Human immunodeficiency virus

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection are toxic and expensive but they increase life expectancy considerably. Treatment should be undertaken only by those experienced in their use. Advice on the management of HIV changes rapidly .

PRINCIPLES OF TREATMENT

Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the development of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and patient tolerance. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. Testing for resistance to antiviral drugs particularly in therapeutic failure should be considered.

INITIATION OF TREATMENT

The optimum time for initiation of antiviral treatment will depend primarily on the CD4 cell count; the plasma viral load and clinical symptoms may also help. Initiating treatment with a combination of drugs ('highly active antiretroviral therapy' which includes 2 nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or 1 or 2 protease inhibitors) is recommended.

SWITCHING THERAPY

Deterioration of the condition (including clinical and virological changes) may require either switching therapy or adding another antiviral drug. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

PREGNANCY AND BREAST-FEEDING

Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral drugs is unknown), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. **All treatment options require careful assessment by a specialist**. Zidovudine monotherapy reduces transmission of infection to the neonate. However, combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother.
Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

POST-EXPOSURE PROPHYLAXIS

Treatment with antiviral drugs may be appropriate following occupational exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer's Expert Advisory Group on AIDS) and local ones may also be available.

DRUGS USED FOR HIV INFECTION

Zidovudine, a nucleoside reverse transcriptase inhibitor (or 'nucleoside analogue'), was the first anti-HIV drug to be introduced. Higher doses of zidovudine alone were used to prevent the AIDS dementia complex but combination therapy including zidovudine at standard doses is now preferred. Other nucleoside reverse transcriptase inhibitors include**abacavir**, **didanosine**, **lamivudine**, **stavudine**, **tenofovir**, and **zalcitabine**.
The protease inhibitors include **amprenavir**, **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir**, and **saquinavir**. Ritonavir in low doses (typically 100 mg twice daily) boosts the activity of amprenavir, indinavir, lopinavir, and saquinavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. A combination of lopinavir with low-dose ritonavir is available. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below).
The non-nucleoside reverse transcriptase inhibitors **efavirenz** and **nevirapine** may interact with a number of drugs metabolised in the liver. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz but it is usually milder. Efavirenz treatment has also been associated with an increased plasma cholesterol concentration.

LIPODYSTROPHY AND METABOLIC EFFECTS

The MHRA (formerly MCA) has advised that combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients (e.g. decreased fat under the skin, increased abdominal fat, 'buffalo humps' and breast enlargement). Protease inhibitors are also associated with metabolic abnormalities such as hyperlipidaemia, insulin resistance, and hyperglycaemia. Clinical examination should include an evaluation of fat distribution; measurement of serum lipids and blood glucose should be considered.

ABACAVIR

Indications: HIV infection in combination with other antiretroviral drugs
Cautions: hepatic impairment (see below and Appendix 2); renal impairment (Appendix 3); **interactions:** Appendix 1 (abacavir)
HYPERSENSITIVITY REACTIONS. Life-threatening hypersensitivity reactions reported—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, lethargy, malaise, headache, myalgia and renal failure; less frequently mouth ulceration, oedema, hypotension, dyspnoea, sore throat, cough, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and anaphylaxis (CSM has identified hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness); rarely myolysis; laboratory abnormalities may include raised liver function tests (see below) and creatine phosphokinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks for 2 months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity
COUNSELLING. Patients should be told the importance of regular dosing (intermittent therapy may increase the risk of sensitisation), how to recognise signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment; patients should be advised to keep Alert card with them at all times
HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis
Contra-indications: pregnancy (Appendix 4); breast-feeding
Side-effects: hypersensitivity reactions (see above), nausea, vomiting, diarrhoea, anorexia, lethargy, fatigue, fever, headache, pancreatitis, lactic acidosis (see above), hepatitis (see above); rash and gastro-intestinal disturbances more common in children

DIDANOSINE

(ddI, DDI)
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Side-effects); history of liver disease (see below); hepatic and renal impairment (see Appendixes 2 and 3); pregnancy; dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur; **interactions:** Appendix 1 (didanosine)
PANCREATITIS. If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic) suspend treatment until diagnosis of pancreatitis excluded; on return to normal values re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated
HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease (especially in hepatitis C treated with interferon alfa and ribavirin), excessive alcohol intake liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or lactic acidosis

