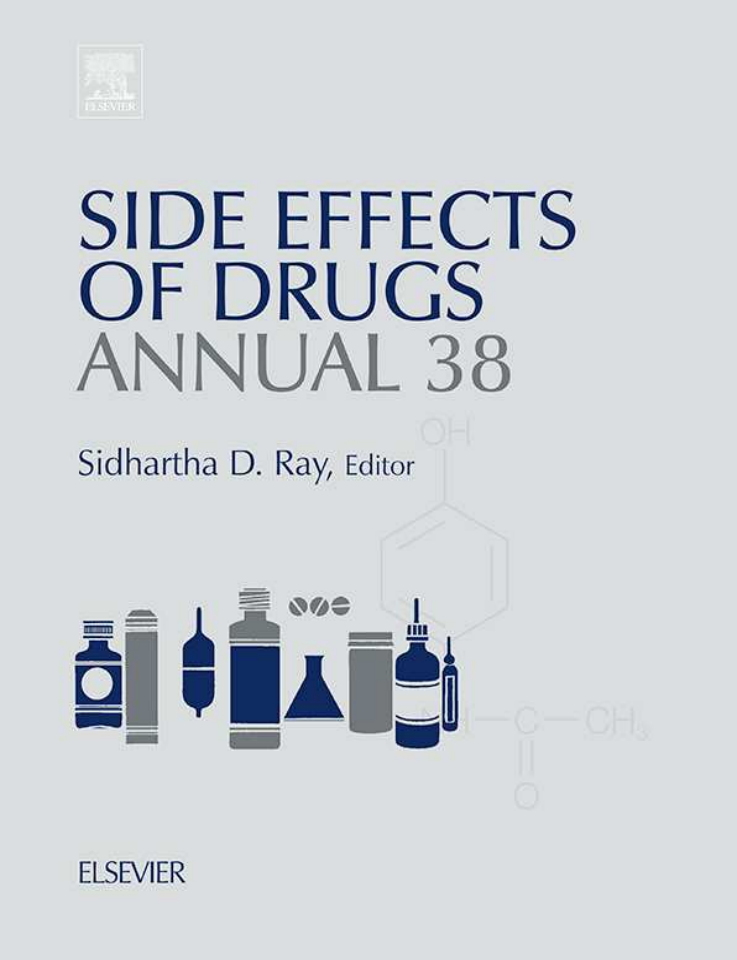

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CHAPTER

27

Antiviral Drugs

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Key to abbreviations and alternative names of some antiviral drugs

3TC	lamivudine (dideoxythiacytidine)
AZT	zidovudine (azidothymidine)
D4T	stavudine (didehydrodideoxythymidine)
DDI	didanosine (dideoxyinosine)
FTC	emtricitabine
SOF	sofosbuvir
TMC 278	rilpivirine
TMC125	etravirine

DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS

Cidofovir [SED-15, 771; SEDA-32, 529; SEDA-33, 577; SEDA-34, 447; SEDA-35, 503; SEDA-36, 401; SEDA-37, 329]

Observational Studies

An open-label, non-randomized, single-dose pilot study reported on the safety and pharmacokinetics of cidofovir in pediatric hematopoietic stem cell transplant (HSCT) recipients with symptomatic adenovirus, nucleoside-resistant cytomegalovirus (CMV) or herpes simplex virus (HSV), and/or human papovavirus infections. Twelve patients were enrolled in the study (median age, 9 years; 33.5 days post-transplantation). Four out of seven patients with adenovirus infection were treated with cidofovir and eventually cleared their infections. Four out of 12 patients died of disseminated viral disease and multi-organ failure. Two out of 12 patients had evidence of acute kidney injury after the first dose, and one of these patients developed chronic kidney disease; two other patients developed late nephrotoxicity. The mean drug half-life was 9.5 h. Pharmacokinetics were similar to those reported for adults, although the drug half-life was significantly longer than that for adults. Cidofovir was well tolerated in the majority of patients [1c].

In another study, the structural, topological and vibrational properties of cidofovir and brincidofovir were studied to understand the structural and functional properties by using density functional theory, natural bond orbital theory, atoms in molecules theory, frontier orbitals and molecular electrostatic potential calculations and the hybrid B3LYP/6-31G method [2c].

Letermovir

Infection with CMV is prevalent in immunosuppressed patients. In solid organ transplant and HSCT recipients, CMV infection is associated with high morbidity and preventable mortality. Prevention and treatment of cytomegalovirus with currently approved antiviral drugs is often associated with side effects that sometimes preclude their use. Moreover, CMV has developed mutations that confer resistance to standard antiviral drugs. During the last decade, there have been calls to develop novel antiviral drugs that could provide better options for prevention and treatment of CMV. Letermovir is a highly specific antiviral drug that is currently undergoing clinical development for the management of CMV infection. It acts by inhibiting the viral terminase complex. Letermovir is highly potent in vitro and in vivo against CMV. Due to a distinct mechanism of action, letermovir does not exhibit cross-resistance with other antiviral drugs. It is predicted to be active against strains that are resistant to ganciclovir, foscarnet, and cidofovir. To date, early-phase clinical trials suggest a very low incidence of adverse effects [3r].

