

Adverse drug reactions

Adverse effects of antiretroviral therapy

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Antiretroviral toxicity is an increasingly important issue in the management of HIV-infected patients. With the sustained major declines in opportunistic complications, HIV infection is a more chronic disease, and so more drugs are being used in more patients for longer periods. This review focuses on the pathogenesis, clinical features, and management of the principal toxicities of the 15 licensed antiretroviral drugs, including mitochondrial toxicity, hypersensitivity, and lipodystrophy, as well as more drug-specific adverse effects and special clinical settings.

Highly active antiretroviral therapy (HAART; a combination of at least three drugs) for HIV-1 infection has led to substantial reductions in morbidity and mortality, and many HAART regimens result in near-complete suppression of HIV-1 replication. HAART is now the standard-of-care therapy.

Several factors have combined to increase our attention on the toxicity of HAART. First, since HIV-1 eradication seems unlikely with current therapy,^{1,2} HAART will need to be indefinite for clinical benefits to be preserved. Second, the severity of the HIV epidemic led to accelerated licensing of many antiretroviral agents, often with very little known about long-term safety. Third, the sustained benefits of HAART have led to far greater numbers of HIV-1-infected patients receiving at least three drugs for greater periods of time. Moreover, drug-related toxicity is being increasingly recognised because of the declining incidence of HIV-1-associated opportunistic disease. Lastly, there are now 15 antiretroviral drugs available in four drug classes and so the number of possible HAART combinations is huge. Choosing between many of these combinations is, therefore, increasingly dependent upon knowledge of antiretroviral toxicities.

Mitochondrial toxicity

Nucleoside and monophosphorylated nucleotide-analogue reverse-transcriptase inhibitors (NRTIs and NtRTIs, respectively) are both phosphorylated intracellularly to active triphosphate forms, and are then incorporated into new DNA strands synthesised by HIV reverse transcriptase.^{3,4} The lack of a 3' hydroxyl in NRTIs and NtRTIs results in HIV DNA chain termination.

The major toxicities of NRTI and NtRTI therapy, particularly over the medium-term to long-term, are thought to be secondary to inhibition of mitochondrial DNA polymerase γ , resulting in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation.^{5,6} These include myopathy (zidovudine);

neuropathy (stavudine, didanosine, zalcitabine); hepatic steatosis and lactic acidemia (didanosine, stavudine, zidovudine); and possibly also peripheral lipodystrophy (possibly all NRTIs, although predominantly with stavudine); and pancreatitis (didanosine). The principal features and known prevalence rates of these toxicities are shown in table 1. The most serious mitochondrial toxicities are lactic acidosis and pancreatitis; mortality was 80% in patients with plasma lactate concentrations greater than 10 mmol/L. Although lactic acidosis is rare, lactic acidemia is far more common (about 15%), and is often associated with mild constitutional symptoms, mild increases in concentrations of liver enzymes, and peripheral lipodystrophy.⁷ NRTIs and NtRTIs active against other viruses can also exert mitochondrial toxicity (fialuridine, ganciclovir, aciclovir, and cidofovir), at least in vitro.⁸

Mitochondrial toxicities at the clinical level are generally gradual in onset and offset, but may occur within days of the start of therapy. Overall, their prevalence and severity increase with more prolonged therapy. Some, such as peripheral neuropathy and renal tubular acidosis, may worsen for several weeks after drug cessation (the so-called "coasting" phenomenon). Similarly, the capacity of tissue to recover after cessation of reverse-transcriptase inhibitors varies. This capacity may be dependent upon tissue regenerative capacity, the duration and severity of the toxicity, and the duration of therapy. For example, didanosine-induced pancreatitis usually resolves rapidly and completely although we do not know what occurs at the tissue level. In contrast, peripheral neuropathy improves slowly and there may be a permanent deficit, especially if it is severe, or if cessation of therapy is delayed.

Another striking feature of these toxicities is their relative tissue-specific and drug-specific nature. The "pol- γ hypothesis"^{3,9} suggests that this specificity may be due to tissue-specific drug penetration and metabolism to the triphosphate form, to tissue-specific polymorphisms in mitochondrial DNA polymerase- γ , to the target tissue's stores of natural nucleotides, and to the dependency of a given tissue upon mitochondria for function. For example, the proximal renal tubular toxicity of adefovir might be due to its selective accumulation within proximal renal epithelia by the protein organic anion transporter 1.¹⁰ Although the weight loss seen with adefovir therapy is unexplained, that this transport molecule is also highly expressed in skeletal muscle is of note.

