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Antiviral drugs

Editor's note: Interferons are covered in Chapter 37.

DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS

Cidofovir (SED-15, 771; SEDA-30, 343; SEDA-31, 477)

Respiratory Cidofovir has been used to treat adenovirus pneumonia in four pediatric lung transplant recipients (1°). Two developed bronchiolitis obliterans, one of whom underwent retransplantation with a good outcome. The other developed tracheomalacia and required continuous low-flow oxygen and positive pressure ventilation through a tracheostomy.

Urinary tract Of six hemopoietic stem cell transplant recipients, who were given cidofovir 5 mg/kg/week for 2 weeks, then on alternate weeks for a minimum of four (range 1–7) doses, three developed adenovirus hepatitis, two had colitis and one had nephritis (2°). All had CD34+ selected grafts and/or graft-versus-host disease and all had a CD4 count under 100 × 10^9/l. The patients were pre-hydrated and given probenecid and intravenous immunoglobulin 1–2 g/kg/week followed by 0.5 mg/kg on alternate weeks for a minimum of four doses. Two patients died of infection and four responded. None required withdrawal of treatment because of adverse effects. Baseline creatinine was slightly raised (167 μmol/l) in the patient with hepatitis and improved with cidofovir. Most of the patients had transient increases in creatinine as the number of doses increased.

Cidofovir 5 mg/kg/week or 1 mg/kg on alternate days adjusted to creatinine clearance was used to treat 11 hemopoietic stem cell transplant recipients with invasive adenoviral infection, including three with pneumonia, one with hepatitis, four with hemorrhagic colitis and three with hemorrhagic cystitis (3°). All had concomitant intravenous immunoglobulin, and those with colitis had in addition one or more of oral immunoglobulin, ribavirin, or donor lymphocyte infusion. They varied in their degree of immunocompromise and the presence of graft-versus-host disease and some had leukocyte-depleted allografts. Six died. There was nephrotoxicity in two cases.

In a retrospective study of 19 recipients of hemopoietic stem cell transplants, mean age 42 years, who were given a mean of 4.5 (range 3–6) weekly doses of cidofovir 1 mg/kg without probenecid for BK virus-associated hemorrhagic cystitis, 84% had graft-versus-host disease and were taking corticosteroids at the time of diagnosis (4°). There was no significant rise in creatinine in 14; 5 had renal insufficiency, but in all cases there were other potential causes.
only 3 cases could cidofovir have played a role. In those with normal renal function, 80–100% of the cidofovir was recovered from the urine, raising the possibility of therapeutic intravesicular administration.

DRUGS ACTIVE AGAINST HERPESVIRUSES (SEDA-29, 301; SEDA-30, 343; SEDA-31, 478)

Aciclovir

Psychiatric Hemodialysis has been successfully used to treat an aciclovir-induced psychosis (5A).

- A 70-year-old man with rectal carcinoma and end-stage renal failure on hemodialysis was given intravenous aciclovir. He developed delirium, visual and auditory hallucinations, disorientation in place and time, and impaired recent memory. He recovered fully after 3 consecutive days of hemodialysis.

Urinary tract Reports of renal insufficiency associated with the use of intravenous aciclovir continue to appear (6A). In a retrospective review of 126 children there was no effect of dose per kilogram, age, or sex on nephrotoxicity (7). The predictors of aciclovir nephrotoxicity were the concomitant use of nephrotoxic drugs and impaired glomerular filtration rate (GFR) at baseline.

Fetotoxicity It has been suggested that maternal use of aciclovir may be associated with necrotizing enterocolitis in the neonate (8A).

Valaciclovir

Immunologic An acute allergic reaction to valaciclovir has been described (9A).

- A 50-year-old woman developed general malaise, diffuse pruritus, angioedema of the hands and feet, and reduced consciousness and faintness within 5 minutes of taking valaciclovir 500 mg for genital herpes. Skin prick tests for aciclovir were positive.

Urinary tract As with aciclovir, renal insufficiency has been reported with valaciclovir (10A)

- A 73-year-old Japanese man with cardiomyopathy and chronic renal disease was admitted with anuria, systemic edema, and renal dysfunction after taking valaciclovir 1 g tds 5 days for Herpes zoster infection with a non-steroidal anti-inflammatory drug. He was briefly dialysis-dependent but made a full recovery.

DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

Adefovir (SEDA-15, 35; SEDA-30, 344; SEDA-31, 480)

Observational studies In patients with lamivudine-resistant HBe antigen (HBeAg)-negative disease, adefovir 10 mg alone (n = 14) or in combination with lamivudine (n = 28) caused a fall in creatinine clearance requiring a modification in adefovir dose in two patients on combined therapy; both had underlying liver cirrhosis (11c). One developed reduced liver function and biopsy showed steatohepatitis. One on adefovir monotherapy developed gastric cancer. Five on combined therapy with underlying cirrhosis developed hepatocellular carcinoma, but this was not statistically significant.

Adefovir 10 mg/day in combination with lamivudine 300 mg/day has been used in 11 patients with recurrent hepatitis B virus infection after liver transplant (12c). All patients with chronic hepatitis B pre-transplant underwent a period of preoperative treatment and peri-operative prophylaxis with lamivudine and hepatitis B immunoglobulin with or without adefovir if lamivudine-resistant. No patient had adverse effects necessitating drug withdrawal, but one required a dosage adjustment because of a rise in creatinine from 106 to 150 µmol/l. Three had a recurrence of hepatocellular carcinoma, two
of whom died 12 and 14 months after starting adefovir therapy and one of whom continued to be positive for hepatitis B virus DNA.

**Drug–drug interactions Entecavir** The interaction of entecavir 1 mg/day with adefovir 10 mg/day has been studied in a fixed-sequence crossover study in 26 healthy adults (13). The results suggested that combination therapy can be safely administered without the need for dosage adjustment of either drug. There was headache in nine subjects and dysmenorrhea in two when they took entecavir alone.

**Amantadine**

See ‘Drugs active against influenza viruses: ion channel inhibitors’, below.

**Entecavir**

**Drug–drug interactions Adefovir** The interaction of entecavir 1 mg/day with adefovir 10 mg/day has been studied in a fixed-sequence crossover study in 26 healthy adults (13). The results suggested that combination therapy can be safely administered without the need for dosage adjustment of either drug. There was headache in nine subjects and dysmenorrhea in two when they took entecavir alone.

**Lamivudine** *(SED-15, 1989, SEDA-30, 344; SEDA-31, 480)*

**Observational studies** In 33 treatment-naïve HBeAg-positive children who took lamivudine and high-dose interferon alpha 2a combination therapy, *flu-like symptoms* and *anorexia* were the commonest adverse effects (90 and 76%); *weight loss, nausea, vomiting, arthralgia,* and *loss of hair* were also noted (14). In an open study of the pharmacokinetics of lamivudine in 12 patients receiving peritoneal dialysis, *eye redness* *(n = 2)* and *diarrhea* *(n = 2)* were the commonest adverse events (15).

**Comparative studies** In a double-blind, Phase III, randomized, controlled trial of lamivudine 100 mg/day *(n = 687)* versus telbivudine 600 mg/day *(n = 680)*, *creatine kinase activity was raised* in patients receiving lamivudine (3.1%) and telbivudine (7.5%) and fell spontaneously during drug treatment to grade 2 or lower in 74% of those taking lamivudine and 67% of those taking telbivudine (16). Grade 3 or 4 *rises in transaminases* during treatment were more frequent with lamivudine than with telbivudine.

**Ribavirin**

**Observational studies** High-dose ribavirin during an outbreak of severe acute respiratory syndrome in Toronto was associated with a high rate of adverse events: *anemia* (odds ratio [OR] = 3.0; 99% confidence interval [CI] = 1.5, 6.1), *hypomagnesemia* (OR = 21; 99% CI = 5.8, 73), and *bradycardia* (OR = 2.3; 99% CI = 1.0, 5.1) (17). The risks of anemia, hypomagnesemia, and bradycardia attributable to ribavirin were 27%, 45%, and 17% respectively. The authors concluded that the use of high-dose ribavirin is appropriate only for the treatment of infectious diseases for which ribavirin has proven clinical efficacy, or in the context of a clinical trial. They further stated that ribavirin should not be used empirically for the treatment of viral syndromes of unknown origin.

**Skin** Occasional *rashes* in areas of drug contact and *conjunctival irritation* occurred when aerosolized ribavirin was used for 10 months in an infant with immunodeficiency (18a).

**Telbivudine**

**Musculoskeletal** In a double-blind, Phase III, randomized, controlled trial of lamivudine 100 mg/day *(n = 687)* versus telbivudine 600 mg/day *(n = 680)*, *raised creatine kinase activity* was more common in patients
who took telbivudine and it fell spontaneously during drug treatment to grade 2 or lower in 67% of those who took telbivudine and 74% of those who took lamivudine. Myopathy (characterized by muscle pain, weakness, and moderately raised creatine kinase activity before and during treatment) was reported in one patient after telbivudine therapy for 11 months. When telbivudine was withdrawn, the creatine kinase activity normalized within 1 month and the symptoms resolved over 9–12 months (16C).

In a randomized controlled trial of indinavir, saquinavir and lopinavir in combination with low-dose ritonavir in 656 patients, median total cholesterol increased by 0.5 mmol/l in the patients with the highest minimum drug plasma concentrations (23A).

Gastrointestinal In a retrospective observational study of highly active antiretroviral therapy (HAART), 27 of 50 patients who took indinavir in combination with zidovudine and lamivudine developed nausea and were significantly more likely to stop taking the treatment than those who were taking zidovudine + lamivudine + tenofovir (24).

In a long-term follow-up study of 200 asymptomatic HIV-positive participants for 157 weeks taking a combination of indinavir, lamivudine, and zidovudine, 40 stopped treatment because of adverse effects, of which nausea (69%), diarrhea (37%), and abdominal pain (28%) were the most common (25).

The most common adverse events in 21 of 151 patients in a prospective study of once-daily saquinavir + ritonavir and two nucleoside reverse transcriptase inhibitors (NRTIs) were abdominal discomfort, diarrhea, and vomiting (26). Similar findings were seen by other investigators (27A).

Liver In 199 HIV/hepatitis C co-infected patients, failure to achieve a sustained viral response, NRTI therapy, didanosine, and stavudine were significantly associated with worsening of hepatic fibrosis in 34 (17%) (28). After multivariate analysis, didanosine (OR = 3.34; 95% CI = 1.39, 7.96) and failure to have a sustained viral response (OR = 9.05; 95% CI = 2.06, 40) remained significantly associated with worsening of fibrosis.