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Foscarnet [SED-15, 1447; SEDA-34, 448; SEDA-35, 504; SEDA-36, 403; SEDA-37, 329]

Observational Study

The safety and efficacy of foscarnet was evaluated in people diagnosed with CMV antigenemia following bone marrow transplantation between unrelated people and the administration of foscarnet. The study examined 59 patients at the National Cancer Center Hospital between June 2004 and November 2011. Renal dysfunction was observed in 11 cases (Grade 1 in 3 cases, Grade 2 in 7 cases, and Grade 3 in one case). The drug was discontinued or the dose was adjusted in 4 cases. Hypocalcemia was observed in 27 cases, hypokalemia in 17 cases, and hypomagnesemia in 17 cases. In the following cases, the severity of bone marrow suppression turned to Grade 4 following the start of treatment: 2 cases of leucopenia, 5 cases of decreased platelet count, 2 cases of decreased hemoglobin level in the blood, and 4 cases of a decreased neutrophil counts were observed. The authors' conclusion was that foscarnet may be safely and effectively used as a remedy for CMV antigenemia following bone marrow transplantation between unrelated people [4c].

Foscarnet-induced adverse drug reaction (ADR) in the Beijing, China from March 2008 to December 2014 in CMV patients has been reported. The study evaluated 152 case reports received from Beijing drug Adverse Reaction Monitoring Center. The type and time of ADR, the age of patient, the gender and nationality of patient, serious adverse reactions, allergy history, administration, dosage, preparation, the indication, ADR history, ADR involved organ and system, the causal relationship, treatments and prognosis were retrospectively analyzed. The ADR induced by foscarnet more often occurred in patients aged from 31 to 60, appearing within 24 h (55.3%) after drug administration. ADR involved different systems and organs, predominantly the renal function and epileptic seizures [5C].

A case report demonstrated the difficulties in managing CMV retinitis in severely immunocompromised patients. A 40-year-old man diagnosed with HIV in 2011, had a CD4 count of 50 cells/μL and a HIV viral load 10 000 000 copies/mL. At the time, he was also diagnosed with diffuse large B cell lymphoma with liver metastasis. He received chemotherapy, achieved virological suppression on antiretroviral therapy and his CD4 count rose to 120 cells/μL. Six months later, he was diagnosed with CMV retinitis. CMV load in the plasma was 400 000 and 600 000 copies/mL in the cerebrospinal fluid (CSF). Intravitreal ganciclovir and foscarnet were administered with IV ganciclovir for 3 weeks, after which the patient was discharged home on maintenance treatment of oral 900 mg valganciclovir daily. His CD4 count was 140 cells/μL, HIV viral load was undetectable and plasma CMV load was 16 000 copies/mL. Ten weeks later, he had a drop in visual acuity from 6/38 to hand movements in the right eye. Detachment of the right retina and active retinal inflammation in the left eye, along with ataxia and nystagmus were observed. The CMV load in the plasma was 550 000 and 198 554 copies/mL in the CSF. UL 97 mutations C592G and C607Y, associated with ganciclovir resistance were detected in peripheral blood but not in CSF. Intravitreal ganciclovir and foscarnet were administered to the left eye in conjunction with systemic antiviral therapy with IV foscarnet and ganciclovir. Subsequently, there was significant improvement in left retina with no evidence of active inflammation and 4 weeks later his CMV load in both plasma and CSF was undetectable. IV foscarnet monotherapy was continued for additional 4 weeks until CD4 count rose above 100 cells/μL. There was significant reduction in CMV load and retinal improvement when IV foscarnet combined with ganciclovir was given [6A].

Ganciclovir and Valganciclovir [SED-15, 1480; SEDA-34, 449, SEDA-35, 504, SEDA-36, 404, SEDA-37, 330]

Observational Study

A multicenter, double-blind, placebo-controlled, randomized clinical trial reported on valganciclovir for the prevention of complications of late CMV infection after HSCT at the Fred Hutchinson Cancer Research Center. Patients were randomly assigned to receive valganciclovir (900 mg once per day) or matching placebo between 1999 and 2008. The study drug was withdrawn when CMV viral load was greater than 1000 copies/mL or greater than five times than the baseline, and preemptive therapy was started with IV ganciclovir (5 mg/kg twice daily) or valganciclovir (900 mg twice daily); if neutropenia was detected, foscarnet (90 mg/kg twice daily) was used. The number of patients with adverse events (AEs) and serious AEs did not differ. More patients with drug-related Grade 2 AEs were reported in the valganciclovir group, which was driven by neutropenia (40% in the placebo group vs. 55% in the valganciclovir group), but there were no differences between the groups at Grade 3 or greater levels. The proportion of patients with gastrointestinal or renal AEs did not differ between groups [7C].

Five cases of renal transplant recipients at the University of Chicago Medical Center with resistant CMV infection were successfully treated with leflunomide. Five renal transplant recipients (2 simultaneous pancreas/kidney transplants, 3 deceased donor kidney transplants) were diagnosed with ganciclovir-resistant CMV infection from 2003 to 2011. Of the 4 patients who had resistance genotype testing, 3 showed a UL97 mutation and 1 patient had a clinically resistant CMV infection. All patients received CMV prophylaxis with valganciclovir for 3 months. All 5 patients received other antiviral agents (e.g. ganciclovir, foscarnet), and in 4 patients, viremia was cleared before leflunomide was initiated as

maintenance therapy. The beneficial effect of leflunomide in this setting warrants further investigation. The only known AEs is abnormal liver function tests. In light of the long half-life of teriflunomide (~15 days), it may take several weeks for liver function tests to return to normal after discontinuation of the drug. In the authors' opinion leflunomide is effective in preventing viral recurrence, when used with short-term foscarnet in treating ganciclovir-resistant CMV infection [8c].