Diagnosis of mitochondrial toxicity is difficult only if patients are receiving other drugs with overlapping toxicities. Furthermore, no diagnostic (metabolic or

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Organ	Features			Rate (%)	Drug(s)*	Specific therapy†	Potentially aggravated by‡
	Clinical	Laboratory	Histopathological				
Muscle	Fatigue, myalgia, proximal weakness, wasting	↑Creatine kinase	"Ragged red fibres", disrupted cristae	17	AZT	..	Corticosteroids
Heart	Dilated cardiomyopathy	..	As for skeletal muscle	Rare	AZT
Nerve	Distal pain, numbness, paraesthesia, reduced reflexes/power	Nil	Axonal degeneration	10–30	ddC=d4T >ddl>3TC	Tricyclic anti-depressant valproate	Vinca alkaloids, isoniazid
Liver	Hepatomegaly, nausea, ascites, oedema, dyspnoea, encephalopathy	↑Liver enzymes, lactic acidemia¶ ↑Anion gap ↓Bicarbonate	Micro/macrovessicular steatosis	<1§	All except 3TC and ABC	? Riboflavin	Azoles, rifamycins, NNRTIs/protease inhibitors
Pancreas	Abdominal pain	↑Amylase	..	<1–6	ddl>3TC/ddC	..	Alcohol, pentamidine
Fat	? Peripheral lipoatrophy ? Lipomata	? Lactic acidemia	Apoptosis	50	d4T>others

Toxicities of the muscle, heart, nerve, and liver are known; those of the pancreas and fat are possible.

AZT=zidovudine, ddC=zalcitabine, ddl=didanosine, d4T=stavudine, 3TC=lamivudine, NNRTI=non-nucleoside reverse transcriptase inhibitor.

*Mitochondrial toxicity of abacavir (ABC) has not been reported.

†Cessation of the causative drug(s) is generally required to allow for reversal; improvements are often slow or partial, depending on the target organ's regenerative capacity.

‡A complete list of drugs that might aggravate mitochondrial toxicity can be found at www.hivatisa.org/trtgdlms.html Adult/Adolescent.

§Symptomless increases in liver aminotransferase concentrations (with normal bilirubin) are more common (5–15%). ¶Lactic acidemia occurs in about 15% of patients receiving NRTI therapy, often with mild constitutional symptoms, lipoatrophy, or raised concentrations of liver enzymes.

Table 1: **Known and possible mitochondrial toxicities of nucleoside and nucleotide-analogue HIV reverse-transcriptase inhibitors**

serological) assay predicts who will develop toxicity. In particular, plasma NRTI concentrations do not reflect intracellular NRTI-triphosphate concentrations. Measurement of the latter is difficult and time-consuming, and may only be relevant if the target organ is sampled.

Of course, most patients treated with NRTIs or NtRTIs do not develop mitochondrial toxicity. Factors that may contribute to toxicity include underlying organ dysfunction (eg, chronic liver disease and NRTI-associated hepatic steatosis, prior pancreatitis and didanosine, prior NRTI-associated neuropathy and stavudine), concomitant HIV-1 opportunistic disease, and particularly the administration of other drugs with similar toxicity profiles (eg, peripheral neuropathy, vinca alkaloids and zalcitabine or didanosine).^{4,11,12}

The management of mitochondrial toxicities is generally limited to cessation of the causative drug and sometimes of other drugs that might exacerbate the condition. Co-administration of other drugs, including other antiretroviral

agents, with potentially additive or synergistic toxicities should of course be avoided. Given that toxicity can be of late onset, clinical screening for drug toxicity should be done throughout therapy.

Several agents have been used in the treatment of congenital mitochondrial diseases with limited success.^{13,14} These agents include essential vitamin coenzymes (thiamine and riboflavin), electron acceptors (vitamin C), antioxidants (compound Q), and L-carnitine. Patients with zidovudine-induced myopathy and NRTI-induced peripheral neuropathy have been shown to have reduced concentrations of L-carnitine. Nevertheless, adefovir is routinely given with L-carnitine (to avoid toxicity from its dipovoxil moiety), and clearly does not prevent all renal toxicity. The usefulness of these agents in the treatment or prevention of NRTI and NtRTI-induced mitochondrial disease is unknown.