Contra-indications: breast-feeding
Side-effects: diarrhoea, nausea, vomiting, abdominal pain, peripheral neuropathy especially in advanced HIV infection—suspend (reduced dose may be tolerated when symptoms resolve), headache, fatigue, rash, hyperuricaemia (suspend if raised significantly); less frequently, pancreatitis (see also under Cautions), abnormal liver function tests (see also under Cautions); rarely, flatulence, dry mouth, parotid gland enlargement, anorexia, sialadenitis, hepatitis, liver failure, anaphylactic reactions, fever, arthralgia, mylagia, rhabdomyolysis, dry eyes, retinal and optic nerve changes (especially in children), alopecia, diabetes mellitus, hypoglycaemia, anaemia, leucopenia, and thromobcytopenia

LAMIVUDINE

(3TC)
Indications: see preparations below
Cautions: renal impairment (Appendix 3), hepatic disease (see below); pregnancy (Appendix 4); **interactions:** Appendix 1 (lamivudine)
HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution (particularly in obese women) in liver disease, liver enzyme abnormalities, or risk factors for liver disease; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis. Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine. When treating chronic hepatitis B with lamivudine, monitor liver function tests at least every 3 months and serological markers of hepatitis B every 6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue after discontinuation)—consult product literature
Contra-indications: breast-feeding
Side-effects: nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia, and red cell aplasia; lactic acidosis; raised liver enzymes and serum amylase reported
Dose: see preparations below

STAVUDINE

(d4T)
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: history of peripheral neuropathy (see below); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; hepatic disease (see below); renal impairment (Appendix 3); pregnancy (Appendix 4); **interactions:** Appendix 1 (stavudine)
PERIPHERAL NEUROPATHY. Suspend if peripheral neuropathy develops—characterised by persistent numbness, tingling or pain in feet or hands; if symptoms resolve satisfactorily on withdrawal and if stavudine needs to be continued, resume treatment at half previous dose
HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease (especially in hepatitis treated with interferon alfa and ribavirin), liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or lactic acidosis
Contra-indications: breast-feeding
Side-effects: peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes (see above) and serum amylase; neutropenia, thrombocytopenia

TENOFOVIR DISOPROXIL
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: renal impairment (Appendix 3)—test renal function and serum phosphate before treatment, then every 4 weeks (weekly if given with nephrotoxic drug e.g. cidofovir), interrupt treatment if renal function deteriorates or serum phosphate decreases; pregnancy (Appendix 4); **interactions:** Appendix 1 (tenofovir)
Contra-indications: breast-feeding

Side-effects: diarrhoea, nausea, vomiting, flatulence, hypophosphataemia

ZALCITABINE

(ddC, DDC)
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: patients at risk of developing peripheral neuropathy (see below); pancreatitis (see also below)—monitor serum amylase in those with history of elevated serum amylase, pancreatitis, alcohol abuse, or receiving parenteral nutrition; cardiomyopathy, history of congestive cardiac failure; hepatotoxicity (see below); pregnancy (women of childbearing age should use effective contraception during treatment); renal impairment (Appendix 3); **interactions:** Appendix 1 (zalcitabine)
PERIPHERAL NEUROPATHY. Discontinue immediately if peripheral neuropathy develops—characterised by numbness and burning dysaesthesia possibly followed by sharp shooting pains or severe continuous burning and potentially irreversible pain; extreme caution and close monitoring required in those at risk of peripheral neuropathy (especially those with low CD4 cell count for whom risk is greater and those receiving another drug known to cause peripheral neuropathy)
PANCREATITIS. Discontinue permanently if clinical pancreatitis develops; suspend if raised serum amylase associated with dysglycaemia, rising triglyceride, decreasing serum calcium or other signs of impending pancreatitis until pancreatitis excluded; suspend if treatment required with another drug known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); caution and close monitoring if history of pancreatitis (or of elevated serum amylase) or if at risk of pancreatitis
HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or history of alcohol abuse or hepatitis; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis
Contra-indications: peripheral neuropathy (see also above); breast-feeding
Side-effects: peripheral neuropathy (discontinue immediately, see also above); oral ulcers, nausea, vomiting, dysphagia, anorexia, diarrhoea, abdominal pain, constipation; pharyngitis; headache, dizziness; myalgia, arthralgia; rash, pruritus, sweating, weight loss, fatigue, fever, rigors, chest pain, anaemia, leucopenia, neutropenia, thrombocytopenia, disorders of liver function; less frequently pancreatitis (see also above), oesophageal ulcers (suspend treatment if no response to treatment for specific organisms), rectal ulcers, jaundice and hepatocellular damage (see also under Cautions); other less frequent side-effects include taste, hearing and visual disturbances, tachycardia, cardiomyopathy, congestive heart failure, dyspnoea, seizures, tremor, movement disorders, mood changes, sleep disturbances, alopecia, hyperuricaemia and renal disorders