A retrospective study reported on 71 HIV-infected patients who had detectable CMV viremia between 1 January 2007 and 31 December 2007. The study evaluated the efficacy and safety of pre-emptive anti-CMV therapy (PACT). Sixteen patients who had lower CD4 cell counts and higher blood CMV DNA levels received PACT (valganciclovir). The cumulative incidence of CMV end-organ disease (EOD) and death at 1 year was 44% and 21% in patients with and without PACT, respectively ($p = 0.013$). Both PACT and high blood CMV DNA levels were significantly associated with CMV EOD and death in an unadjusted analysis. Five patients with PACT experienced severe drug-related AEs. Safety data were available for 14 of the 16 patients who received PACT, and severe drug-related AEs occurred in 5 (36%). Three patients treated with valganciclovir experienced Grade 3 or 4 neutropenia ($n = 2$), or Grade 3 anemia ($n = 1$), all received hematopoietic growth factors and one received a blood transfusion. Of note, only one patient in the PACT group received zidovudine (AZT), but no safety data were available for this patient. Two patients treated with foscarnet experienced Grade 3 and 4 metabolic AEs (hypocalcaemia ($n = 2$), hypophosphatemia [$n = 1$]) [9C].

Combination Study

Although no licensed drugs are available for therapy of congenital CMV infection, ganciclovir and its oral prodrug, valganciclovir, were administered to symptomatic infants to improve neuro-developmental and auditory outcome. Other potentially efficacious drug therapies for congenital CMV disease are foscarnet and cidofovir, which are administered in a few cases. A literature search was reported looking for evidence on pharmacokinetics, efficacy, and side effects of ganciclovir/valganciclovir and the other two antiviral drugs [10R].

DRUGS ACTIVE AGAINST HERPES VIRUSES [SEDA-32, 530; SEDA-33, 577; SEDA-34, 450; SEDA-35, 507; SEDA-36, 407; SEDA-37, 332]

Acyclovir

Observational Studies

A retrospective case–control study of patients admitted to Children's Hospital Colorado from October 2006 to January 2009 who received treatment doses of IV acyclovir has been reported. Renal dysfunction occurred in 131 of 373 (35%) of the patients studied. Median times to risk, injury, and failure were 0.8, 0.7, and 1.4 days, respectively. In aggregate analyses, failure cases were older, had greater BMI and weight, and received fewer doses of acyclovir compared with failure controls. Urinalysis abnormalities were seen in 18 of 42 (43%), 14 of 23 (61%), and 4 of 9 (44%) cases with results available in the risk, injury, and failure groups, respectively, compared with 45 of 113 (40%) of controls. Hematuria, proteinuria, white blood cells, and granular casts were the most common findings in patients with renal dysfunction, but without significant differences between cases and controls. No patients required dialysis. Authors found that the concomitant ceftriaxone administration with acyclovir is a risk factor [11C].

Neurological

A retrospective observational study evaluated the role of antiviral therapy in immunocompromised patients with HSV meningitis. Authors reviewed the charts of 53 patients with CSF specimens positive for HSV-1 or HSV-2 by polymerase chain reaction (PCR) between July 2000 and November 2012 in Minneapolis, Minnesota. Six patients with meningitis did not receive antivirals, whereas the remaining patients were treated with an oral antiviral ($n = 11$ [26.2%]), combination IV and oral therapy ($n = 22$ [52.4%]), or IV acyclovir alone ($n = 3$ [7.1%]). Authors recommend treating immunocompromised patients with HSV meningitis with a 7–10-day course of specific antiviral therapy to improve neurologic outcomes [12c].

A 58-year-old Japanese man, who underwent surgery to remove a thymoma at the age of 54, acutely developed speech difficulties and was admitted on suspicion of stroke. Vital signs were normal except for a mild fever (37.8 °C). His general condition was normal (height: 160 cm, weight: 60 kg). Brain MRI demonstrated multiple lesions in the frontal lobes. Although the CSF findings were normal, acyclovir (10 mg/kg, three times a day) was administered, and his fever and neurological symptoms fully recovered. Later neurological examination revealed the reappearance of motor aphasia and mild right hemiparesis. The MRI demonstrated an increase in size of the lesion in the left cingulate gyrus, an abnormal signal intensity lesion in the left corona radiata, and edematous swelling of the bilateral medial temporal regions. The patient's serum had increased levels of CMV pp65 antigen-positive leukocytes and the patient was diagnosed as having Good's syndrome, resulting in opportunistic infections in the brain. Since the patient was positive for CMV antigen, antiviral therapy was performed using ganciclovir, 5 mg/kg, twice a day for 2 weeks, along with immunoglobulin replacement therapy (5 g/day, for 3 days). The patient became free from

any neurological symptoms for 1 year, and the brain lesions were improved without any AEs [13A].

A 65-year-old woman who was diagnosed with a multidermatomal herpes zoster infection and taking valacyclovir, 1 g every 8 h along with prednisone, developed neurological abnormalities. Antiviral drugs were discontinued in the patient and dialysis started. Serum acyclovir levels significantly dropped after the first two sessions of hemodialysis and the patient returned to baseline from neurological disorders. The authors suggests that patients with a history of herpes zoster infection and CDK are the population most vulnerable to develop acyclovir-induced neurotoxicity[14A].

Immune Response

Fifty-one patients were recruited from Birmingham Heartlands Hospital to evaluate the immune response to acyclovir, of which 24 were CMV-seropositive (median age 41 years; range 21–74 years). Patients were receiving long-term treatment with acyclovir at a dose of 400 mg twice a day for suppression of recurrent herpesvirus (HSV-1 and HSV-2) infection. The treatment duration ranged between 1 and 108 months with a median of 28 months. Acyclovir treatment was able to reduce the functional immune response against the late CMV protein, and the absolute frequency of CD8+ T cells specific for IE-1 and pp65 using a panel of HLA-peptide tetramers. The study revealed that acyclovir therapy has the potential to reduce some components of the CMV-specific T cell response [15c].