Hypersensitivity

Drug hypersensitivity typically manifests as an erythematous, maculopapular, pruritic, and confluent rash with or without fever (figure 1, panel 1).¹⁵ The rash is most prominent on the body and arms and usually begins after 1–3 weeks' therapy. Constitutional features (fever, rigors, myalgias, and arthralgias) are often prominent, and can precede the rash (particularly with abacavir) or occur without rash. Stevens-Johnson syndrome or toxic epidermal necrolysis develops in less than 0.5% of patients, but has not been reported with abacavir. Rash or fever occurring more than 8 weeks after onset of therapy is almost always due to another agent. In contrast, patients with prior hypersensitivity or exposure (including to a related drug) can develop reactions within hours of the first dose.

Drug hypersensitivity in HIV-1-infected patients is about 100 times more common than in the general population.¹⁶ The overall size of the problem is substantial; drug hypersensitivity complicated 3–20% of all prescriptions in one large series.¹⁷ All licensed non-nucleoside reverse-transcriptase inhibitors (NNRTIs; nevirapine, delavirdine, and efavirenz), the NRTI abacavir, and the protease inhibitor amprenavir, are common antiretroviral drugs that cause hypersensitivity, which is rare with other NRTIs or protease inhibitors.

Diagnosis of hypersensitivity is based on clinical criteria. Diagnosis can be difficult particularly if there is isolated



Figure 1: **Drug hypersensitivity reaction**

Panel 1: Clinical features of HIV-associated drug hypersensitivity**Principal features**

- Morbilliform/maculopapular rash
- Fever (often precedes rash)
- Myalgias, fatigue
- Mucosal ulceration

Less common features (<5%)

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Anicteric hepatitis
- Hypotension
- Acute interstitial nephritis
- Acute interstitial pneumonitis

fever; other causes such as infection, malignancy, or immune reconstitution need to be considered.¹⁸ Identifying the cause can be difficult if patients are receiving more than one potentially causative drug; perhaps the most useful clues are the time to onset after the start of therapy, and the fact that abacavir is more likely than other causes of hypersensitivity (eg, nevirapine) to cause a constitutional reaction (table 2). Hypersensitivity reactions to abacavir may include symptoms suggestive of upper or lower respiratory-tract infection. To avoid diagnostic confusion, abacavir should probably not be started during such an infection. Unfortunately, no demographic, metabolic, or immunological factor, including a history of drug hypersensitivity, has been identified that predicts the development of antiretroviral hypersensitivity, including more severe reactions.

The pathogenesis of hypersensitivity is unknown. Suggested causes and mechanisms include the degree of immunodeficiency or immune activation, the longer duration and higher doses of therapy, altered drug metabolism associated with glutathione deficiency or slow acetylator phenotype, and co-existing infections with cytomegalovirus or Epstein-Barr virus.¹⁵ Cytokines are probably involved, given the prominence of constitutional symptoms and the common presence of activated epidermal keratinocytes and of infiltrating CD8 lymphocytes and macrophages that produce interleukin 6, interleukin 1 β , and tumour necrosis factor α .¹⁹

About 50% of antiretroviral hypersensitivity resolves spontaneously despite continuation of therapy. Therapy should be stopped if there is mucosal involvement, blistering, exfoliation, clinically significant hepatic dysfunction (eg, tender hepatomegaly, aminotransferase concentrations greater than five times baseline), fever greater than 39°C, or intolerable fever or pruritus. The dose of nevirapine should not be increased if a reaction to the 200 mg/day, 2-week lead-in dose is present at day 14. Reactions may worsen temporarily after cessation of drug

therapy, particularly with drugs with longer half-lives. The effectiveness of supportive measures such as antipyretics and antipruritics is unproven, but such agents are commonly used. Glucocorticoids are ineffective for the prevention of nevirapine hypersensitivity.²⁰

Rechallenge is possible for mild-to-moderate NNRTI hypersensitivity, but not for abacavir, since several deaths have been attributed to abacavir rechallenge. Since its safety is not established, NNRTI rechallenge should be medically observed, preferably in hospital. The rate of NNRTI cross-hypersensitivity is not known, so new NNRTI therapy in patients with prior severe hypersensitivity to another NNRTI should also be monitored. Desensitisation is unstudied and, although useful for sulphonamide hypersensitivity, may be inappropriate for antiretroviral hypersensitivity, since it would necessitate a period of subtherapeutic drug concentration and so favour development of drug resistance—a major and readily inducible problem, particularly with NNRTIs.