ZIDOVUDINE

(Azidothymidine, AZT)
Note.
The abbreviation AZT which has sometimes been used for zidovudine has also been used for another drug
Indications: HIV infection in combination with other antiretroviral drugs; monotherapy for prevention of maternal-fetal HIV transmission (see notes above under Pregnancy and Breast-feeding)
Cautions: haematological toxicity (blood tests at least every 2 weeks for first 3 months then at least once a month, early disease with good bone marrow reserves may require less frequent tests e.g. every 1–3 months); vitamin B12 deficiency (increased risk of neutropenia); reduce dose or interrupt treatment according to product literature if anaemia or myelosuppression; renal impairment (Appendix 3); hepatic impairment (see below and Appendix 2); risk of lactic acidosis, (see below); elderly; pregnancy; **interactions:** Appendix 1 (zidovudine)
HEPATIC DISEASE. Potentially life threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease (especially in chronic hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women), suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or lactic acidosis
Contra-indications: abnormally low neutrophil counts or haemoglobin values (consult product literature); neonates with hyperbilirubinaemia requiring treatment other than phototherapy, or with raised transaminase (consult product literature); breast-feeding

Side-effects: anaemia (may require transfusion), neutropenia, and leucopenia (all more frequent with high dose and advanced disease); also include, nausea and vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes (see also under Cautions); chest pain, dyspnoea, cough; influenza-like symptoms, headache, fever, paraesthesia, neuropathy, convulsions, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus, pigmentation of nail, skin and oral mucosa

AMPRENAVIR
Indications: HIV infection in combination with other antiretroviral drugs in patients previously treated with other protease inhibitors
Cautions: hepatic impairment (Appendix 2); pregnancy (Appendix 4); diabetes; haemophilia; avoid vitamin E supplements (vitamin E included in formulation); oral solution contains propylene glycol—avoid in hepatic impairment, in severe renal impairment (Appendix 3), in pregnancy, and avoid concomitant metronidazole, disulfiram, or preparations containing alcohol or propylene glycol; increased susceptibility to propylene glycol toxicity in slow metabolisers; **interactions:** Appendix 1 (amprenavir)
RASH. Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—rash usually resolves within 2 weeks and may respond to antihistamines
Contra-indications: breast-feeding
Side-effects: see notes above; also reported, rash including rarely Stevens-Johnson syndrome (see also above); tremors, oral or perioral paraesthesia, mood disorders including depression

INDINAVIR
Indications: HIV infection in combination with nucleoside reverse transcriptase inhibitors
Cautions: hepatic impairment (Appendix 2); ensure adequate hydration to reduce risk of nephrolithiasis; diabetes; haemophilia; pregnancy (Appendix 4); metabolism of many drugs inhibited if administered concomitantly, **interactions:** Appendix 1 (indinavir)
Contra-indications: breast-feeding
Side-effects: see notes above; also reported, dry mouth, hypoaesthesia, dry skin, hyperpigmentation, alopecia, paronychia, interstitial nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children); haemolytic anaemia