Famciclovir

Renal Function

Abnormal penciclovir blood concentration increased by famciclovir has been reported in a 91-year-old woman admitted for anorexia and general fatigue. The patient was diagnosed as having dehydration based on the blood test. The patient, receiving 1500 mg of famciclovir per day developed acute renal failure. Famciclovir was discontinued immediately, and the patient was advised to drink more water, which improved the renal condition [16A].

Famciclovir combined with oxymatrine improved clinical efficacy, prevented the development of liver fibrosis, and improved the T lymphocyte subsets in peripheral blood in patients with chronic severe viral hepatitis B [17c].

Valacyclovir

Skin Lesions

Acyclovir and valacyclovir allergies were rarely reported in the literature. A 60-year-old woman was admitted with a stage III non-secretory multiple myeloma and a history of hypothyroidism secondary to Hashimoto's thyroiditis. She underwent induction chemotherapy and eventual auto-HSCT. Her home medications included a compounded thyroid supplement and occasional ibuprofen with no known drug allergies. Her induction chemotherapy consisted of bortezomib, lenalidomide, liposomal doxorubicin, and dexamethasone. She was started on aspirin 81 mg daily, zolpidem 5 mg at bedtime and valacyclovir 500 mg daily on day 1 of chemotherapy. On day 15 of induction chemotherapy, she developed an urticarial-type rash bilaterally on her torso and, back thighs, which was treated with a 10-day methylprednisolone administration. Two weeks later, her rash had subsided. She was re-challenged with valacyclovir and similar symptoms reappeared, without any other systemic manifestations. These sequences of reactions were due to oral valacyclovir. Two months later, she returned for stem cell mobilization with filgrastim followed by high dose melphalan (200 mg) and auto-HSCT. The day prior to her auto-HSCT she was started on levofloxacin 500 mg daily, fluconazole 400 mg daily and famciclovir 500 mg daily for prophylaxis. By day 11 post-HSCT, she stopped anti-fungal and bacterial prophylaxis and continued antiviral prophylaxis without any reported issues. After 6 months, post-HSCT famciclovir and sulfamethoxazole/trimethoprim were discontinued. She continues to be in remission without any transplant or infection-related complications [18A].

DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

Adefovir [SED-15, 35; SEDA-32, 530; SEDA-33, 578; SEDA-34, 452; SEDA-35, 507; SEDA-36, 409; SEDA-37, 333]

Urinary Tract

Adefovir (ADV), a nucleotide analog, has moderate potency and potential nephrotoxicity. ADV was recommended by certain scholars because it has less drug resistance ratio than lamivudine (LMV). In a prospective double-blind study, 252 patients diagnosed with chronic hepatitis B virus (HBV) infection between January 2006 and August 2014 were recruited and screened for resistance to ADV. The patients were randomly divided into three groups: LMV+ADV ($n=88$), telbivudine (LdT)+ADV ($n=84$), entecavir (ETV) + ADV ($n=80$). The patients were administered with LMV 100 mg a day; LdT 600 mg once a day; ADV 10 mg once a day; ETV 0.5 mg once a day. All the patients tolerated treatment well, and no patient discontinued the therapy. At week 36 of treatment, the rate of side effects in the LMV+ADV group was 1.1%, with one patient demonstrating blood urea nitrogen (BUN)

elevation (14.2 mmol/L). In the LdT + ADV group, the rate was 1.2%, with one patient demonstrating BUN elevation (14.7 mmol/L) and one patient with creatine kinase elevation (138.6 μmol/L), the rate of side effects happening in the ETV + ADV group was 1.3%, with one patient demonstrating BUN elevation (14.6 mmol/L). At week 96 of treatment, the rate of side effects happening in the LMV + ADV 4.5%, with two patients having blood urea BUN elevation (mean 13.9 mmol/L), one patient having diarrhea, and one patient having nausea; the ratio of side effects in the LdT + ADV group was 7.1%, with two patients having BUN elevation (mean 14.5 mmol/L), one patient having creatine kinase elevation (142.3 μmol/L). The rate of side effects in the ETV + ADV group was 5.0%, with two patients having BUN, one patient having headache, and one patient having dizziness. None of the patients developed acute renal failure or myopathy during the rescue therapy. The patients suffering side effects recovered after undergoing symptomatic treatments [19c].

Comparative Study

The efficacy of tenofovir (TDF) in 3TC-resistant patients with a suboptimal response to 3TC plus ADV was reported. HBV serological markers and biochemistry were assessed at baseline at weeks 12, 24, and 48. Resistance surveillance and side effects were monitored during therapy. Fifty-nine patients were randomized to switch to TDF ($n=28$) or continuation with 3TC plus ADV ($n=31$). No significant differences were found between the groups at baseline [20c].

The clinical effects of ADV combined with ETV in the treatment of chronic HBV in 68 patients with decompensated cirrhosis has been reported. In these patients, ADV combined with ETV treatment effectively delayed the progression of liver cirrhosis, improved the liver function and sleep quality, and reduced the risk of hepatocellular carcinoma [21c].

A retrospective study conducted in Korean population evaluated the efficacy of TDF treatment for more than 6 months in 151 nucleos(t)ide-naïve HBV patients. The study found that the cumulative rates of virologic response at 6, 9, 12, and 18 months were 47.0%, 59.4%, 67.9%, and 69.3%, respectively. Most of the AEs were mild. No significant changes were observed in serum creatinine and phosphorus levels [22C].