Lipodystrophy syndrome*Clinical and metabolic features*

A syndrome (or syndromes) of lipodystrophy affecting HIV-1-infected patients was first described only 2 years ago. The main clinical features are peripheral fat loss (presumed lipoatrophy in the face, limbs, and buttocks) and central fat accumulation (within the abdomen, breasts, and over the dorsocervical spine [so-called “buffalo hump”], as well as other lipomata; figure 2, panel 2).^{21,22} These changes have been objectively confirmed by dual-energy X-ray absorptiometry (DEXA) and abdominal computed tomography. These studies, mainly in adult males, have generally shown overall fat loss, although preliminary data suggest that fat accumulation may predominate in women.²³

The overall prevalence of at least one physical abnormality in recent reports^{21,23–25} and in abstracts presented at 1999 AIDS meetings is about 50% after 12–18 months of therapy. The differences between these prevalence rates (which ranged from 18 to 83%) may also have been confounded by patients’ sex, age, and type and duration of antiretroviral therapy, and the lack of an objective and validated case definition.

Metabolic features significantly associated with lipodystrophy and protease-inhibitor therapy include hypertriglyceridaemia, hypercholesterolaemia, insulin resistance (raised C-peptide and insulin concentrations) and type 2 (generally non-ketotic) diabetes mellitus.^{23,24,26,27} Dyslipidaemia at concentrations associated with increased cardiovascular disease occurs in about 70% of patients. These metabolic abnormalities are more profound in those receiving protease inhibitors, and also in those with lipodystrophy. More recently, lipoatrophy has also been associated with low-grade lactic acidaemia and liver

Drug	Rash				Other features	Rechallenge
	Rate (%)	Proportion with grade 3–4 (%)	Proportion requiring discontinuation (%)	Onset (days)		
Nevirapine	17	6–8	7	14–21	Hepatitis (1%), fever (15%), mucosal involvement, SJS/TEN (0–3%)	If rash at 400 mg/day dose and no grade 3–4 feature
Delavirdine	18	4	4	7–14	Headache	No data
Efavirenz	10	0–7	2	..	CNS syndrome (42%, cessation in 3%), teratogen in monkeys	No data
Abacavir	3	..	3	9	Nausea, fever (80%), constitutional symptoms, no SJS/TEN reported	Never
Amprenavir	20	3	3	10	Fever (7%)	No data

SJS=Stevens-Johnson syndrome, TEN=toxic epidermal necrolysis, CNS=central nervous system.

Table 2: Clinical features of hypersensitivity to antiretroviral drugs



Figure 2: **Clinical features of lipodystrophy**

dysfunction, but in the absence of lipid or glycaemic changes.⁷ Neither lipodystrophy nor protease-inhibitor therapy has been associated with significant differences in concentrations of testosterone, sex-hormone binding globulin, prolactin, cortisol, complement, or tumour necrosis factor α , all of which are involved in adipocyte homeostasis. Leptin concentrations are low, consistent with reduced fat mass.

The prevalence of diabetes mellitus is about 8–10%; most cases are identified after oral glucose loading.^{24,27} Few cases seem to have symptoms such as polyuria, blurred vision, or weight loss, and ketoacidosis is rare. A further 15% of patients have impaired glucose tolerance. Most cases of diabetes have been identified in recipients of protease inhibitors, but a causal relation has not been established. No risk factor for the development of diabetes in protease-inhibitor recipients has been identified. Why diabetes is less common than the physical changes and dyslipidaemia is unclear, although development of type 2 diabetes usually involves both insulin resistance and impaired insulin secretion.

Pathogenesis

The pathogenesis of the syndrome is unknown. One hypothesis suggests that it might be due to inhibition of lipid and adipocyte regulatory proteins that have partial homology to the catalytic site of HIV-1 protease, to which protease inhibitors all bind.²⁸ In-vitro studies have shown that protease inhibitors can inhibit lipogenesis, and that indinavir may do this via altered retinoid acid signalling.^{29,30}

More recently, some features of this syndrome have been suggested to represent mitochondrial toxicity of NRTIs, since lipoatrophy and buffalo hump have been reported in patients who have received only NRTIs in association with lactic acidemia, and both can occur in HIV-uninfected patients with mitochondrial defects.^{7,25,31}

There are other possible mechanisms. Although many features are suggestive of Cushing's syndrome, the possibility that lipodystrophy syndrome might occur via a similar mechanism seems to have been excluded.²² Fat accumulation could be a refeeding effect associated with improved appetite in the setting of suppression of HIV-1 replication; this mechanism would not explain lipoatrophy, however. The syndrome is unlikely to be a direct effect of