In a retrospective study of 868 HIV-positive subjects (94% men), first-line therapy was efavirenz, lamivudine, and zidovudine; women of child-bearing potential were given nevirapine instead of efavirenz. An efavirenz-based regimen was used in 825 and 39 received a nevirapine-based regimen (29C). During the first year 48 subjects took isoniazid prophylaxis and 214 received

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**DRUGS ACTIVE AGAINST HIV: COMBINATIONS**

**Cardiovascular** Syncope occurred in a young man after he took tenofovir, emtricitabine and nevirapine for primary human immunodeficiency virus-1 (HIV-1) infection for 6 weeks and resolved after withdrawal of the antiretroviral drugs (19A).

**Metabolism** The hemochromatosis gene polymorphism HFE 187C>G and possibly mitochondrial haplogroup J gave relative protection against lipoatrophy during antiretroviral drug therapy in a trial in which 96 patients were randomized to didanosine + stavudine or zidovudine + lamivudine, combined with efavirenz and/or nelfinavir in AIDS Clinical Trials Group (ACTG) 384 sub-study A5005s (20C).

Stavudine had a less favorable effect on lipid profile and caused more lipoatrophy than abacavir (38% versus 4.8%) in a randomized, open trial, stratified by viral load and CD4 cell count, in which 237 adults with HIV infection were assigned to stavudine (n = 122) or abacavir (n = 115), both combined with lamivudine and efavirenz (21C).

There were dose-related increases in total cholesterol, LDL cholesterol, and triglycerides in an open study in 56 seronegative volunteers, with persistent increases 2 weeks after withdrawal (22C).
antituberculosis therapy (2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 4 months of rifampicin and isoniazid). Of a random sample of 133 tested, 17% were hepatitis B surface antigen (HBsAg)-positive. There was grade 2 or worse hepatotoxicity in 97 subjects (11%) and 40 had a first episode of grade 3 or 4 hepatotoxicity. Antituberculosis therapy (adjusted hazard ratio [HR] = 8.5; 95% CI = 2.7, 27) and HBsAg (adjusted HR = 3.0; 95% CI = 1.3, 7.0) were strongly associated with hepatotoxicity. However, hepatotoxicity had little impact on symptoms, the need for hospitalization and the need for a change in antiretroviral drug regimen. The use of isoniazid preventive therapy during antiretroviral drug therapy did not increase the risk of hepatotoxicity.

Three adults developed nodular regeneration of the liver while taking HAART regimens containing atazanavir, fosamprenavir, and indinavir (30A).

**Pancreas** In the large EuroSIDA study there was no association between an increased incidence of pancreatitis and cumulative exposure to antiretroviral drugs generally, or to didanosine and stavudine in particular (31C). There were 43 (9 presumptive) pancreatic events in 9678 individuals during 33,742 person-years (1.27 per 1000 person-years). The incidences among those with no, 2 or less, and over 2 years of exposure to antiretroviral drugs, including stavudine and didanosine, were 1.24, 1.73, and 0.78 per 1000 person-years, respectively. In multivariate analysis, higher baseline CD4 cell counts were associated with a reduced risk of pancreatitis.

**Urinary tract** Of 445 HIV-positive patients who started to take tenofovir, 51 (11%) had reduced renal function (32C). Multivariate analysis showed a significant association between reduced renal function and concurrent use of amprenavir and didanosine, age over 50 years and lower baseline weight. There was an association between concomitant use of tenofovir and amprenavir and reduced kidney function in 441 patients (OR = 3.5).

Acute interstitial nephritis was seen on renal biopsy in three HIV-positive patients taking amprenavir + tenofovir; it resolved after drug withdrawal (33A).

In a randomized controlled trial of indinavir, saquinavir, and lopinavir in combination with low-dose ritonavir in 656 patients, there was no apparent dose-related association with renal adverse events (23C).

**Immunologic** An allergic reaction with possible cross-reactivity to didanosine and tenofovir has been reported (34A).

- A 25-year-old woman tested positive for HIV-1 and was given a once-a-day regimen including tenofovir plus emtricitabine and efavirenz. After 10 days she developed a diffuse rash with fever and glossitis. Efavirenz was withdrawn but her conditions worsened over the next 3 days, so both tenofovir and emtricitabine were withdrawn, with dramatic resolution of symptoms within 24 hours. After 10 days she was given zidovudine plus didanosine and ritonavir-boosted fosamprenavir. After 1 week she again developed a diffuse rash and the treatment was withdrawn. She restarted zidovudine and didanosine 7 days later and within a few days the rash appeared again. Under observation she was given zidovudine and atazanavir and after 8 days lamivudine and low-dose ritonavir. She remained well, except for mild hyperbilirubinemia, during the next 5 months.

**Fetotoxicity** There is equivocal evidence of a relation between in utero NRTI exposure and mitochondrial dysfunction in HIV-negative children born to HIV-infected women. In 1037 HIV-negative children, possible cases with unexplained signs of mitochondrial dysfunction according to the Enquête Perinatale Française criteria were identified in a retrospective review (35C). Associations between possible mitochondrial dysfunction and both overall in utero NRTI exposure and the trimester of first in utero NRTI exposure were estimated by exact logistic regression. Cases \( n = 20 \) were significantly more likely to be boys and to be born in earlier years than non-cases.
(n = 1017). There was no association between overall in utero NRTI exposure and mitochondrial dysfunction. In unadjusted models there were higher odds of first in utero exposure in the third trimester to lamivudine (OR = 3.76 versus unexposed; 95% CI = 1.09, 12) and to zidovudine + lamivudine (OR = 3.29 versus unexposed; 95% CI = 0.96, 10) among cases than non-cases. When adjusted for year of birth, the odds of first exposure in the third trimester to lamivudine (OR = 11; 95% CI = 1.9, 76) and zidovudine + lamivudine (OR = 9.8; 95% CI = 1.7, 72) were significantly higher among cases than non-cases. Incomplete data precluded control of possible confounding by maternal viral load and psychoactive drug use.

**Drug–drug interactions**

**Combination of antiretroviral drugs** Reports of renal toxicity with the combination of tenofovir and didanosine in children suggest that this combination should be avoided (36). Combination of saquinavir with darunavir + ritonavir is currently not recommended as plasma concentrations of darunavir are increased (37).

**Buprenorphine** Atazanavir and atazanavir + ritonavir both resulted in increased metabolite concentrations of buprenorphine, and dosage reduction of buprenorphine is recommended; there was no change in the concentrations of the protease inhibitors (38).

**Warfarin** In two patients who were taking a non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine, or a protease inhibitor, nelfinavir or lopinavir + ritonavir, and two nucleoside analogues, high doses of warfarin were required to maintain therapeutic INRs (39). Warfarin has two enantiomers, R-warfarin and S-warfarin, which are substrates of CYP3A4 (R-warfarin), CYP1A2 (R-warfarin), and CYP2C9 (S-warfarin). Protease inhibitors and NNRTIs have variable effects on CYPs: induction, inhibition, or mixed effects. The increased warfarin doses required in these two patients may have been caused by induction of CYP3A4 by nevirapine, of CYP2C9 by nelfinavir, or of CYP2C9 by lopinavir + ritonavir.

**DRUGS ACTIVE AGAINST HIV: NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)**

- **Abacavir** (SED-15, 3; SEDA-29, 303; SEDA-30, 348; SEDA-31, 482)
- **Gastrointestinal** In patients with AIDS-associated dementia ADC taking optimal stable background antiretroviral therapy including either abacavir or placebo there was significantly more nausea in those who took abacavir (40).

**Immunologic** Three patients developed painful lymphadenopathy shortly after starting to take abacavir, mimicking immune reconstitution syndrome (41). They also had a fever and a rash and all were HLA-B*5701-positive. They recovered after withdrawal of abacavir.

Abacavir hypersensitivity occurred in a 36-year-old man after he switched from a twice-daily to a once-daily regimen (42). In a 52-year-old woman, abacavir hypersensitivity presented as acute fibrinous and organizing pneumonia, with dyspnea, hypoxia, and bilateral infiltrates (43).

**Susceptibility factors**

**Genetic** A sequence variation in the HIV reverse transcriptase codon 245 has been associated with host HLA-B*5701 in 392 HIV-infected, antiretroviral drug-naive adults, and the relation between the codon 245 variation and premature abacavir withdrawal was investigated in 982 treated individuals (44). Only one of 24 subjects with B*5701 harbored virus with the clade B ‘wild-type’ amino acid 245V, compared with 278 of 368
who did not have B*5701. The sensitivity and specificity of codon 245 substitutions for predicting HLA-B*5701 were 96% and 75% respectively, and the positive and negative predictive values were 20% and 99.6% respectively. The authors argued that the reverse transcriptase codon 245 could be adopted as a simple, low-cost screening method to identify individuals who could be safely treated with abacavir when detection of HLA-B*5701 is not rapidly and easily available.

**Drug–drug interactions** Alcohol Three patients had possible reactions to alcohol while taking abacavir (45A). One had a disulfiram-like reaction (nausea, facial flushing, tachycardia) repeatedly on rechallenge with alcohol. Another described a feeling of being drunk after small amounts of alcohol. A third had malaise after increasing his alcohol intake. The authors suggested that abacavir might inhibit alcohol dehydrogenase.

**Didanosine** (SED-15, 1113; SEDA-29, 303; SEDA-30, 348; SEDA-31, 483)

**Urinary tract** Fanconi syndrome and nephrogenic diabetes insipidus associated with didanosine have been reported (46A).

- A 40-year-old man developed polydipsia, polyuria, fatigue, and weight loss after taking didanosine, lamivudine and boosted atazanavir for 2 years. He had hypophosphatemia, hypouricemia, hypercholesemic metabolic acidosis with a normal anion gap, normoglycemic glycosuria, and low-molecular-weight proteinuria. The plasma antidiuretic hormone (ADH) concentration was high at 4.8 pg/ml (reference range 1.4–4.4 pmol/l). The didanosine was replaced with another protease inhibitor and the other medications remained unchanged. He improved slowly.

**Drug–drug interactions** Ganciclovir It has been suggested that ganciclovir and its prodrug valganciclovir inhibit purine nucleoside phosphorylase (PNP) in a similar manner to tenofovir and increase didanosine concentrations, reducing its efficacy (47A).

- A 68-year-old woman with HIV and cytomegalovirus enteritis was given valganciclovir, lamivudine, didanosine, and lopinavir + ritonavir. After 3 months, her viral load fell to less than 50 copies/ml and the CD4+ cell count was $317 \times 10^3/\text{L}$. Over the next 9 months her viral load remained suppressed, but the CD4+ cell count fell to $83 \times 10^3/\text{L}$ and she had symptoms of didanosine toxicity. Didanosine was replaced with abacavir, leading to complete recovery of the CD4+ cell count and resolution of symptoms.

Reduction of the dosage of didanosine or substitution with an alternative antiretroviral drug may be necessary when ganciclovir is used.