Combination

Sixty-eight patients were enrolled in a study to understand the effect of Peg-IFN α-2 α combined with ADV in HBV postpartum women with normal levels of ALT and high levels of HBV DNA. Thirty (30/68) patients were switched to CPIA treatment after childbirth, 93.3% (28/30) achieved virological response, 56.7% (17/30) achieved Hepatitis B virus e antigen (HBVeAg) seroclearance and 26.7% (8/30) cleared HBsAg after the treatment period. The HBV DNA and HBVeAg levels before CPIA treatment were negatively associated with HBeAg seroclearance. HBVsAg and HBVeAg levels in week 12 and week 24 after CPIA treatment were negatively associated with HBsAg seroclearance. Thirty-eight (38/68) patients did not receive antiviral treatment after childbirth, and none of them had HBVeAg or HBVsAg clearance. Authors suggests that it is safe to treat postpartum women who have HBV with a combination of drugs [23c].

DIRECT-ACTING ANTIVIRAL PROTEASE INHIBITORS [SEDA-35, 508; SEDA-36, 409; SEDA-37, 334]

Boceprevir

Intraocular pressure increased in patients with hepatitis C virus (HCV) treated with Peg-IFN-a-2a, RBV, and boceprevir [24c].

Hematological Toxicity

A cohort study involving 81 liver transplant patients (Male: 76%, mean age: 55.8 ± 9.7 years) with severe HCV recurrence (F3 or F4: $n=34$ (42%)) has been reported. The patients were treated with boceprevir ($n=36$) or telaprevir ($n=45$). A premature discontinuation of anti-HCV therapy due to a serious AE reported in 22 patients (27%) due to boceprevir. Hematological toxicity was reported as a side effect of boceprevir in 95% of patients, infections in 28% and death in 7% [25c].

Telaprevir

Observational Study

An observational study was reported to evaluate the safety and efficacy of telaprevir (TVR), in combination with Peg-IFNa-2b and RBV in 3563 chronic HCV patients. Patients were treated with TVR, Peg-IFN and RBV for 12 weeks followed by Peg-IFN and RBV for 12 weeks (triple therapy). Serious ADR were observed in 96.5% patients. ADR related to skin disorders and anemia were frequently observed in addition to serious renal dysfunction [26C].

The safety and efficacy of a triple therapy in HCV and HIV co-infected patients was reported. Five hundred eighty-four patients from 24 health care settings in Austria, Germany, Spain, Switzerland and the United Kingdom were included in the observational study. The patients, who were over 18 years old and were co-infected with HIV, were given triple therapy against HCV including BOC or TVR in combination with Peg-IFN plus RBV with HCV genotype 1 at the time of starting

therapy. Patients received a three-drug combination based on Peg-IFN alfa-2a or Peg-IFN alfa-2b at a dose of 180 μg or 1.5 μg/kg once per week, respectively, and oral RBV at daily doses of 800–1200 mg. BOC was administered orally at doses of 800 mg every 8 h for 44 weeks. Oral TVR was given at doses of 750 mg every 8 h or 1125 mg twice a day during the first 12 weeks of therapy. Of these, 159 patients reached the 60-week follow-up analysis. Treatment was discontinued due to AEs in 13/159 (8.2%; 95% CI: 4.4–13.6%) subjects. Any AE were reported in 38/46 (82.6%) of the patients treated with BOC and 92/113 (81·4%) of those treated with TVR. Grade 3 or 4 anemia was reported in 9 (7%) patients, Grade 3 or 4 thrombocytopenia was observed in 22 (17.2%) patients and 21 (16.4%) individuals presented Grade 3 or 4 neutropenia. Erythropoietin was administered to 36 (22.6%) individuals and nine (5.7%) received blood transfusion. General dose reductions of Peg-IFN and RBV were reported in 16 (17.4%) and 40 (43.5%) patients of the 92 subjects, respectively [27C].

Triple therapy involving TVR, Peg-IFN and RBV were reported to improve antiviral efficacy but had potentially severe AEs in patients with chronic HCV [28c].

TVR treatment has caused elevated levels of serum creatinine and anemia in chronic HCV patients [29c]. Another study involving 112 patients infected with hepatitis C genotype 1 treated with Peg-IFN/RBV/TVR triple therapy developed significant renal impairment and anemia [30].

Bacterial infection as an AE of TVR-based triple therapy in HCV patients has been reported. Bacterial infections occurred in 21 of the 430 (4.9%) patients during TVR-based triple therapy. Among these subjects, 71.4% (15 of 21) experienced bacterial infections during the initial 8 weeks of treatment. Urinary tract infections were observed in 2.8% of cases (12 of 430) and were more prevalent in women (11 of 215, 5.1%) than in men (1 of 215) [31c].

A multicenter center study in patients with recurrent advanced HCV, who had undergone liver transplants showed serious AEs on TVR-based triple therapy [32c].

Skin Toxicity

Skin eruption has been reported as a side effect caused by TVR in a case study. A 53-year-old male patient with genotype 1 HCV cirrhosis, who was not previously treated for the disease, was treated with Peg-IFN-a in a single 180-μg subcutaneous injection, weekly with 1250 mg oral RBV per day and 750 mg oral TVR three times daily. After 4 weeks of treatment, a non-pruriginous erythematous macule was observed in the right inframammary region, which was treated with dexamethasone cream. On ninth week, the patient showed nausea, confluent pruriginous maculopapular eruption, lesions on more than 50% of the body surface, enanthem and ulcers on the oral mucosa, as well as purpuric lesions on the legs. TVR was removed from the treatment course with maintenance of Peg-IFN and RBV until the end of the 48 weeks. Orobase triamcinolone was applied to the lesions of the oral mucosa and clobetasol cream to the cutaneous lesions, which cured the eruption within 15 days of treatment. Twelve to 24 weeks of the treatment, the PCR-HCV remained negative and the patient did not present recurrence of the cutaneous lesions [33A].