HIV-1, given that the syndrome is mostly seen in patients receiving HAART, that lipodystrophy and its severity are independent of plasma HIV-1 load,^{21,24} and that lipodystrophy can occur in recently infected patients who receive HAART.³²

Risk factors for lipodystrophy have not been calculated prospectively. Studies to date have suggested that risk factors may include low bodyweight before therapy, raised C-peptide and triglyceride concentrations after about 1 year of therapy, the total duration of HAART, use of the dual protease inhibitor combination ritonavir-saquinavir (rather than individual protease inhibitors such as saquinavir, indinavir, or nelfinavir), and use of the nucleoside analogue, stavudine.^{7,21,24,25} Whether there is a definite hierarchy of causative drugs has also not been shown.

Diagnosis

The physical features of lipodystrophy syndrome are diagnosed on examination or patient's report (preferably both). No objective variable obtained by DEXA or computed tomography seems reliable for diagnosis, perhaps because of the large natural variability in body-fat mass and distribution. In addition, the presence of abdominal obesity, insulin resistance, or hyperlipidaemia are not useful individually for diagnosis, since these are common in the general population. A combination of, or changes in, clinical, metabolic, and imaging variables might be useful; this possibility is currently being studied.

Panel 2: Features of lipodystrophy syndrome

Clinical (lipodystrophy)

- Peripheral lipoatrophy:
Face, arms, legs, buttocks
- Central fat accumulation:
Intra-abdominal, dorsocervical spine, breasts, other lipomata

Metabolic

- Hypertriglyceridaemia
- Hypercholesterolaemia
- Insulin resistance (increased insulin, C-peptide)
- Type 2 diabetes mellitus/impaired glucose tolerance
- Lactic acidemia

Lipodystrophy should not be diagnosed if the patient has had a recent severe illness associated with weight loss.

Drug	Toxic effect
Nucleoside analogues	
Zidovudine	Nausea, headache, nail pigmentation
Didanosine	Nausea, diarrhoea
Zalcitabine	Mouth ulcers
Non-nucleoside analogues	
Efavirenz	Central nervous stimulation
Protease inhibitors	
Saquinavir	Nausea, diarrhoea (more so with soft-gel formulation)
Ritonavir	Perioral paraesthesiae, nausea, diarrhoea, flushing
Indinavir	Renal calculi, hyperbilirubinaemia, reflux oesophagitis, retinoid effects, haemolytic anaemia
Nelfinavir	Diarrhoea, nausea
Amprenavir	Hypersensitivity, perioral paraesthesiae
All	Cytochrome P450 interaction of drug metabolism (especially ritonavir), spontaneous bleeding in haemophiliacs

Table 3: Other antiretroviral drug toxicities

A case definition for lipodystrophy syndrome is clearly needed to further assess the role of drug classes, individual drugs (including drugs in development), and demographic factors in the syndrome; to compare different populations of patients; to standardise recruitment to lipodystrophy studies; and to assist clinicians in diagnosis.

Clinical significance

There are several possible sequelae of lipodystrophy syndrome. First, adherence to antiretroviral therapy could be compromised because of the cosmetic effects, leading to virological and even clinical failure.^{33,34} Second, the metabolic effects could lead to an increase in cardiovascular disease, and several case reports have described premature coronary-artery disease in patients with few or no risk factors that were receiving protease-inhibitor therapy.^{35,36} However, a causal link has not been shown, and there are no data estimating prevalence of, or risk factors for cardiovascular disease in patients receiving HAART. Some cases have developed in patients who received very brief protease-inhibitor therapy and might represent a prothrombotic effect of therapy rather than an atherosclerotic effect. The increase in risk has been estimated from available metabolic data (by use of the Framingham equations) to be 1.4 cardiac events per 1000 years of therapy;³⁷ a worldwide cohort study sponsored by the pharmaceutical industry and the European Medicines Evaluation Agency is addressing this issue. One further risk of occasionally severe hypertriglyceridaemia (concentrations >20 mmol/L) seen with protease-inhibitor therapy may be pancreatitis, but this association remains unproven.

Patients with diabetes mellitus or impaired glucose tolerance are at increased risk of microvascular diabetic disease such as retinopathy, neuropathy, and nephropathy over the medium-term to long-term. Whether it is appropriate to monitor patients on long-term protease-inhibitor therapy for these conditions is not clear at present.