**Stavudine**

**Metabolism** Lipodystrophy tended to occur more often in 58 HIV/hepatitis C co-infected patients who had severe weight loss than in 111 other patients (26% versus 18%), and patients who had persistent weight loss over 5% for 24 weeks after the completion of anti-hepatitis C virus (HCV) therapy were more likely to be taking a stavudine-based antiretroviral therapy (48B).

In another study patients with lipoatrophy had higher drug exposure to stavudine than controls (49B). This was reflected in the higher geometric concentration ratios (0.978 and 0.741 respectively) and a higher percentage of ratios over 1.0, representing a drug concentration above the normal population curve (46% versus 23%). In addition, the duration of stavudine therapy was independently associated with lipoatrophy. In a multivariate analysis, both duration of stavudine therapy and a concentration ratio over 1.0 independently correlated with lipoatrophy.

Changes in body habitus occur when stavudine is withdrawn. In 574 HIV-positive women who stopped taking stavudine for over 2.25 years, there were significantly smaller reductions in hip and thigh circumferences compared with the reductions that occurred at 1–2.25 years after stavudine withdrawal (50B).

Stavudine reduces insulin sensitivity and causes mitochondrial toxicity in healthy subjects. In 16 participants without a personal
or family history of diabetes who were randomized to stavudine 30–40 mg bd or placebo for 1 month, insulin sensitivity was significantly reduced by stavudine (51°C). In addition, muscle biopsies in those who took stavudine showed significant reductions in mtDNA/nuclear DNA, but there were no changes in placebo-treated subjects. P magnetic resonance spectroscopy studies of mitochondrial function correlated with measures of insulin sensitivity.

In 125 patients in a retrospective study, symptomatic hyperlactatemia in 114 (91%) was associated with stavudine median duration 13 months (52°C). Nine patients (7.2%) died; those who died had a higher mean lactate concentration (8.0 versus 5.1 mmol/l) and mean A1C activity (164 versus 48 U/l) at the time of diagnosis than those who survived. Those who died had a lower mean weight than those who survived (48 versus 59 kg). By logistic regression, mortality was associated with patients whose body weight was under 45 kg (OR = 9.1; 95% CI = 1.6, 53) and whose serum lactate was over 10 mmol/l (OR = 20; 95% CI = 2.6, 159).

Dosage regimens A meta-analysis of clinical trials conducted before and after regulatory approval of stavudine has shown that a dosage of 30 mg bd has equivalent antiviral efficacy, with some evidence of lower rates of peripheral neuropathy and lipoatrophy, to the standard dosage of 40 mg bd (53°C). It has been suggested that this is the most appropriate dose in resource-limited settings (54°M). Reducing the dosage of stavudine by one-half increased fat mtDNA and bone density and decreased lactate concentrations in a study of 24 patients already taking a standard dose (55°C).

Zidovudine (SED-15, 3713; SEDA-31, 485)

Hematologic Hemoglobin A2 can rise in HIV-infected patients, possibly because of therapy (56°C). In cross-sectional and cohort studies, hemoglobin A2 was often raised in untreated patients, but a further rise during treatment was specifically attributable to zidovudine. The concentration of hemoglobin A2 may be high enough to lead to a misdiagnosis of beta-thalassemia.

Genotoxicity Micronucleated reticulocyte frequencies have been measured as a marker of chromosomal damage in 16 HIV-infected mother–infant pairs, of whom 13 women had taken prenatal zidovudine and 3 antiretroviral drugs without zidovudine (57°C). All the infants received zidovudine for 6 weeks. Venous blood was obtained from women at delivery and from infants at 1–3 days, 4–6 weeks, and 4–6 months of life; cord blood was collected immediately after delivery. Ten cord blood samples (controls) were obtained from infants of HIV-negative women who did not receive antiretroviral therapy. There were 10-fold increases in micronucleated reticulocytes in women and infants who received zidovudine-containing antiretroviral therapy prenatally and no increases in the other women and infants. Micronucleated reticulocytes in the zidovudine-exposed neonates fell over the first 6 months of life to values comparable to cord blood controls. The authors concluded that transplacental zidovudine exposure is genotoxic in humans and they recommended long-term monitoring of zidovudine-exposed infants.

Teratogenicity A possible association between first trimester exposure to zidovudine and an increased risk of hypospadias based on one cohort study has been reported (58°C). Among 2527 live births to 2353 women, defects were identified in 90 babies (3.56 defects per 100 live births). The rate of defects was 3.19 per 100 live births with first-trimester antiretroviral drug exposure, 3.54 per 100 live births with exposure later in pregnancy, and 4.05 of 100 live births with no antiretroviral drug use. Only genital abnormalities, specifically hypospadias, were significantly increased among babies born to women with first-trimester exposure to antiretroviral drugs (7 of 382 male live births) compared with the two other groups (2 of 892 male live
Births. Logistic regression suggested that use of zidovudine in the first trimester was associated with hypospadias (adjusted OR = 11; 95% CI = 2.1, 54).

Pregnancy In a pharmacokinetic study of three doses of zidovudine 300 mg 3-hourly in pregnancy in six subjects, plasma zidovudine concentrations were substantially lower than previously reported during continuous intravenous therapy (59A). In another study in four women who took an initial 600 mg dose followed by two 400 mg doses 3-hourly, the zidovudine AUC and concentrations increased approximately in proportion to the increase in dose but varied 6–7 times (60A). In both cohorts, the pharmacokinetic results suggested erratic absorption.

Drug–drug interactions Co-trimoxazole Combined exposure to zidovudine plus co-trimoxazole caused a clinically significant suppression of humoral immune responses to influenza immunization in 23 HIV-positive patients with CD4 counts above $350 \times 10^9/l$ (61A).

Ribavirin Ribavirin did not inhibit the formation of zidovudine triphosphate in peripheral blood monocytes in 14 patients over 8 weeks (62A).

DRUGS ACTIVE AGAINST HIV: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS) (SED-15, 2553; SEDA-28, 334; SEDA-29, 305; SEDA-30, 349; SEDA-31, 486)

Efavirenz (SED-15, 1204; SEDA-29, 305; SEDA-30, 349; SEDA-31, 486)

The efficacy, resistance profile, adverse effects, and drug interactions of efavirenz have been reviewed (66A).

Psychiatric Neuropsychiatric symptoms provoked by efavirenz have been reviewed (67A). Of 103 patients who took didanosine, lamivudine, and efavirenz for 48 weeks, 19 had neuropsychiatric adverse effects related to efavirenz (68A).

In an evaluation of the effectiveness and adverse effects of a simplification regimen
with tenofovir, lamivudine, and efavirenz in 154 HAART-experienced HIV-1-infected subjects with sustained viral suppression, 9 had psychiatric adverse effects related to efavirenz, leading to drug withdrawal in most cases; the symptoms included nightmares, insomnia, nervousness, and anxiety (69c).

**Metabolism** ACTG study 5095 was a randomized, placebo-controlled, double-blind study designed to compare three protease inhibitor-sparing antiretroviral drug regimens (zidovudine + lamivudine + abacavir; zidovudine + lamivudine + efavirenz; zidovudine + lamivudine + abacavir + efavirenz) in the initial treatment of HIV-1 infection in 1147 subjects (70c). There were modest rises in serum triglycerides, LDL cholesterol, and HDL cholesterol in the two efavirenz-containing arms compared with the triple-nucleoside arm.

**Urinary tract** A renal calculus that occurred in a 47-year-old man taking efavirenz contained efavirenz metabolites (60%) and about 40% of unspecified proteins (71a). This was a between-the-eyes adverse effect of type 1a, definitively implicating efavirenz (72c).

**Breasts** In cohort study from Cambodia, 2 of 343 patients developed gynecomastia while taking a regimen containing efavirenz (73c).

**Susceptibility factors Genetic** Efavirenz is metabolized by CYP2B6. The pharmacokinetics of efavirenz have been studied in 71 children with a G-to-T polymorphism at position 516 of the CYP2B6 gene, which affected its oral clearance (74c). Children with the T/T genotype had a slower oral clearance rate than those with the G/T genotype and the G/G genotype. The fastest clearance was found in children under 5 years of age with the G/G genotype.

The association between efavirenz-induced psychosis and a genetic polymorphism in CYP2B6 has been reported in a child (75a).

• A 12-year-old HIV-positive girl taking lopinavir 400 mg bd, ritonavir 100 mg bd, stavudine 30 mg bd, didanosine 250 mg/day, and efavirenz 600 mg/day developed an overt psychosis. Her serum efavirenz concentration was 7–8 times higher than expected and she had a heterozygous gene polymorphism encoding for the CYP2B6 isoenzyme, which has previously been associated with reduced clearance of efavirenz. The psychotic symptoms resolved gradually after withdrawal of efavirenz.

**Drug–drug interactions Antimalarial drugs** Two healthy volunteers who took amodiaquine plus artesunate and efavirenz had significant asymptomatic rises in liver transaminases, which did not occur in the absence of efavirenz (76c).

**Voriconazole** In a randomized, placebo-controlled, two-period, multiple-dose within-group, fixed-dose sequence study of the interaction of voriconazole 200 mg bd with efavirenz 400 mg/day in healthy men, repeated doses of efavirenz substantially reduced the steady-state mean AUC and Cmax of voriconazole by 80% and 66% respectively (77c). Repeated therapeutic doses of voriconazole moderately increased the steady-state mean AUC and Cmax of efavirenz by 43% and 37% respectively. When voriconazole was co-administered with efavirenz, the incidence of adverse events was similar to that with efavirenz alone.

**Nevirapine**

**Liver** Hepatotoxicity is a major problem with nevirapine (78c). The frequency of large increases in liver enzymes in patients taking efavirenz is 1–8%, whereas in patients taking nevirapine it is 4–18%.

A warning about the increased risk of hepatotoxicity in antiretroviral-naive patients who start to take nevirapine-containing combination antiretroviral therapy has
been issued based on CD4 cut-off values and sex. However, it is unclear whether this higher risk also applies to stable virologically suppressed patients. A meta-analysis of four published randomized studies in 410 patients, including virologically suppressed patients who switched to nevirapine-containing regimens with a follow-up of at least 3 months, has shown that the risks of hepatotoxicity within the first 3 months were 2% and 4% in those with low and high CD4 counts, respectively, with a combined OR of 1.5 (95% CI = 0.4, 5) (79M). The risk of hepatotoxicity at any time during the study was similar in the groups, with a combined HR of 0.8 (95% CI = 0.3, 2.5). The authors concluded that virologically suppressed patients who switch to nevirapine do not have a significantly higher risk of hepatotoxicity or rash when stratified by sex and CD4 cell count.