A 50-year-old woman having HCV genotype 1b experienced TVR-related severe cutaneous eruptions 8 weeks after starting a triple antiviral therapy. Adverse cutaneous reactions were caused by a TVR-induced T-cell dependent immune mechanism in this patient [34c].

Efficacy and safety of TVR, Peg-IFNα-2b and RBV triple therapy in 106 Japanese patients infected with hepatitis C virus genotype 1b has been reported [35C].

Entecavir [SEDA-33, 578; SEDA-34, 452; SEDA-35, 512; SEDA-36, 411; SEDA-37, 335]

Observational Study

A prospective study was conducted in 34 antiviral treatment-naïve patients with chronic HBV who received ETV monotherapy and were followed up for 4 years, the mtDNA contents initially decreased and then increased, while the mtDNA4977 depletion rates first increased and then decreased. A long-term ETV monotherapy induced mitochondrial toxicity in patients with chronic HBV [36E].

A comparative study showed the effectiveness of TDF and ETV in treating chronic HBV. From 2008 to 2013, 189 consecutive treatment-naive chronic HBV patients receiving TDF ($n=41$) or ETV ($n=148$) for severe acute exacerbation participated in this study. Among the patients who survived by week 24, showed no difference between the two groups in the percentage of patients who had a serum creatinine increase of $\geq$0.5 mg/dL from baseline (6.7%) vs. 2.0% in the TDF and ETV groups, respectively. However, a significant reduction in the estimated glomerular filtration rate (eGFR) was found in both groups [37C].

A similar comparative study of the efficacy of TDF and ETV for initial treatment of 90 patients with chronic HBV in China has also been reported [38c].

A retrospective study reported the efficacy and safety of ETV in white patients with chronic HBV. The study was conducted at 23 Spanish centers in 237 chronic HBV patients treated with ETV (0.5 mg/day). The mean age of the cohort was 43 years (range: 19–82 years); 73% were male, 83% were white, and 33% were HBeAg positive. There were no treatment discontinuations due to AEs. Three patients were diagnosed with hepatocellular carcinoma at months 12, 30 and 54, and six experienced hepatic decompensation during follow-up [39C].

Ribavirin [SEDA-33, 578; SEDA-34, 452; SEDA-35, 512; SEDA-36, 412; SEDA-37, 335]

Neurological

A study was conducted to evaluate neuropsychiatric AEs of interferon-based treatment for HCV in standard multidisciplinary clinical practice. Patients with chronic HCV who completed treatment with Peg-IFN and RBV between 2005 and 2013 were included in the study. All patients underwent a multidisciplinary follow-up during treatment. During treatment, 1679 neuropsychiatric AEs in 618 patients (86.2%) generated 1737 clinical interventions. Fifty-seven (3.3%) neuropsychiatric AEs were severe and 2 (0.1%) life-threatening (suicidal attempts). Most neuropsychiatric AEs (1555 events, 92.6%) resolved without sequelae. Psychiatric medication was required in 289 patients (40.3%) [40C].

A prospective cohort study in 30 patients (median age 59 years and 57% of women) with HCV associated–mixed cryoglobulinemia vasculitis has been reported. All patients received antiviral therapy with Peg-IFNα-2a (180 μg/week, $n=20$) or 2b (1.5 μg/kg/week, $n=10$), subcutaneously plus RBV (600–1200 mg/day orally) for 48 weeks. Treatment with the protease inhibitor consisted of oral administration of TVR at a dose of 750 mg three times daily for 12 weeks or boceprevir at a dose of 800 mg three times daily for 44 weeks ($n=13$). The main side effects of antiviral therapy included fatigue (87%), neutropenia (78.3%), anemia (73.9%), thrombocytopenia (65.2%), infection (47.8%), pruritus (39.1%), depression (21.7%), and nausea (21.7%). A high incidence of serious AEs (14 patients) was observed during the 72 weeks of follow-up [41c].

Telbivudine [SEDA-33, 582; SEDA-34, 455; SEDA-35, 515; SEDA-36, 412; SEDA-37, 335]

One study examined 153 chronic hepatitis B patients infected with HBV variants resistant to 3TC. Patients were divided into two groups: the TDF monotherapy group included 33 patients and the combination therapy group (TDF plus 3TC or LdT) had 120 patients. No patient experienced any significant renal dysfunction during the treatment period. Authors conclude that TDF monotherapy has antiviral efficacy comparable to that of TDF plus 3TC or LdT combination therapy [42C].

Vertical Transmission

A prospective long-term study evaluated the efficacy of LdT in preventing vertical transmission of HBV from mothers to their infants. Four hundred and fifty hepatitis B e antigen-positive pregnant women with HBV DNA levels greater than 106 IU/mL were studied. Two hundred seventy-nine women received LdT (600 mg/day) during weeks 24–32 of gestation, and 171 women who were unwilling to take antiviral drugs participated as controls. Mother-to-child transmission of HBV was determined by detection of hepatitis B surface antigen and HBV DNA in the infant 6 months after birth. None of the infants whose mothers were given LdT tested positive for of hepatitis B surface antigen at 6 months, compared with 14.7% of infants in the control group ($p=5.317\times10^{-8}$). Levels of HBV DNA also decreased among women given LdT. No severe AEs or complications were observed in women or infants treated with LdT [43C].