Management

There is no proven therapy for any component of lipodystrophy syndrome. Factors that would affect a decision to treat any feature would include presence of symptoms, the patient's status, the likelihood that a particular HAART regimen would be long-term, the severity of any feature, and the presence of one or more cardiovascular risk factors.

Increased exercise can decrease central fat accumulation, but at the expense of increased peripheral fat wasting.³⁸ The role of diet has not been assessed. Certainly, no diet should interfere with antiretroviral drug absorption or the overall wellbeing of the patient. Uncontrolled data suggest that

gemfibrozil and atorvastatin might be safe and have some efficacy in lowering lipids.³⁹ A consensus statement recently recommended treatment of dyslipidaemia in accordance with the recommendations of the National Cholesterol Education Programme. This programme involves a trial of diet plus exercise, followed by a fibrate for hypertriglyceridaemia and either pravastatin or atorvastatin for hypercholesterolaemia.⁴⁰ Treatment of lipids alone may not affect cardiovascular risk, however, if diabetes is not also addressed (and vice versa).

Some potential agents can cause problems. Anabolic steroids are anabolic for muscle not fat, although increased muscle mass may partly disguise fat loss. Subcutaneous or intralesional growth hormone can reduce intra-abdominal adiposity and the size of buffalo humps, respectively, but if given parenterally, they can worsen lipoatrophy or precipitate diabetes.⁴¹ Some statins (lipid-lowering agents) and glitazones (insulin sensitisers and possible peripheral adipocyte growth factors) are metabolised by cytochrome P450 3A (which is inhibited by protease inhibitors), so their use with protease inhibitors could increase the risks for myositis and hepatitis, respectively. The statin least likely to interact adversely with protease inhibitors is probably pravastatin.⁴²

Surgery (excision or liposuction) has been done on some patients with severe fat accumulation, although fat can reaccumulate within a matter of months.⁴³ There have been no reports of implant surgery for fat wasting—an approach used for some forms of congenital lipodystrophy.

One theoretical treatment option is withdrawal or substitution of HAART. Again, uncontrolled data suggest that protease-inhibitor substitution with nevirapine, and stavudine withdrawal might improve fat accumulation and lipoatrophy, respectively.^{44,45} Several randomised studies are currently assessing this strategy.

Other adverse events and special circumstances

Numerous antiretrovirals have specific adverse effects, many of uncertain pathogenesis (table 3), and others cause problems in particular circumstances. General principles of management are given in panel 3, and some common adverse effects are discussed below.

Zidovudine

Anaemia and granulocytopenia affect about 5–10% of patients who receive zidovudine, and are more common in those with more advanced HIV disease and possibly those receiving chemotherapy, ganciclovir, hydroxyurea, pyrimethamine, and interferon- α (www.hivatis.org/trtgdlns.html#AdultAdolescent).⁴⁶ Supportive therapy with erythropoietin or granulocyte colony-stimulating factor is possible, but is probably not an effective long-term strategy. These effects are commonly thought to be due to mitochondrial toxicity, but this assumption has not been verified. Other adverse effects of uncertain pathogenesis include nausea, anorexia, headache, and fatigue. These effects occur early in therapy in about 5–10% of patients, but are often transient despite continued therapy. Zidovudine should not be co-administered with stavudine because of likely antagonism.

Hydroxyurea

Hydroxyurea remains a relatively understudied (and unlicensed) therapy for HIV-1 infection. Its mode of action could be predominantly via inhibition of ribonucleotide reductase, leading to reduced concentrations of endogenous nucleotides (especially adenine monophosphate), and therefore to greater activity of NRTI-

Panel 3: General principles of management of antiretroviral drug toxicity**Drug initiation**

- Start drugs with non-overlapping toxicities and small risk of interaction with existing therapy
- Consider clinical setting:

Pregnancy

Paediatric

Injecting drug user

Chronic hepatitis B or C

Haemophilia

Postexposure prophylaxis

Adverse reaction

- Dose reductions not advised because of potential for drug resistance
- In patients with good control of viral replication:
 - If possible, immediately switch to drug with different toxicity profile (if aetiology certain)
 - Stop all drugs, particularly if severe reaction, then consider new regimen with different toxicity profile (if aetiology uncertain)
- In patients with uncontrollable viral replication:
 - Stop responsible drug; initiate new agent with different toxicity profile (but if possible aim for new regimen with improved antiviral activity)

Post adverse reaction

- Rechallenge should be medically supervised but is contraindicated with hypersensitivity to:

Abacavir

Nevirapine 200 mg/day dose

Mucosal involvement

Grade 3–4 rash

- Desensitisation probably inappropriate because of potential for induction of viral resistance

triphosphates.⁴⁷ The major adverse effects of hydroxyurea are nausea, vomiting, alopecia, and bone-marrow suppression, and seem to be more common in those with more advanced HIV-1 disease.⁴⁸ CD4 lymphocyte counts decline on average by about 100 cells/ μ L, but no increase in opportunistic infections has been found. By effectively increasing NRTI-triphosphate concentrations, especially those of didanosine, modest increases in peripheral neuropathy and pancreatitis have been seen (unpublished observations).