LOPINAVIR WITH RITONAVIR
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: hepatic impairment—avoid if severe (Appendix 2, Kaletra®); renal impairment (Appendix 3, Kaletra®); haemophilia; pregnancy (Appendix 4, Kaletra®); diabetes; pancreatitis (see below); **interactions:** Appendix 1 (Kaletra®)
PANCREATITIS. Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed
Contra-indications: breast-feeding (Appendix 5, Kaletra®)
Side-effects: see notes and Cautions above; also reported, dry mouth, influenza-like syndrome, appetite changes, hypertension, palpitations, thrombophlebitis, vasculitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dyskinesia, peripheral neuritis; Cushing's syndrome, hypothyroidism, sexual dysfunction, dehydration, oedema, lactic acidosis, arthralgia, abnormal vision, otitis media, tinnitus, acne, alopecia, dry skin, skin discoloration, nail disorders, sweating; raised bilirubin and lowered sodium also reported in children

NELFINAVIR
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: hepatic and renal impairment; diabetes; haemophilia; pregnancy; **interactions:** Appendix 1 (nelfinavir)
Contra-indications: breast-feeding
Side-effects: see notes above; also reported, fever

RITONAVIR

Indications: progressive or advanced HIV infection in combination with nucleoside reverse transcriptase inhibitors; low doses used to increase effect of some protease inhibitors
Cautions: hepatic impairment; diabetes; haemophilia; pregnancy; pancreatitis (see below); **interactions:** Appendix 1 (ritonavir)
PANCREATITIS. Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed
Contra-indications: severe hepatic impairment; breast-feeding
Side-effects: see notes and Cautions above; also reported, diarrhoea (may impair absorption—close monitoring required), throat irritation, vasodilatation, syncope, hypotension; circumoral and peripheral paraesthesia, hyperaesthesia, seizures, raised uric acid, dry mouth and ulceration, cough, anxiety, fever, pain, decreased thyroxine, sweating, electrolyte disturbances, increased prothrombin time

SAQUINAVIR
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: hepatic impairment (Appendix 2); renal impairment (Appendix 3); diabetes; haemophilia; pregnancy (Appendix 4); **interactions:** Appendix 1 (saquinavir)
Contra-indications: severe hepatic impairment (Appendix 2), breast-feeding
Side-effects: see notes above; also reported, buccal and mucosal ulceration, peripheral neuropathy, mood changes, fever, nephrolithiasis

EFAVIRENZ
Indications: HIV infection in combination with other antiretroviral drugs
Cautions: hepatic impairment (avoid if severe; Appendix 2); severe renal impairment; pregnancy (Appendix 4); elderly; history of mental illness or seizures; **interactions:** Appendix 1 (efavirenz)
RASH. Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—rash usually resolves within 1 month
Contra-indications: breast-feeding
Side-effects: rash including Stevens-Johnson syndrome (see also above); dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration (administration at bedtime especially in first 2–4 weeks reduces CNS effects); nausea; less frequently vomiting, diarrhoea, hepatitis, depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo; also reported abdominal pain, raised serum cholesterol, elevated liver enzymes (especially if seropositive for hepatitis B or C), hepatic failure, pancreatitis, convulsions, gynaecomastia, pruritus, blurred vision

NEVIRAPINE
Indications: progressive or advanced HIV infection, in combination with at least two other antiretroviral drugs
Cautions: hepatic impairment (see below and Appendix 2); history of chronic hepatitis (greater risk of hepatic side-effects), pregnancy (Appendix 4); **interactions:** Appendix 1 (nevirapine)

HEPATIC DISEASE. Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually occurring in first 8 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then every 3–6 months; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction
Note. If treatment interrupted for more than 7 days re-introduce with 200 mg daily (CHILD 4 mg/kg daily) and increase dose cautiously
RASH. Rash, usually occurring in first 8 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, swelling, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves
COUNSELLING. Patients should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if symptoms develop
Contra-indications: breast-feeding; severe hepatic impairment

Side-effects: rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also Cautions above); hepatitis or jaundice reported (see also Cautions above); nausea, vomiting, abdominal pain, diarrhoea, headache, drowsiness, fatigue, fever; hypersensitivity reactions (may involve hepatic reactions and rash, see Cautions above); also reported, anaphylaxis, angioedema, urticaria, neuropsychiatric reactions, anaemia