The aim of a retrospective study was to determine whether these recommendations are of use in preventing adverse effects (80O). Drug-naive patients (n = 142) who started treatment with nevirapine were divided into two groups; those with high or low CD4 counts (n = 61 and 81 respectively). There were rashes in 4 patients in the high-CD4 group and in 12 of those in the low-CD4 group and hepatotoxicity in 3 and 5 patients respectively. The authors concluded that the advice not to use nevirapine in drug-naive patients at increased risk of toxicity on the basis of sex and CD4 cell count does not seem to be useful in preventing adverse effects.

In a retrospective study, 582 patients (72% men) received 744 nevirapine-based HAART regimens (81L). During 10% of treatments, there were grade 3 or greater increases in transaminase activities, an overall incidence rate of 5.3 cases per 100 person-years. This led to treatment withdrawal in 3.9% of cases.

In a retrospective study of over 1000 pregnant women taking nevirapine-containing regimens, 93% started or continued nevirapine during the first and second trimesters (82A). Concurrent chronic hepatobiliary disorders slightly increased the likelihood of hepatotoxicity. Of seven patients who had liver dysfunction, six previously had had hepatitis C and gall bladder disease.

**Skin** Widespread vitiligo after erythroderma has been attributed to nevirapine (83A).

- A 34-year-old man developed erythroderma, a high fever and hepatitis after taking nevirapine for 1 month. There was jaundice and a confluent macular rash on the arms, legs, trunk, and face. Histology showed a parakeratotic epidermis with focal spongiosis, necrotic keratinocytes and vacuolar degeneration of the basal layer, together with moderate edema and a perivascular mononuclear cell infiltrate, with some eosinophils in the upper dermis. The lesions faded on withdrawal of nevirapine and administration of oral glucocorticoids, but took around 6 months to finally subside.

**Drug rash with eosinophilia and systemic symptoms (DRESS)** has been associated with nevirapine in a child (84A).

- A 12-year-old girl took a nevirapine-containing regimen for 4 months and had recurrent episodes of fever, cough, sore throat, nausea, and vomiting 2–4 weeks apart. A chest X-ray showed mild bronchial wall thickening with left lower lobe atelectasis or a mild infiltrate. Her temperature was 40°C and she had a tachycardia of 145/minute. She had a generalized maculopapular confluent blanching rash, but no target lesions or blisters, conjunctival injection, nasal congestion, a hyperemic posterior pharynx, and several bilateral non-tender cervical lymph nodes. The liver was enlarged by 4 cm but the spleen was not palpable. The white blood cell count was 9.7 × 10⁹/l, with a marked eosinophilia (31%). She was successfully treated with intravenous immunoglobulin and antiretroviral drug withdrawal.

Nevirapine-induced Stevens–Johnson syndrome has been reported as having been misdiagnosed as viral keratitis (85A).

**Immunologic** In a retrospective study of trough plasma concentrations of nevirapine and five oxidative metabolites in 1357 patients with rashes or liver function abnormalities during the first 6 weeks of treatment and controls matched for glucocorticoid use, CD4 cell count, sex,
race, and hepatitis B/C status, 49 case-control pairs were studied (86). Women had significantly greater exposure than men to nevirapine and four of the five metabolites at week 2, but the plasma concentrations were comparable by week 4. There were no strong relationships between plasma concentrations of nevirapine or any of its five metabolites and case-defining events. The authors commented that systemic exposure to 12-hydroxynevirapine and 4-carboxynevirapine, hypothesized to be reactive intermediates for immune-mediated adverse reactions, were comparable between the cases and controls and were comparable in proportion to nevirapine exposure.

**Pregnancy**  In a retrospective, five-center comparison in HIV-1-infected women who took nevirapine as part of combination antiretroviral therapy during pregnancy, 15 of 235 eligible women (6.4%) developed a rash and 8 (3.4%) developed **hepatotoxicity**, including 4 with a co-existent **rash**, giving a combined incidence of 19 potential cases of nevirapine toxicity during pregnancy (8.1%) (87). Alternative causes of rash or hepatotoxicity were suspected in 7 cases, and only 10 mothers (5.8%) stopped taking nevirapine. Of the 170 women who started taking nevirapine during pregnancy, 13 (7.6%) developed a rash and 8 (4.7%) hepatotoxicity. Only 2 of 65 women (3.1%) with nevirapine exposure before pregnancy had had a rash.

**Susceptibility factors Genetic**  HLA typing and demographic and immunological susceptibility factors for reactions to nevirapine and efavirenz have been studied in 21 HIV-positive patients with rashes (88). Isolated rashes were significantly associated with HLA-DRB101. There were no cases of liver toxicity nor any association with the percentage of CD4 cells.

In 326 HIV-1-positive individuals, 309 of whom were Japanese, 42% of those who had hypersensitivity reactions to nevirapine had HLA-Cw8, compared with only 10% of the others and 9–14% of the general Japanese population (89). In the former group, four patients, including one who developed hepatotoxicity, had HLA-Cw*0801 and one had HLA-Cw*0803. Among the others, three patients had HLA-Cw*0801. There were no significant differences in the frequencies of other HLA alleles between the two groups.

**Drug dosage regimens**  Nevirapine has a long half-life and could be given once a day, but the risk of rashes and concerns over liver toxicity preclude the routine use of once-daily dosing. However, tolerance to high concentrations of nevirapine can develop when doses are increased slowly during the start of therapy. It is therefore theoretically possible that the benefits of once-daily dosing could be achieved without excess toxicity by switching to once-daily nevirapine after several months of twice-daily administration (90).

However, in the DAUFIN study, a twice-daily regimen of zidovudine 300 mg + lamivudine 150 mg + nevirapine 200 mg was compared with a once-daily regimen of lamivudine 300 mg + tenofovir 245 mg + nevirapine 400 mg (91). The study was stopped after early virological failure was observed in 8 of 36 once-daily patients. Resistance mutations accumulated during treatment, with high rates of K65R mutations and severe NNRTI resistance profiles indicative of continuing viral replication caused by suboptimal nevirapine plasma trough concentrations, possibly due to non-adherence. Non-B-subtype infection (subtypes A and C not stated) was observed in 4 of 10 patients with virological failure. The authors suggested that once-daily dosing can be introduced after induction of viral suppression has been achieved with a twice-daily regimen.

**Drug–drug interactions**  **Fluconazole**  Co-administration of nevirapine 200 mg/day with fluconazole 400 mg/day results in markedly increased trough plasma nevirapine concentrations compared with nevirapine
alone (92). In a retrospective study in 112 patients who were given nevirapine-based therapy with or without fluconazole 200 or 400 mg/day, mean nevirapine concentrations were 6.5 mg/l without fluconazole and 11.4 with fluconazole. One patient taking fluconazole developed hepatitis. Six of those who did not take fluconazole developed nevirapine-related rashes. There were no differences in 36-week antiviral efficacy between the two groups.

DRUGS ACTIVE AGAINST HIV: PROTEASE INHIBITORS (SED-15, 2586; SEDA-29, 306; SEDA-30, 351; SEDA-31, 487)

Atazanavir

Liver Hyperbilirubinemia and jaundice occurred during administration of atazanavir in all 23 healthy volunteers taking part in a 30-day follow-up study; there was a 52% increased minimum plasma concentration with co-administration of darunavir (93).

Hair Alopecia has been reported with ritonavir-boosted atazanavir (94).

Drug–drug interactions Rifampicin Concomitant usage of rifampicin with regimens including atazanavir should be avoided, as they result in subtherapeutic concentrations of atazanavir (95).

Tenofovir Atazanavir increased tenofovir concentrations in an open, crossover study in 30 healthy volunteers (96).

Fosamprenavir

Placebo-controlled studies Rashes and gastrointestinal disturbances were the most frequently reported adverse effects in a randomized controlled trial of fosamprenavir + ritonavir in treatment-naive HIV-infected patients (97).

Indinavir

Gastrointestinal Of 30 patients taking ritonavir + indinavir 400/100 mg in an open pilot study in Mali, one reported nausea (98). In a prospective study of 70 sub-Saharan African patients taking indinavir, 22 had severe vomiting (99).

Liver Rises in serum unconjugated bilirubin concentrations were reported in the Pivotal Phase III Trial. The mechanism is thought to be direct inhibition of bilirubin conjugation by competitive inhibition of UDP glucuronosyltransferase. Patients with polymorphisms in the UGT 1A1 gene are more likely to develop hyperbilirubinemia (100).

Urinary tract Indinavir causes nephrolithiasis and renal impairment as a result of crystallization in the urinary tract and resultant inflammation (101). Continuation of the drug with some improvement in renal function is possible with drug concentration monitoring. Co-factors such as concomitant co-trimoxazole therapy and environmental temperature increase the risk (100R). Using indinavir + ritonavir at the lower doses of 400 and 100 mg bd seems to reduce these adverse effects. Hematuria and flank pain each occurred in 38 patients in a study of asymptomatic HIV-infected individuals who took indinavir in a long-term follow-up study over 157 weeks (25).
Pregnancy  In a study of 16 pregnant women taking indinavir, two women and eight infants developed hepatotoxicity and had increased concentrations of indinavir, suggesting increased intestinal/hepatic CYP3A activity during pregnancy (103\textsuperscript{A}).

Nelfinavir

Metabolism  Of 111 pregnant women 15 taking nelfinavir developed gestational diabetes compared with none taking zidovudine monotherapy and two of 43 taking NRTIs and NNRTIs; the risk of gestational diabetes was increased in those with hepatitis C or who had begun HAART before pregnancy (104\textsuperscript{c}).

Nails  Paronychia has been reported in a case report occurring during nelfinavir treatment (105\textsuperscript{A}).

Ritonavir

Drug–drug interactions  Fluticasone  Cushing’s syndrome and adrenal suppression can be caused if protease inhibitors increase systemic glucocorticoid concentrations. Iatrogenic Cushing’s syndrome has been attributed to ritonavir by an interaction with fluticasone (106\textsuperscript{A}).

- A 16-year-old girl who had taken various antiretroviral drugs eventually took stavudine, lamivudine, and ritonavir and then used inhaled fluticasone + salmeterol for bronchiectasis. After 3 months she had excessive weight gain, increased appetite, fatigue, facial edema, marked acne, stretch marks on her limbs and abdomen, hypercholesterolemia, hypertriglyceridemia and amenorrhea. Cushing’s syndrome was attributed to an interaction of fluticasone with ritonavir, which was changed to efavirenz. There was a gradual improvement within 30–60 days, with reduced edema and stretch marks and return of menstruation.

A similar case involved a 14-year-old girl (107\textsuperscript{A}).

Saquinavir

Observational studies  In the ASPIRE 1 study, 7 of 17 healthy volunteers who took saquinavir + ritonavir for 3 months developed grade 3 gastrointestinal adverse effects and seven had hyperbilirubinemia (108\textsuperscript{c}). In the ASPIRE 2 study there was hyperbilirubinemia in 8 of 16 healthy volunteers.