Efavirenz

The most common adverse effects of efavirenz are in the central nervous system, and include dizziness, insomnia, somnolence, impaired concentration, vivid dreams, nightmares, and mania. These reactions occur in about 40% of patients in the first few days to weeks, but are severe enough to warrant discontinuation in only 3%, since most symptoms resolve spontaneously. Similar reactions are rare with nevirapine or delavirdine.

Indinavir

Indinavir is poorly water-soluble and can crystallise in urine, causing obstruction anywhere between the renal tubules and the urethra. This obstruction can present as renal colic, but also as nondescript abdominal pain, painless haematuria, urinary frequency, or a gradual symptomless rise in serum creatinine concentrations.⁴⁹ These adverse effects are more common in hot weather and in those with high plasma indinavir concentrations.^{50,51} Patients should be advised to consume at least 1.5 L water daily, and more in hot weather or if consuming alcohol. A single episode of colic (which can occur in up to 10% of patients) probably does not require cessation of therapy, since recurrences occur in only 50% of patients who recommence indinavir.

Indinavir seems to be unique among the protease inhibitors in being associated with adverse effects similar to

those seen with retinoid therapy, namely alopecia, dry skin, dry lips, and ingrowing nails.^{52,53} Stimulation of retinoid signalling by indinavir has been shown in vitro.³⁰

Ritonavir

Ritonavir can cause numerous dose-dependent side-effects, including perioral and peripheral paraesthesiae (15%), fatigue (8%), and headache (3%), whose aetiologies are unknown.^{54,55} These effects do not seem to be less common in those receiving its liquid or capsule formulations. Similar paraesthesiae can also occur with amprenavir.

Gastrointestinal effects

Virtually all antiretroviral medications can cause nausea, vomiting, or diarrhoea early in therapy, but these are often transient. Among the NRTIs, nausea is most common with zidovudine and didanosine (partly because of the latter's antacid buffer). Nausea can also occur with any protease inhibitor. Indinavir is also associated with oesophageal reflux (about 3%), but should not be given with antacids, because the salts in the antacids can bind to indinavir and prevent its absorption. For the same reason, indinavir should not be given at the same time as didanosine. For substantial reflux, H₂ blockers and proton-pump inhibitors are acceptable options.

Diarrhoea is probably most common with protease inhibitors, particularly nelfinavir (grade 3–4 in 20%), full-dose ritonavir, and soft-gel saquinavir.⁵⁶ Bulking agents (eg, psyllium), loperamide, and occasionally dietary modifications can be useful.

Hepatitis

Most antiretroviral agents have been associated with hepatic toxicity. NRTIs can cause hepatic steatosis, generally after more than 6 months of therapy, probably via mitochondrial toxicity. NNRTIs can cause hepatitis in the first 2–3 months of therapy, sometimes as part of a hypersensitivity reaction. Protease inhibitors can also cause hepatitis by an unknown mechanism, particularly in patients co-infected with hepatitis B or C and with raised hepatic aminotransferase concentrations, and less commonly have been associated with variceal bleeding in patients with cirrhosis.⁵⁷

Some cases of hepatitis with antivirals seem to represent a side-effect of an improved immune response, where immune restoration leads to recognition of hepatitis B or C in chronic carriers, and results in a clinical episode of hepatitis with seroconversion.⁵⁸ What proportion of hepatic reactions to any antiretroviral is caused by such a mechanism is not known.

Unconjugated hyperbilirubinaemia can occur with indinavir (about 7%) but does not represent liver toxicity. Isolated increases in γ -glutamyltransferase concentrations with some agents probably represent enzyme induction and do not warrant changes to therapy. Lastly, withdrawal of lamivudine may result in a hepatic flare in 25% of chronic hepatitis B carriers.

