and how often this should occur. Some clinicians also monitor insulin and c-peptide levels.

Osteoporosis

Protease inhibitors have been associated with osteopenia and osteoporosis, especially in association with tobacco smoking and low body weight. Evidence of the benefits for monitoring people taking these drugs using DEXA scanning is not yet available. Attention to nutrition, exercise and smoking cessation is important. The appropriate use of osteoporosis medications is as yet unclear for people with HIV taking protease inhibitors.

Renal calculi

Indinavir is known to cause renal calculi in up to 10% of people and the rate may be higher when indinavir is taken in combination with ritonavir. Attention to hydration, especially in hot weather, is important for people taking this medication and therapeutic drug monitoring may be beneficial.

Anaemia

Zidovudine can cause significant anaemia and bone marrow suppression. Regular blood count monitoring is required.

Skin effects

Nevirapine can cause a severe life threatening Stevens-Johnson syndrome and people commencing this medication need to be warned to look out for the development of rash and ulceration. Indinavir may cause dry skin, mouth and eyes, nail disturbances and hair loss. Many other antiretroviral medications cause dermatological side effects and advice from a dermatologist specialising in the management of people with HIV may be required.

Hypersensitivity

A hypersensitivity reaction can occur with abacavir. This reaction occurs usually within six weeks of commencing abacavir with symptoms including fever, nausea, vomiting, diarrhoea, malaise and rash. This can cause potentially lethal anaphylaxis if people are rechallenged with this drug and this is absolutely contraindicated. People commencing abacavir should be warned to immediately report any of the symptoms or signs of possible hypersensitivity.

Other potential problems

Interactions with other drugs

There are many potential drug interactions both between individual antiretroviral medications and with other classes of drugs. Checking for potential interactions is essential each time a new medication is prescribed for people taking antiretrovirals. Some complementary medications (eg, St John's wort) and recreational drugs (eg, ecstasy) can also cause interactions especially with protease inhibitors. Life threatening interactions can be caused by concomitant use of protease inhibitors or delavirdine with terfenadine/astemizole (nonsedating antihistamines), cisapride (can cause arrhythmias), lovastatin (can cause rhabdomyolysis), and midazolam/triazolam (can lead to prolonged sedation). There are not specific contraindications for use with other benzodiazepines such as diazepam, oxazepam, or temazepam.

Pregnancy

Many antiretrovirals, especially NNRTIs and protease inhibitors, have not been studied in pregnancy with sufficient thoroughness to enable recommendations to be made about their safety and efficacy. The significant reductions in perinatal HIV transmission rates with the use of zidovudine, lamivudine and nevirapine, currently seem to far outweigh any potential harm.

Compliance issues

Adhering to a multiple medication regimen can be a significant challenge for many people with HIV. As examples, some medications need to be taken one hour before food, some two hours after food, some with food, some three times a day, some just before bed. Quantities may also be high with saquinavir (Fortovase) requiring up to 18 capsules a day while delavirdine and ritonavir each requiring up to 12 tablets/capsules daily. If people miss doses or are unable to

follow dosing recommendations, the reduced concentration of drug may result in the development of drug resistant strains of HIV which can result in failure of the current regimen and difficulty in finding new suitable regimens as there is often significant cross resistance within each class of antiretroviral medication.

Conclusion

The management principles for patients requiring antiretroviral medications are outlined in Table 2.

If one of your patients on antiretroviral medications presents with a problem that may be a side effect of their medication, their antiretroviral prescriber should be directly consulted. The Australasian Society for HIV Medicine offers courses for Gps on the primary care management of people with HIV and the use of antiretroviral medications (<http://www.ashm.org.au>).

Many people with HIV require significant support and counselling and treatment advice to assist them to minimise the impact of their required medication regimen on their daily lives. There is an important role here for the GP. Identification and management of side effects may also assist in improving adherence.

Summary of Important Points

- Antiretroviral medications are associated with significant problems including side effects, drug interactions and compliance difficulties.
- Safe careful prescribing behaviour and monitoring by clinicians can reduce the impact of many of the side effects of antiretroviral medications used in the treatment of HIV.
- Lipodystrophy syndrome can be a very distressing side effect of the use of protease inhibitors and its development may result in a need to stop this class of medication.
- Many people with HIV require significant support and counselling and treatment advice to assist them to minimise the impact of their required medication regimen on their daily lives.