Neurological

A randomized, open-label, international, multicenter study compared the combination of LdT plus Peg-IFN vs. monotherapy in 159 adults HBV patients. Patients were divided into three groups. All received LdT 600 mg once daily for 104 weeks. In addition, 50 patients received Peg-IFN 180 μg subcutaneously once per week for the first 52 weeks, 55 patients received LdT 600 mg once daily for 104 weeks, and 54 patients received Peg-IFN 180 μg subcutaneously once per week for 52 weeks. Despite the different drug exposure times, the percentage of patients who experienced AEs was higher in the Peg-IFN monotherapy group (90.7%) and in the combination-therapy group (88.0%) than in the LdT monotherapy group (70.4%). No patient died during the study and the rates of SAEs in the combination therapy were higher when compared to other groups. Peripheral neuropathy occurred in 8 patients and was judged as being a drug-related serious AE; of these, 7 cases occurred in the combination-therapy group and, at the last follow-up, 3 patients had improved and 4 completely recovered. One case of peripheral neuropathy occurred in the LdT monotherapy group and, at the last follow-up, the patient showed improvement. The most frequent AEs in the Peg-IFN monotherapy group were headache (17 [32%]), pyrexia (14 [26%]) and alopecia (15 [28%]), while discontinuation due to AEs occurred in 3 patients (feeling abnormal, neutropenia and impotence). In the LdT monotherapy group, the most frequent AEs were upper respiratory tract infections ($n=11$, 20%) and headache ($n=9$, 17%). On-treatment ALT flares were 6% (3/47) in the LdT plus Peg-IFN combination group and 4% (2/53) in each monotherapy group [44C].

Faldaprevir

The safety of faldaprevir, deleobuvir, and ribavirin in patients with chronic HCV infection was reported in a recent study. The most frequent AEs with faldaprevir, deleobuvir, and RBV in patients with or without cirrhosis were mild or moderate gastrointestinal and skin AEs [45c].

Sofosbuvir [SEDA-37, 335]

Sofosbuvir (SOF)-based regimens appear to be well tolerated with headache and fatigue being the most common side effects [46R].

A recent analysis showed that the combination of SOF and simprevir was more effective than RBV. A prospective open-label study looked at 82 patients with chronic HCV genotype 1 A infection and Child's Grade A cirrhosis. Patients were enrolled from 2 clinics in Atlanta, Georgia, from December 2013 through January 2014. Subjects were assigned randomly to groups given simeprevir (150 mg/day) and SOF (400 mg/day) ($n=58$ in the final analysis) or Peg-IFN-a-2b (1.5 mcg/kg/week), ribavirin (1000–1200 mg/day), and SOF (400 mg/day) ($n=24$ in the final analysis) [47C].

An open-label, non-randomized study reported on direct-acting antiviral regimens in non-cirrhotic patients with HCV was conducted at National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. Treatment-naive and predominantly African American patients with HCV genotype 1 infection and early-stage liver fibrosis were enrolled from January 2014 to May 2015. Forty-nine of 50 patients completed 4 weeks of treatment with study medications, and primary endpoint results were obtained for them. Twenty-five patients received a 3-drug regimen consisting of ledipasvir and SOF plus GS-9451 for 4 weeks, and 25 received a 4-drug regimen consisting of ledipasvir, SOF, GS-9451, and GS-9669 for 4 weeks. Forty-eight percent (12 of 25) of patients receiving the 3-drug regimen and 72% (18 of 25) of those receiving the 4-drug regimen had mild AEs reported. The most common AEs were fatigue, diarrhea, and headache. Two serious AEs occurred: vertigo for 3 days in a patient with a heart rate of 57 beats/min who was not receiving antiarrhythmic agents, and angioedema. Both events occurred in patients receiving the 4-drug regimen but were deemed to be unrelated to the study drugs [48C].

A randomized, phase 2, open-label study was conducted at 48 U.S. sites with 377 treatment-naive non-cirrhotic patients. The patients having HCV genotypes 1–6 were randomly assigned to SOF, 400 mg, with velpatasvir, 25 or 100 mg, for 12 weeks. Another group of patients with genotype 1 or 2 HCV infection was randomly assigned to SOF, 400 mg, and velpatasvir, 25 or 100 mg, with or without ribavirin for 8 weeks. The AEs were reported in 262 (69%) patients. AEs experienced by more than 10% of patients were fatigue (21%), headache (20%), and nausea (12%). One patient committed suicide. Incidence of fatigue, insomnia, and rash were higher in patients treated with ribavirin-containing regimens. One patient, a 19-year-old white woman with genotype 1 HCV infection who was receiving 8 weeks of SOF plus velpatasvir, 25 mg (group 1), developed mild abdominal pain, mild palpitations, and moderate dizziness on treatment day 6 [49C].

A prospective cohort study reported on fibrosing cholestatic hepatitis (FCH) patients in France and Belgium from October 2013 through April 2014. Twenty-three FCH patients were included in the study on the effects of antiviral agents with recurrence of HCV infection after liver transplantation. Most of the patients had genotype 1 infections that had not responded to previous treatment; 4 patients were co-infected with HIV. Treatment regimens were divided into 2 groups: SOF + RBV + Peg-IFNα (SOF + RBV group; $n=8$) SOF + daclatasvir + RBV (SOF + daclatasvir group; $n=15$). Dosages were 400 mg/day for SOF and 60 mg/day for daclatasvir, whereas the RBV was given at different concentrations, 400 mg ($n=5$), 600 mg ($n=2$), 800 mg ($n=8$), and 1000 mg ($n=6$). The planned duration of treatment was 24 weeks for all regimens. All patients survived, without re-transplantation, until week 36. There was no Grade 3 or 4 AEs related to SOF or daclatasvir and no significant interactions among drugs. Fifteen patients (65%) experienced at least 1 serious AEs, which were considered unrelated to drugs. Infection was the most common AE, including urinary tract infection ($n=4$), spontaneous bacterial peritonitis ($n=3$), undetermined sepsis ($n=3$), fungal infection ($n=1$), and cytomegalovirus reactivation ($n=1$). Most infections (93%) were observed within the first 8 weeks of treatment, before achievement of complete clinical response. Other clinical AEs included ascites, severe denutrition, and hepatic encephalopathy, all directly related to FCH. Anemia was observed in almost two thirds of patients and led to a RBV dose reduction (up to 200 mg/day) in 61% and discontinuation in 22% of cases. Mild to moderate renal failure was observed in 43% of cases, but creatinine values remained stable over time during treatment and follow-up periods. Severe renal failure (eGFR, <30 mL/min) was observed in 1 patient during a septic episode, but values returned to normal after infection resolution. One patient on SOF + daclatasvir displayed worsening of cholestasis with bilirubin level greater than 100 μmol/L at week 12. Cholestasis persisted after discontinuing daclatasvir at week 16, and improved the condition after SOF stopped at week 24 [50c].