Tipranavir

Tipranavir is a non-peptide protease inhibitor approved for use in patients with resistant strains of HIV (109\textsuperscript{R}, 110\textsuperscript{M}, 111\textsuperscript{R}). Its pharmacokinetics, efficacy, and adverse effects in children and adolescents have been reviewed (112\textsuperscript{R}). It can be used in combination with ritonavir.

Observational studies  In a 24-week multi-center, double-blind, randomized, dose-finding trial of ritonavir-boosted tipranavir in 216 patients, the most common adverse events were diarrhea, nausea, vomiting, fatigue, and headache (113\textsuperscript{C}).

Hematologic  Tipranavir boosted with ritonavir caused an increased risk of bleeding in 3 of 30 HIV-infected patients with hemophilia (114\textsuperscript{c}).

Intracranial hemorrhage  has been reported in a patient taking tipranavir (115\textsuperscript{A}).

Liver  Tipranavir is associated with an excess of grade 3/4 rises in liver enzyme compared with other ritonavir-boosted protease inhibitors (116\textsuperscript{R}).

Pancreas  Acute pancreatitis associated with hypertriglyceridemia has been reported in a patient taking tipranavir + ritonavir (117\textsuperscript{A}).
• A 42-year-old man taking tenofovir 300 mg/day, trizivir (zidovudine, lamivudine, and abacavir) one tablet bd, and tipranavir 500 mg bd + ritonavir 200 mg bd drank six standard alcoholic drinks 2 days before admission and developed marked tenderness in the epigastric region and a raised serum lipase at 113 IU/l (reference range below 65 IU/l). An abdominal computed tomography (CT) scan showed pancreatic edema with peripancreatic fluid consistent with acute pancreatitis. Ultrasonography showed a mildly dilated common bile duct with no evidence of cholelithiasis and CT cholangiography showed no evidence of gall-stone pancreatitis. The presumed diagnosis was alcohol-induced pancreatitis. He was managed conservatively by withdrawal of medications, intravenous fluids, and slow resumption of oral intake. However, within 12 days he again developed severe epigastric pain. He denied further alcohol use. The serum concentration of triglycerides was 99 mmol/l, and retrospective testing of blood samples taken during the earlier illness also showed marked hypertriglyceridemia. Tipranavir + ritonavir was withdrawn, efavirenz given, and tenofovir and trizivir continued. His triglyceride concentrations fell to 10.3 mmol/l 3 weeks later and 4.8 mmol/l 12 months later without specific intervention.

Skin Porphyria cutanea tarda has been reported after the introduction of tipranavir + ritonavir to a backbone of tenofovir and lamivudine (118A).

• A 59-year-old heterosexual woman switched to a tipranavir-containing therapy after virological failure. After 5 days she developed a rash accompanied by nausea, vomiting, malaise, and hyperamylasemia. All antiretroviral drugs were withdrawn, she improved, and treatment was restarted. Although the lesions were resolving, several blisters appeared on her hands, mainly on the fingers, along with itching and skin fragility on her arms. Aciclovir was ineffective and 1 month later the itch and blisters worsened. Urine concentrations of protoporphyrin and coproporphyrin were about 100 and 10 times higher than normal.

Drug resistance Virological response rates in tipranavir-treated individuals were reduced when the number of baseline protease inhibitor mutations was five or more. Individuals who took tipranavir without concomitant enfuvirtide and had five or more baseline protease inhibitor mutations began to lose antiviral response at weeks 4–8. However, individuals taking enfuvirtide with tipranavir achieved more than 1.5 log10 reductions in viral load from baseline at 24 weeks, even if they had five or more baseline protease inhibitor mutations. Virological response rates to tipranavir were reduced when the baseline phenotype for tipranavir had a greater than threelfold shift in the 50% effective concentration (EC50) from reference. The most common protease inhibitor mutations that were associated with virological failure were L10I/V/S, I13V, L33V/I/F, M36V/I/L V82T, V82L, and I84V.

Drug–drug interactions Interactions with tipranavir + ritonavir have been reviewed (120R). Tipranavir is metabolized by CYP3A and tipranavir + ritonavir in vitro inhibits CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A and induces glucuronidase and P-glycoprotein.

Protease inhibitors Ritonavir-boosted tipranavir, alone and in combination with comparator protease inhibitors, has been studied in 315 HIV-infected patients (121C). The addition of tipranavir + ritonavir 2 weeks after single protease inhibitor therapy reduced plasma trough concentrations of lopinavir, saquinavir, and amprenavir by 52%, 80%, and 56% respectively. The efficacy of a dual protease inhibitor regimen depended on the presence of tipranavir, and additional recycled protease inhibitors had limited activity, even in drug-resistant patients with plasma trough concentrations regarded as likely to be adequate. However, there are no clear guidelines about adequate trough concentrations of antiretroviral drugs.
Oseltamivir

Psychiatric Oseltamivir-induced worsening of delirium has been reported in an 83-year-old man, whose symptoms resolved 2 days after withdrawal (122A). Japanese authorities advised against using oseltamivir in adolescents aged 10–19 years after two suicides during 2007 and more than 100 reports of neuropsychiatric events identified during post-marketing surveillance, including delirium, convulsions, and encephalitis (123R). However, it is not clear whether these events were due to the influenza or the drug; in Phase III trials, there were similar incidences of neurological and psychiatric events in both treated and untreated patients (124R). Of 1113 patients enrolled in a Japanese neuraminidase inhibitor treatment study, 11 had neuropsychiatric symptoms, in 4 cases before the start of treatment (125C). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have advised doctors to monitor patients for abnormal behavior throughout treatment (123R).

Gastrointestinal Acute hemorrhagic colitis has been associated with oral oseltamivir in a 61-year-old man, who developed abdominal pain, diarrhea and hematochezia after taking two doses of oseltamivir (126A).

In a systematic review of three trials of neuraminidase inhibitors for preventing and treating influenza in 1500 children, 977 of whom had laboratory-confirmed influenza, those who took oseltamivir had vomiting more often than untreated children but withdrawal was rarely required (127M).

Drug resistance Resistance occurs in under 1% of healthy adults but occurs more often in children, from 5.5% up to 18% in one study, although a lower dosage regimen was used in that study. Resistance is often seen among immunocompromised patients. It was reported in two of eight patients infected with H5N1 and was associated with a fatal outcome. Resistance is associated with loss of fitness (128R). In 2008 widespread resistance emerged in H1N1 influenza, but it remains to be seen whether its circulation is sustained after the emergence of oseltamivir-sensitive swine vH1N1.

Susceptibility factors Genetic There was no evidence of a difference in AUC1–20 of oseltamivir or its active metabolite oseltamivir carboxylate between 14 Japanese subjects and 14 Caucasian subjects, or between children aged 1–2 years old and adults (129R).

Zanamivir

Systematic reviews A meta-analysis of the adverse effects of zanamivir in children showed that it was no worse than placebo (127M).

Drugs active against influenza viruses: ion channel inhibitors (SED-15, 105 3051; SEDA-31, 269)

Comparative studies In a randomized controlled trial in patients with chronic hepatitis C treated with interferon-alfa 2a alone \( n = 53 \), with amantadine 100 mg bd \( n = 111 \), with ribavirin \( n = 106 \) or with amantadine + ribavirin \( n = 108 \), there was a sustained virological response in 13\%, 6\%, 18\%, and 22\% respectively (130C). This was statistically different between interferon + amantadine and triple therapy but not between interferon + ribavirin and triple therapy. The spectra and frequencies of adverse effects were similar in all four treatment arms. However, six patients
withdrew because of adverse effects, three of them in an arm containing amantadine.

In two groups of non-responders with HCV genotype 1 chronic infection taking interferon and ribavirin, with or without amantadine 200 mg/day, viral load fell more markedly in the group taking triple therapy including amantadine, but the response rates at the end of treatment were not significantly different (131\textsuperscript{c}). Although analysis of the viral ion channel p7 showed selective pressure during therapy, no specific residues appeared to be linked to the effect of amantadine on the virus. The authors suggested that this implied that the antiviral effect of amantadine is non-specific and related to reduced endosomal acidification and therefore reduced transport of hepatitis C by a pH-dependent pathway.

In a multicenter study of 75 non-responders with chronic hepatitis C randomized to interferon monotherapy \((n = 26)\), dual therapy with ribavirin \((n = 24)\) and triple therapy with additional amantadine 200 mg/day \((n = 25)\), amantadine did not increase the frequency or severity of adverse effects (132\textsuperscript{C}).

In 22 patients with chronic hepatitis C genotype 1b, with high viral loads treated with interferon-beta for 4 weeks followed by interferon-alfa 2b, ribavirin, and amantadine 150 mg/day for 22 weeks, there was a sustained virological response in 7. Only one patient had to stop taking amantadine, because of the adverse effect of light-headedness (133\textsuperscript{c}).

In 15 renal transplant recipients with chronic hepatitis C, doses of ribavirin monotherapy \((n = 7)\) or ribavirin + amantadine \((n = 8)\) were adjusted according to creatinine clearance (134\textsuperscript{c}). There was no difference between treatment groups with respect to liver enzymes, hepatitis C viremia, liver histology, or renal function. Anemia, the main adverse effect, was most notable in those with a creatinine clearance below 50 ml/minute. Other adverse effects included leukopenia, mood disorders and profuse sweating. Only one of those who received combination therapy were still taking amantadine after 12 months; two completed treatment but with ribavirin alone. Four of those taking monotherapy completed treatment. Neither regimen was clearly superior to no treatment, but the study was small and probably underpowered.

**Sensory systems** In a post-marketing surveillance study of patients with a new diagnosis of corneal disease and new prescriptions for amantadine over 2 years, 36 (0.27\%) of 13137 patients developed Fuchs dystrophy (corneal edema) (135\textsuperscript{C}). The relative risk of corneal edema was 1.7 (95\% CI = 1.1, 2.8); in 12 patients (0.09\%) the diagnosis was made in the first month.

**Drug resistance** Amantadine is unreliable in the management of influenza because of the emergence of widespread resistance. This is notable in the H3N2 subtype and most H5N1 subtypes, but some seasonal H1N1 remains sensitive to amantadine (128\textsuperscript{b}). However, in 2009, a novel pandemic strain vH1N1 influenza emerged, resistant to amantadine.

**References**

1. Doan ML, Mallory GB, Kaplan SL, Dishop MK, Schecter MG, McKenzie ED, Heinle JS, Eldemir O. Treatment of adenovirus pneumonia with cidofovir in pediatric lung transplant recipients. J Heart Lung Transplant 2007;26(9):883–9.

2. Neofytos D, Ojha A, Mookerjee B, Wagner J, Filicko J, Ferber A, Dessain S, Grosso D, Brunner J, Flomenberg N, Flomenberg P. Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. Biol Blood Marrow Transplant 2007;13(1): 74–81.