Cytochrome P450 interactions

Many protease inhibitors and the NNRTIs efavirenz and delavirdine interact with cytochrome P450 isoforms, perhaps the most significant being CYP3A4 and CYP2D6. Such interactions can occur in either direction, leading to increases or decreases in the concentrations of a given protease inhibitor or another drug or drug class. Patients should be made aware of common potential interactions and outcomes before starting therapy, including decreased concentrations of oral contraceptives (leading to pregnancy); and increased concentrations of: some non-

sedating antihistamines, macrolides, and cisapride (torsade de point arrhythmias); rifabutin and rifampicin (polyarthritis and hepatitis); benzodiazepines and opiates (sedation); ergot derivatives (vasospasm); sildenafil (hypotension); and recreational drugs such as methylenedioxymethamphetamine. Safe alternatives with a given class are often available (eg, loratadine instead of astemizole or terfenadine; lorazepam instead of midazolam).

One positive side-effect of ritonavir is the inhibition of cytochrome-P450-mediated metabolism of other protease inhibitors.⁵⁹ This inhibition allows for fewer and less frequent doses of other protease inhibitors. Since this inhibition occurs at very low ritonavir doses (as low as 100 mg twice daily), dual protease-inhibitor regimens including ritonavir and saquinavir, indinavir, lopinavir, or amprenavir are common, although not licensed.

Pregnancy

Most antiretroviral regimens, especially NNRTIs and protease inhibitors, have not been studied in pregnancy with sufficient thoroughness to enable recommendations to be made as to safety and efficacy. No antiretroviral has been rated by the Food and Drug Administration as category A (well demonstrated lack of risk to human fetuses in the first trimester). Drugs rated as category B (safe in animal studies) are didanosine, saquinavir, ritonavir, and nelfinavir.

Preliminary data suggest that the NRTIs zidovudine and lamivudine rarely cause neurological and metabolic disease via mitochondrial damage when given perinatally,⁶⁰ although these findings have not been confirmed. Any risk needs clarification, although the reductions in perinatal HIV transmission rates with zidovudine, lamivudine, and nevirapine seem to far outweigh the potential harm.⁶¹ If confirmed, surveillance might also be needed for those receiving postexposure prophylaxis against HIV-1 transmission with NRTIs.

Efavirenz has caused cranial malformations in monkey fetuses and so is contraindicated in pregnancy or when pregnancy is possible. Other drugs also rated as category C (animal fetal toxicity proven or not studied) are delavirdine and, at very high doses, zalcitabine and zidovudine. The risk of hyperbilirubinaemia-induced kernicterus with perinatal indinavir is unknown, as is the risk of protease-inhibitor-associated gestational diabetes mellitus.

Injecting drug users

Several drugs can interfere with the metabolism of methadone. This effect may lead to an increase (delavirdine) or decrease (nevirapine, efavirenz) in plasma concentrations and so to sedation or withdrawal, respectively.⁶² Methadone can also significantly increase plasma zidovudine concentrations.

Haemophilia

Most protease inhibitors seem to result in increased rates of spontaneous bleeding (bruising, haemarthrosis, and rarely intracranial haemorrhage) in haemophiliacs, leading to greater factor VIII requirements.⁶³ This toxicity is not seen in recipients without haemophilia. The mechanism of this toxicity could be via inhibition of platelet function.⁶⁴

Postexposure prophylaxis

Combination therapy for about 4 weeks after high-risk exposure to HIV-1 is recommended.⁶⁵ Zidovudine monotherapy greatly decreases transmission, but 25–35% of patients cannot tolerate this or triple combination therapy for 4 weeks.⁶⁶ Serious side-effects similar to those seen in HIV-infected patients have been reported. Which regimen is best tolerated in this setting is unknown.

Future directions

The type and timing of antiretroviral therapy will be increasingly influenced by their potential toxicities as well as by more traditional biological criteria. Toxicities will also have an impact on patients' tolerability and adherence to often complex antiretroviral regimens, particularly for patients receiving so-called salvage or intensification regimens, which can comprise up to seven antiretroviral drugs. Therefore, assays that predict or more readily diagnose drug-induced toxicity are needed. Therapeutic drug monitoring of protease inhibitors is one possibility, given that toxicity of many protease inhibitors is concentration-dependent, although antiviral potency should not be sacrificed at the expense of tolerability if possible. However, whether such monitoring will improve clinical outcomes is not known. Lastly, the improving awareness of adverse effects will continue the impetus to development of improved second-generation and third-generation antiretroviral compounds.

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