3. Symeonidis N, Jakubowski A, Pierre-Louis S, Jaffe D, Pamer E, Sepkowitz K, O’Reilly RJ, Papanicolaou GA. Invasive adenoviral
infections in T-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis 2007;9(2):108–13.
4. Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant 2007;39(12):783–7.
5. Yang HH, Hsiao YP, Shih HC, Yang JH. Acyclovir-induced neuropsychosis successfully recovered after immediate hemodialysis in an end-stage renal disease patient. Int J Dermatol 2007;46(8):883–4.
6. Mihara A, Mori T, Nakazato T, Ikeda Y, Okamoto S. Acute renal failure caused by intravenous acyclovir for disseminated varicella zoster virus infection. Scand J Infect Dis 2007;39(1):94–5.
7. Schreiber RJ, Wolpin J, Koren G. Determinants of aciclovir-induced nephrotoxicity in children. Paediatr Drugs 2008;10(2):135–9.
8. Montjaux-Régis N, Chanot A, Olivier P, Damase-Michel C, Mengelle C, Glorieux I, Casper C. Entérocolite ulcéronécrosante chez un nouveau-né à terme. Rôle de l’acyclovir? [Necrotizing enterocolitis in a full-term infant. Is acyclovir involved?] Arch Pediatr 2007;14(12):1420–3.
9. Ebo DG, Bridts CH, De Clerck LS, Stevens WJ. Immediate allergy from valacyclovir. Allergy 2008;63(7):941–2.
10. Sugimoto T, Yasuda M, Sakaguchi M, Koyama T, Uzu T, Kashiwagi A, Isshiki K, Kanasaki M. Oliguric acute renal failure following oral valacyclovir therapy. Quart J Med 2008;101(2):164–6.
11. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBcAg-negative chronic hepatitis B. Hepatology 2007;45(2):307–13.
12. Akyildiz M, Karasu Z, Zeytunlu M, Aydin U, Ozacar T, Kilic M. Adeovir dipivoxil therapy in liver transplant recipients for recurrence of hepatitis B virus infection despite lamivudine plus hepatitis B immunoglobulin prophylaxis. J Gastroenterol Hepatol 2007;22(12):2130–4.
13. Bifano M, Yan JH, Smith RA, Zhang D, Grasela DM, LaCreta F. Absence of a pharmacokinetic interaction between entecavir and adefovir. J Clin Pharmacol 2007;47(10):1327–34.
14. Yilmaz A, Akcam M, Gelen T, Artan R. Lamivudine and high-dose interferon alpha 2a combination treatment in naive HBeAg-positive immunooactive chronic hepatitis B in children: an East Mediterranean center’s experience. Eur J Pediatr 2007;166(3):195–9.
15. Asari A, Iles-Smith H, Chen YC, Naderer OJ, Johnson MA, Yuen GJ, Otto V, Dunn JA, Gokal R. Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. Br J Clin Pharmacol 2007;64(6):738–44.
16. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA, Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007;357(25):2576–88.
17. Muller MP, Dresser L, Raboud J, McGeer A, Rea E, Richardson SE, Mazzulli T, Loeb M, Louie M, Canadian SARS, Network. R. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. Pharmacotherapy 2007;27(4):494–503.
18. Stankova J, Carret AS, Moore D, McCusker C, Mitchell D, Davis M, Mazier B, Jabado N. Long-term therapy with aerosolized ribavirin for parainfluenza 3 virus respiratory tract infection in an infant with severe combined immunodeficiency. Pediatr Transplant 2007;11(2):209–13.
19. Lybaek D, Larsen CS. Syncope as a probable side effect to combination antiretroviral therapy initiated during primary HIV-1 infection. Sex Health 2008;5(1):69–71.
20. Hulgan T, Tebas P, Canter JA, Mulligan K, Haas DW, Dubé M, Grinspoon S, Robbins GK, Motsinger AA, Kalimanpur ARAIDS Clinical Trials Group 384 and A5005s Study Teams. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. J Infect Dis 2008;197(6):858–66.
21. Podzamczer D, Ferrer E, Sanchez P, Gatell JM, Crespo M, Fisac C, Lonca M, Sanz J, Niubo J, Veloso S, Libre JM, Barrufet P, Ribas MA, Merino E, Ribera E, Martinez-Lacasa J, Alonso C, Aranda M, Pulido F, Berenguer J, Delegido A, Pedreira JD, Lérida A, Rubio R, Del Rio LABCDE (Abacavir vs. d4T ( stavudine) plus efavirenz) Study Team. Less lipoatrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. J Acquir Immune Defic Syndr 2007;44(2):139–47.

22. Rosenkranz SL, Yarasheski KE, Para MF, Reichman RC, Morse GD. Antiretroviral drug levels and interactions affect lipid, lipoprotein, and glucose metabolism in HIV-1 seronegative subjects: a pharmacokinetic–pharmacodynamic analysis. Metab Syndr Relat Disord 2007;5(2):163–73.

23. Justesen US, Fox Z, Pedersen C, Cahn P, Gerstoft J, Clumec N, Losso M, Peters B, Obel N, Castagna A, Dragsted UB, Lundgren JD, MaxCm1 and 2 trial groups. Pharmacokinetics of two randomized trials evaluating the safety and efficacy of indinavir, saquinavir and lopinavir in combination with low-dose ritonavir: the MaxCm1 and 2 trials. Basic Clin Pharmacol Toxicol 2007;101(5):339–44.

24. Luque A, Hulse S, Wang D, Shahzad U, Tzanman E, Antenozzi S, Smith B. Assessment of adverse events associated with antiretroviral regimens for postexposure prophylaxis for occupational and nonoccupational exposures to prevent transmission of human immunodeficiency virus. Infect Control Hosp Epidemiol 2007;28(6):695–701.

25. McMahon DK, Dinubile MJ, Meibohm AR, Marino DR, Robertson MN, for the Protocol 060 Study GroupEfficacy, safety, and tolerability of long-term combination antiretroviral therapy in asymptomatic treatment-naive adults with early HIV infection. HIV Clin Trials 2007;8(5):269–81.

26. Marin-Niebla A, Lopez-Cortes LF, Ruiz-Valderras R, Viciana P, Mata R, Gutierrez A, Pascual R, Rodriguez M. Clinical and pharmacokinetic data support once-daily low-dose boosted saquinavir (1,200 milligrams saquinavir with 100 milligrams ritonavir) in treatment-naive or limited protease inhibitor-experienced human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2007;51(6): 2035–42.

27. Stephan C, Carlebach A, Rottmann C, Haberl A, Dauer B, von Hentig N, Kurowski M, Staszewski S. Dose reduction effective in alleviating symptoms of saquinavir toxicity. Int J STD AIDS 2007;18(2):81–4.

28. Bani-Sadr F, Lapidus N, Bedossa P, De Boever CM, Perronne C, Halfon P, Sol S, Carrat F, Cacoub P, French National Agency for Research on AIDS; Viral Hepatitis-HC02-Ribavic Study Team. Progression of fibrosis in HIV and hepatitis C virus–coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. Clin Infect Dis 2008;46 (5):768–74.

29. Hoffmann CJ, Charalambous S, Thio CL, Martin DJ, Pemba L, Fielding KL, Churchyard GJ, Chaisson RE, Grant AD. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. AIDS 2007;21(10):1301–8.

30. Arey B, Markov M, Ravi J, Prevette E, Batts K, Nadir A. Nodular regenerative hyperplasia of liver as a consequence of ART. AIDS 2007;21(8):1066–8.

31. Smith CJ, Olsen CH, Mocroft A, Viard JP, Staszewski S, Panos G, Staub T, Blaxhult A, Vetter N, Lundgren JD. The role of antiretroviral therapy in the incidence of pancreatitis in HIV-positive individuals in the EuroSIDA study. AIDS 2008;22(1):47–56.

32. Crane HM, Kestenbaum B, Harrington RD, Kitahata MM. Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir. AIDS 2007;21(11):1431–9.

33. Schmid S, Opravil M, Modell M, Huber M, Pfammatter R, Keusch G, Ambuhl P, Wuthrich RP, Moch H, Varga Z. Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. Virchows Arch 2007;450(6):665–70.

34. Ripamonti D, Maggiolo F, Suter F. Possible allergic cross-reaction to didanosine and tenofovir in an HIV-1-infected woman. AIDS 2007;21(8):1059–60.
35. Brogly SB, Ylitalo N, Mofenson LM, Oleske J, Van Dyke R, Crain MJ, Abzug MJ, Brady M, Jean-Philippe P, Hughes MD, Seage 3rd GR. In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. AIDS 2007;21(8):929–38.
36. Hawkins S, Ball C. Adverse events experienced by three children taking tenofovir and didanosine in combination. HIV Med 2007;8(6):411.
37. Sekar VJ, Lefebvre E, Marién K, De Pauw M, Vangeneugden T, Hoetelmans RM. Pharmacokinetic interaction between darunavir and saquinavir in HIV-negative volunteers. Ther Drug Monit 2007;29(6):795–801.
38. McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, Pade P, Rainey PM. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend 2007;91(2–3):269–78.
39. Fulco PP, Zingone MM, Higginson RT. Possible antiretroviral therapy–warfarin drug interaction. Pharmacotherapy 2008;28(7):945–9.
40. Brew BJ, Halman M, Catalan J, Sacktor N, Price RW, Brown S, Atkinson H, Clifford DB, Simpson D, Torres G, Hall C, Power C, Marde R, Mc Arthur JC, Symonds W, Romero C. Factors in AIDS dementia complex trial design: results and lessons from the abacavir trial. PLoS Clin Trials 2007;2(3):e13.
41. García JT, González PR, Hernández-Mora MG, Novoa SR, Quintana FB, Lahoz JG, Vázquez VS. Large lymphadenopathies complicating the abacavir hypersensitivity reaction. AIDS 2007;21(16):2254–6.
42. Gervasoni C, Vigano O, Grinelli E, Ortu M, Galli M, Rusconi S. Abacavir hypersensitivity reaction after switching from the twice-daily to the once-daily formulation. AIDS Patient Care STDs 2007;21(1):1–3.
43. Yokogawa N, Alcid DV. Acute fibrinous and organizing pneumonia as a rare presentation of abacavir hypersensitivity reaction. AIDS 2007;21(15):2116–7.
44. Chui CK, Brumme ZL, Brumme CJ, Yip B, Phillips EJ, Montaner JS, Harrigan PR. A simple screening approach to reduce B*5701-associated abacavir hypersensitivity on the basis of sequence variation in HIV reverse transcriptase. Clin Infect Dis 2007;44(11):1503–8.
45. Barber TJ, Marett B, Waldron S, Portsmouth S, Mackie NE, Weston R, Winston A. Are disulfiram-like reactions associated with abacavir-containing antiretroviral regimens in clinical practice?. AIDS 2007;21(13):1823–4.
46. D’Ythurbide G, Goujard C, Méchar F, Blanc A, Charpentier B, Snanoudj R. Fanconi syndrome and nephrogenic diabetes insipidus associated with didanosine therapy in HIV infection: a case report and literature review. Nephrol Dial Transplant 2007;22(12):3656–9.
47. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine–valganciclovir interaction. Ann Pharmacother 2007;41(3):512–7.
48. Bani-Sadr F, Lapidus N, Melchior JC, Ravaux I, Bensalem M, Rosa I, Cacoub P, Pol S, Perronne C, Carrat F. Severe weight loss in HIV/HCV-coinfected patients treated with interferon plus ribavirin: incidence and risk factors. J Viral Hepat 2008;15(4):255–60.
49. ter Hofstede HJ, Koopmans PP, Burger DM. Stavudine plasma concentrations and lipoatrophy. J Antimicrob Chemother 2008;61(4):933–8.
50. Tien PC, Schneider MF, Cole SR, Justman JE, French AL, Young M, DeHovitz J, Nathwani N, Brown TT. Relation of stavudine discontinuation to anthropometric changes among HIV-infected women. J Acquir Immune Defic Syndr 2007;44(1):43–8.
51. Fleischman A, Johnsen S, Systrø DM, Hrovat M, Farrar CT, Frontera W, Fitch K, Thomas BJ, Torriani M, Côté HC, Grinspoon SK. Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. Am J Physiol Endocrinol Metab 2007;292(6):E1666–73.
52. Manosuthi W, Prasithsirikul W, Chumphathat N, Sunisuklappon B, Athichathanabadi C, Chimsuntorn S, Sungkanuparph S. Risk factors for mortality in symptomatic
hyperlactatemia among HIV-infected patients receiving antiretroviral therapy in a resource-limited setting. Int J Infect Dis 2008;12(6):582–6.

53. Hill A, Ruxrungham K, Hanvanich M, Katlama C, Wolf E, Soriano V, Milinkovic A, Gatell J, Ribera E. Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. Expert Opin Pharmacother 2007; 8(5):679–88.

54. Makinson A, Moing VL, Kouanfack C, Laurent C, Delaporte E. Safety of stavudine in the treatment of HIV infection with a special focus on resource-limited settings. Expert Opin Drug Saf 2008;7(3):283–93.

55. McComsey GA, Lo Re 3rd V, O’Riordan M, Walker UA, Lebrecht D, Baron E, Mounzer K, Frank I. Effect of reducing the dose of stavudine on body composition, bone density, and markers of mitochondrial toxicity in HIV-infected subjects: a randomized, controlled study. Clin Infect Dis 2008;46(8):1290–6.

56. Wilkinson MJ, Bain BJ, Phelan L, Benzie A. Increased haemoglobin A2 percentage in HIV infection: disease or treatment? AIDS 2007;21(9):1207–8.

57. Witt KL, Cunningham CK, Patterson KB, Kissling GE, Dertinger SD, Livingston E, Bishop JB. Elevated frequencies of micro-nucleated erythrocytes in infants exposed to zidovudine in utero and postpartum to prevent mother-to-child transmission of HIV. Environ Mol Mutagen 2007;48(3–4):322–9.

58. Watts DH, Li D, Handelsman E, Tilson H, Paul M, Foca M, Vajaranant M, Diaz C, Tuomala R, Thompson B. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. J Acquir Immune Defic Syndr 2007;44(3):299–305.

59. Mirochnick M, Rodman JH, Robbins BL, Fridland A, Gandía J, Hitti J, Bardeguez A, Rathore MH, Gonzalez García A, Cababasay M, Samson P, Moftenson L, Bryson YJ, Dorenbaum A. Pharmacokinetics of oral zidovudine administered during labour: a preliminary study. HIV Med 2007;8(7):451–6.

60. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. Curr HIV/AIDS Rep 2007;4(3):135–40.

61. Feola DJ, Garvy BA, Rapp RP, Thornton AC. Blunted humoral response to influenza vaccination in patients exposed to zidovudine plus trimethoprim–sulfamethoxazole. Pharmacotherapy 2007;27(7):937–47.

62. Aweeka FT, Kang M, Yu JY, Lizak P, Alston B, Chung RT, AIDS Clinical Trials Group 5092s Study Team. Pharmacokinetic evaluation of the effects of ribavirin on zidovudine triphosphate formation: ACTG 5092s Study Team. HIV Med 2007; 8(5):288–94.

63. Dominguez S, Ghosh J, Peytavin G, Izedine H, Wirden M, Ktorza N, Miller M, Aubron-Olivier C, Tylesinski A, Calvez V, Deray G, Katlama C. Efficacy and safety of tenofovir double-dose in treatment-experienced HIV-infected patients: the TENOPLUS study. J Med Virol 2007;79(2):105–10.

64. Morillo Verdugo R, Gil Navarro MV, Abdel-Kader Martín L, Castillo Muñoz A, Baños Roldán U, Artacho Criado S. Análisis de las causas y factores predictivos de discontinuación del tratamiento con tenofovir en pacientes VIH pretratados. [Analysis of the causes and predictive factors for discontinuing treatment with tenofovir in pretreated HIV patients.] Farm Hosp 2007;31(4):200–5.

65. Papaleo A, Warszawski J, Salomon R, Julien V, Veber F, Dechaux M, Blanche S. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. Pediatr Infect Dis J 2007;26(10):949–51.

66. Maggiolo F Efavirenz Expert Opin Pharmacother 2007;8(8):1137–45.

67. Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf 2007;6(2):147–54.

68. Sánchez-Conde M, Palacios R, Sanz J, Rodríguez-Novoa S, Rivas P, Santos J, Sola J, Asensi V, de Mendoza C, Estrada V, Barreiro P, González-Lahoz J, Jiménez-Nacher I, Soriano V. Efficacy and safety of a once daily regimen with efavirenz, lamivudine, and didanosine, with and without food, as initial therapy for HIV Infection: the ELADI study. AIDS Res Hum Retroviruses 2007;23(10):1237–41.

69. Arrizabalaga J, Arazo P, Aguirrebengoa K, García-Palomó D, Chocarro A, Labarga P,
Muñoz-Sánchez MJ, Echevarría S, Oteo JA, Uriz J, Letona S, Farías MC, Peralta G, Pinilla J, Ferrer P, Alvarez ML, Iribarren JA. Effectiveness and safety of simplification therapy with once-daily tenofovir, lamivudine, and efavirenz in HIV-1-infected patients with undetectable plasma viral load on HAART. HIV Clin Trials 2007;8(5):328–36.

70. Shikuma CM, Yang Y, Glesby MJ, Meyer 3rd WA, Tashima KT, Ribaudo HJ, Webb N, Bastow B, Kuritzkes DR, Gulick RM. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 Infection (AIDS Clinical Trials Group Study A5095). J Acquir Immune Defic Syndr 2007;44(5):540–50.

71. Izzedine H, Valantin MA, Daudon M, Mohand HA, Caby F, Katlama C. Efavirenz urolithiasis. AIDS 2007;21(14):1992.

72. Aronson JK, Hauben H. Anecdotes that provide definitive evidence. BMJ 2006;333:1267–9.

73. Ferradini L, Laureillard D, Prak N, Ngeth C, Fernandez M, Pinoges L, Puertas G, Taburet AM, Ly N, Rouzioux C, Balkan S, Quillet C, Delfraissy JF. Positive outcomes of HAART at 24 months in HIV-infected patients in Cambodia. AIDS 2007;21(17):2293–301.

74. Saitoh A, Fletcher CV, Brundage R, Alvero C, Fenton T, Hsia K, Spector SA. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. J Acquir Immune Defic Syndr 2007;45(3):280–5.

75. Lowenhaupt EA, Matson K, Qureishi B, Saitoh A, Pugatch D. Psychosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. Clin Infect Dis 2007;45(10):e128–30.

76. German P, Greenhouse B, Coates C, Dorsey G, Rosenthal PJ, Charlebois E, Lindegardh N, Havlir D, Aweeke FA. Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz. Clin Infect Dis 2007;44(6):889–91.

77. Liu P, Foster G, LaBadie RR, Gutierrez MJ, Sharma A. Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. J Clin Pharmacol 2008;48(1):73–84.

78. Rivero A, Mira JA, Pineda JA. Liver toxicity induced by non-nucleoside reverse transcriptase inhibitors. J Antimicrob Chemother 2007;59(3):342–6.

79. De Lazzari E, León A, Arnaiz JA, Martínez E, Knobel H, Negredo E, Clotet B, Montaner J, Storfer S, Asenjo MA, Mallolas J, Miró JM, Gatell JM. Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts. HIV Med 2008;9(4):221–6.

80. Knobel H, Guelar A, Montero M, Carmona A, Luque S, Berenguer N, González A. Risk of side effects associated with the use of nevirapine in treatment-naive patients, with respect to gender and CD4 cell count. HIV Med 2008;9(1):14–8.

81. Maggiolo F, Arici C, Airoldi M, Ripamonti D, Quinzan G, Gregis G, Ravasio V, Bombana E, Suter F. Reasons for discontinuation of nevirapine-containing HAART: results from an unselected population of a large clinical cohort. J Antimicrob Chemother 2007;59(3):569–72.

82. Manfredi R, Calza L. Safety issues about nevirapine administration in HIV-infected pregnant women. J Acquir Immune Defic Syndr 2007;45(3):365–8.

83. Ramirez-Hernandez M, Sanchez-Sierra B, Martinez-Escribano JA. Widespread vitiligo after erythromerda caused by nevirapine in a patient with AIDS. Acta Derm Venereol 2007;87(5):442–3.

84. Santos RP, Ramilo O, Barton T. Nevirapine-associated rash with eosinophilia and systemic symptoms in a child with human immunodeficiency virus infection. Pediatr Infect Dis J 2007;26(11):1053–6.

85. Jain V, Shome D, Natarajan S. Nevirapine-induced Stevens–Johnson syndrome in an HIV patient. Cornea 2008;27(3):366–7.

86. Hall DB, Macgregor TR. Case-control exploration of relationships between early rash or liver toxicity and plasma concentrations of nevirapine and primary metabolites. HIV Clin Trials 2007;8(6):391–9.

87. Natarajan U, Pym A, McDonald C, Velisetty P, Edwards SG, Hay P, Welch J, de Ruiter A, Taylor GP, Anderson J. Safety of nevirapine in pregnancy. HIV Med 2007;8(1):64–9.

88. Vitezica ZG, Milpied B, Lonjour C, Borot N, Ledger TN, Lefebvre A, Hovnanian A.
HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. AIDS 2008;22(4):540-1.

Gatanaga H, Yazaki H, Tanuma J, Honda M, Genka I, Teruya K, Tachikawa N, Kikuchi Y, Oka S. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. AIDS 2007;21(2):264-5.

Cooper CL, van Heeswijk RP. Once-daily nevirapine dosing: a pharmacokinetics, efficacy and safety review. HIV Med 2007;8(1):1-7.

Clotet B. Once-daily dosing of nevirapine in HAART. J Antimicrob Chemother 2008;61(1):13-6.

Manosuthi W, Athichathanabadi C, Uttayamakul S, Phoorisri P, Sunghanparph S. Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. BMC Infect Dis 2007;7:14.

Sekar VJ, Lefebvre E, De Marez T, Spinosa-Guzman S, De Pauw M, De Paepe E, Vangeneugden T, Hoetelmans RM. Pharmacokinetics of darunavir (TMC114) and atazanavir during coadministration in HIV-negative, healthy volunteers. Drugs R D 2007;8(4):241-8.

Torres HA, Barnett BJ, Arduino RC. Alopecia associated with ritonavir-boosted atazanavir therapy. AIDS 2007;21(10):1391-2.

Mallolas J, Sarasa M, Nomdedeu M, Soriano A, López-Púa Y, Blanco JL, Martínez E, Gatell JM. Pharmacokinetic interaction between rifampicin and ritonavir-boosted atazanavir in HIV-infected patients. HIV Med 2007;8(2):131-4.

Nacher M, Vantilcke V, Mahamat A, El Guedi M, Vaz T, Randrianjohany A, Clyti E, Aznar C, Carme B, Couppié P. Increased incidence of cutaneous mycoses after HAART initiation: a benign form of immune reconstitution disease? AIDS 2007;21(16):2248-50.

Torres HA, Arduino RC. Fosamprenavir calcium plus ritonavir for HIV infection. Expert Rev Anti Infect Ther 2007;5(3):349-63.

Canestri A, Cisse M, Marcelin AG, Peytavin G, Traore E, Assoumou L, Traore O, Koita V, Diallo F, Sangare AT, Sidibé MK, Calvez V, Sylla A, Katlama C, Tubiana R. Experience of indinavir/ritonavir 400/100 mg twice-daily highly active antiretroviral therapy-containing regimen in HIV-1-infected patients in Bamako, Mali: the NOGOMA study. J Acquir Immune Defic Syndr 2007;45(4):477-9.

Danel C, Moh R, Peytavin G, Anzian A, Minga A, Gomis OB, Seri B, Nzunettu G, Gabillard D, Salamon R, Bissagnene E, Anglaret X. Lack of indinavir-associated nephrololgical complications in HIV-infected adults (predominantly women) with high indinavir plasma concentration in Abidjan, Côte d’Ivoire. AIDS Res Hum Retroviruses 2007;23(1):62–6.

Boyd M. Indinavir: the forgotten HIV-protease inhibitor. Does it still have a role? Expert Opin Pharmacother 2007;8(7):957-64.

Gagnon RF, Mehio A, Iqbal S, Tsoukas CM. Néphropathie tubulo-interstitielle associée a l’indinavir. [Indinavir-associated tubulointerstitial renal disease.] Nephrol Ther 2007;3(7):461–2.

Luther J, Giesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. Am J Clin Dermatol 2007;8(4):221-33.

Unadkat JD, Wara DW, Hughes MD, Mathias AA, Holland DT, Paul ME, Connor J, Huang S, Nguyen BY, Watts DH, Mofenson LM, Smith E, Deutsch P, Kaiser KA, Tuomala RE. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. Antimicrob Agents Chemother 2007;51(2):783-6.

Martí C, Peña JM, Bates I, Madero R, de José I, Pallardo LF, Arribas JR, Gonzalez-Garcia J, Gonzalez A, Vazquez JJ. Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003. Acta Obstet Gynecol Scand 2007;86(4):409-15.

Dominguez MV, Ceballos VC, Costa RV, Lara TE, Florencio VD. Paronychia in an HIV-infected patient under nelfinavir therapy. J Eur Acad Dermatol Venereol 2007;21(5):710-1.
106. Pessanha TM, Campos JM, Barros AC, Pone MV, Garrido JR, Pone SM. Iatrogenic Cushing’s syndrome in a adolescent with AIDSs on ritonavir and inhaled fluticasone. Case report and literature review. AIDS 2007;21(4):529–32.

107. St Germain RM, Yigit S, Wells L, Girotto JE, Salazar JC. Cushing syndrome and severe adrenal suppression caused by fluticasone and protease inhibitor combination in an HIV-infected adolescent. AIDS Patient Care STDS 2007;21(6):373–7.

108. King JR, Kakuda TN, Paul S, Tse MM, Acosta EP, Becker SL. Pharmacokinetics of saquinavir with atazanavir or low-dose ritonavir administered once daily (ASPIRE I) or twice daily (ASPIRE II) in seronegative volunteers. J Clin Pharmacol 2007;47(2):201–8.

109. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of treatment-resistant HIV infection. Clin Infect Dis 2007;45(6):761–9.

110. Luna B, Townsend MU. Tipranavir: the first nonpeptidic protease inhibitor for the treatment of protease resistance. Clin Ther 2007;29(11):2309–18.

111. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. Drugs 2008;68(10):1435–63.

112. Courter JD, Girotto JE, Salazar JC. Tipranavir: a new protease inhibitor for the pediatric population. Expert Rev Anti Infect Ther 2008;6(6):797–803.

113. Gathe Jr. JC, Pierone G, Piliero P, Arasteh K, Rubio R, Lalonde RG, Cooper D, Lazzarin A, Kohlbrenner VM, Dohanyi C, Sabo J, Mayers D. Efficacy and safety of three doses of tipranavir boosted with ritonavir in treatment-experienced HIV type-1 infected patients. AIDS Res Hum Retroviruses 2007;23(2):216–23.

114. Arbuthnot C, Wilde JT. Increased risk of bleeding with the use of tipranavir boosted with ritonavir in haemophilic patients. Haemophilia 2008;14(1):140–1.

115. Chrysos G, Gerakari S, Stasini F, Kokkoris S, Kourousis D, Velegraki A. Intracranial haemorrhage possibly related to tipranavir in an HIV-1 patient with cryptococcal meningitis. J Infect 2008;57(1):85–7.

116. de Mendoza C, Morelló J, García-Gascó P, Rodríguez-Novoa S, Soriano V. Tipranavir: a new protease inhibitor for the treatment of antiretroviral-experienced HIV-infected patients. Expert Opin Pharmacother 2007;8(6):839–50.

117. Chapman SJ, Woolley IJ, Visvanathan K, Korman TM. Acute pancreatitis caused by tipranavir/ritonavir-induced hypertriglyceridaemia. AIDS 2007;21(4):532–3.

118. Celesia BM, Onorante A, Nunnari G, Mughini MT, Mavilla S, Massimino SD, Russo R. Porphyria cutanea tarda in an HIV-1-infected patient after the initiation of tipranavir/ritonavir: case report. AIDS 2007;21(11):1495–6.

119. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. AIDS 2007;21(2):179–85.

120. Vourvahis M, Kashuba AD. Mechanisms of pharmacokinetic and pharmacodynamic drug interactions associated with ritonavir-enhanced tipranavir. Pharmacotherapy 2007;27(6):888–909.

121. Walmsley SL, Katlama C, Lazzarin A, Arestéh K, Pierone G, Blick G, Johnson M, Meier U, MacGregor TR, Leith JG. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). J Acquir Immune Defic Syndr 2008;47(4):429–40.

122. Kohan I. Oseltamivir-induced delirium in a geriatric patient. Int J Geriatr Psychiatry 2007;22(9):935–6.

123. Maxwell SR. Tamiflu and neuropsychiatric disturbance in adolescents. BMJ 2007;334(7606):1232–3.

124. Whitley RJ. The role of oseltamivir in the treatment and prevention of influenza in children. Expert Opin Drug Metab Toxicol 2007;3(5):755–67.

125. Kawai N, Ikematsu H, Iwaki N, Maeda T, Kanazawa H, Kawashima T, Tanaka O, Yamauchi S, Kawamura K, Nagai T, Horii S, Hirotsu N, Kashiwagi S. A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. J Infect 2008;56(1):51–7.
126. Matsushita M, Nishihara H, Nishiyama R, Kobayashi Y. Acute hemorrhagic colitis associated with oral administration of oseltamivir for the treatment of influenza A. J Infect Chemother 2007;13(4):267–9.

127. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev 2007;(1):CD002744.

128. Ong AK, Hayden FG, John F Enders Lecture 2006. Antivirals for influenza. J Infect Dis 2007;196(2):181–90.

129. Schentag JJ, Hill G, Chu T, Rayner CR. Similarity in pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian subjects. J Clin Pharmacol 2007;47(6):689–96.

130. Salmerón J, Diago M, Andrade R, Pérez R, Solí R, Romero M, de la Mata M, Grandaos R, Ruiz-Extremera A, Muñoz de Rueda P. Induction doses of interferon-alpha-2a in combination with ribavirin and/or amantadine for the treatment of chronic hepatitis C in non-responders to interferon monotherapy: a randomized trial. J Viral Hepat 2007;14(2):89–95.

131. Castelain S, Bonte D, Penin F, Francois C, Capron D, Dedeurwaerder S, Zawadzki P, Morel V, Wychowski C, Duverlie G. Hepatitis C virus p7 membrane protein quasispecies variability in chronically infected patients treated with interferon and ribavirin, with or without amantadine. J Med Virol 2007;79(2):144–54.

132. Gramenzi A, Andreone P, Cursaro C, Verrucchi G, Boccia S, Giacomoni PL, Galli S, Furlini G, Biselli M, Lorenzini S, Attard L, Bonvicini F, Bernardi M. A randomized trial of induction doses of interferon alone or in combination with ribavirin or ribavirin plus amantadine for treatment of non-responder patients with chronic hepatitis C. J Gastroenterol 2007;42(5):362–7.

133. Uyama H, Nakamura H, Hayashi E, Ogawa H, Enomoto H, Yoshida K, Okuda Y, Yamamoto M, Hada T, Hayashi N. Triple therapy of initial high-dose interferon with ribavirin and amantadine for patients with chronic hepatitis C. Hepatol Res 2007;37(5):325–30.

134. Calanca LN, Fehr T, Jochum W, Fischer-Vetter J, Müllhaupt B, Wüthrich RP, Ambühl PM. Combination therapy with ribavirin and amantadine in renal transplant patients with chronic hepatitis C virus infection is not superior to ribavirin alone. J Clin Virol 2007;39(1):54–8.

135. French DD, Margo CE. Postmarketing surveillance of corneal edema, Fuchs dystrophy, and amantadine use in the Veterans Health Administration. Cornea 2007;26(9):1087–9.