An open-label study was conducted in 151 patients who were naïve to HCV treatment and 52 patients who were previously treated; all of them were co-infected with HIV-1. Previously untreated patients were randomly assigned in a 2:1 ratio to receive either 12 or 8 weeks of daclatasvir at a standard dose of 60 mg plus 400 mg of SOF daily. Previously treated patients underwent 12 weeks of therapy at the same doses. Patients had HCV genotypes 1 through 4 (83% with genotype 1), and 14% had compensated cirrhosis; 98% were receiving antiretroviral therapy. Among patients with genotype 1, a sustained virologic response was reported in 96.4% who were treated for 12 weeks and in 75.6% who were treated for 8 weeks

among previously untreated patients. The most common AEs were fatigue, nausea, and headache. There were no study drug discontinuations because of AEs [51C].

A double-blind trial from October 2013 to October 2014 was conducted in 155 HCV genotype 1 patients having compensated cirrhosis who had not achieved sustained virological response (SVR) after successive treatments with Peg-IFN and protease-inhibitor regimens. The patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg SOF plus weight-based RBV for 12 weeks, or ledipasvir-SOF plus placebo once daily for 24 weeks. One patient discontinued treatment because of AEs while receiving only placebo drug. The most common event in the two groups was asthenia, followed by pruritus and headache in the ledipasvir-SOF plus RBV group and headache and fatigue in the ledipasvir-SOF group [52C].

A phase 2, open-label study reported the efficacy and safety of ledipasvir and SOF, with or without RBV, in patients infected with HCV genotype 3 or 6. The study was conducted in 126 patients with HCV infections at 2 centers in New Zealand from April 2013 through October 2014. Previously untreated patients with HCV genotype 3 were given fixed-dose combination tablet of ledipasvir and SOF ($n=25$) or ledipasvir and SOF along with RBV ($n=26$). Treatment-experienced patients with HCV genotype 3 ($n=50$) received ledipasvir and SOF and RBV. The most common AEs were headache, upper respiratory infection, and fatigue and nausea. Six patients experienced serious AEs. Two of the events, upper abdominal pain and abdominal pain, were treatment related. Only 1 patient, with HCV genotype 3 receiving ledipasvir and SOF alone, discontinued treatment because of an AE. A 49-year-old patient discontinued RBV after acute agitation. Seven patients taking RBV experienced anemia. Six patients had their dose of RBV reduced and one patient discontinued RBV [53C].

SOF plus RBV for the treatment of chronic genotype 4 HCV infection in 60 patients of Egyptian ancestry has been reported. The most common AEs were headache, insomnia, and fatigue. No patients had AEs leading to dose modification, interruption, or discontinuation of SOF [54c].

The challenges for direct-acting antiviral therapy have been reviewed [55R]. The safety of direct-acting antiviral agents in HCV patients co-infected with hepatitis B virus (HBV) or HIV has been evaluated in a recent review [56R].

Simeprevir

A review published the use of simeprevir in HCV treatment and evaluated the efficacy. Grade 3–4 AE, serious AE and treatment withdrawal rates with simeprevir plus Peg-IFN-α/RBV were similar to those with placebo plus Peg-IFN-α/RBV. Skin rashes with simeprevir were mostly mild or moderate; serious photosensitivity reactions rarely reported. Simeprevir is efficacious and generally well tolerated in patients with chronic HCV genotypes 1 and 4 infection [57R].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: COMBINATIONS

Abacavir/Lamivudine

Observational Study

Between 1998 and 2011, 1309 HIV-infected patients from different countries in Europe who had a chronic HCV infection were treated with a combination of Peg-IFN and RBV. Patients using an ABC-containing regimen showed no difference in response to HCV treatment compared to those using an FTC + TDF-containing backbone [58C].

Abacavir/Lamivudine/DTG

A randomized, double-blind, non-inferiority study in 833 ART-naive HIV-1 patients evaluated the safety and efficacy of 50 mg DTG + ABC/3TC vs. efavirenz (EFV)/TDF/FTC. Of the 833 participants, 342 in the DTG + ABC/3TC arm and 310 in the efavirenz/TDF/FTC arm were treated for 96 weeks. Nine drug-related serious AEs occurred in the efavirenz/TDF/FTC arm compared with 2 (<1%) in the DTG + ABC/3TC arm through week 144. During the double-blind phase, ABC hypersensitivity was reported in 5 participants (1%) in the EFV/TDF/FTC arm and in 2 participants (0.5%) in the DTG + ABC/3TC arm. Two fatalities were previously reported in the week 48 analysis; no additional fatalities occurred through week 144. Two new drug-related SAEs occurred, 1 in the EFV/TDF/FTC arm (renal failure between week 48 and week 96) and 1 in the DTG + ABC/3TC arm (osteonecrosis between week 96 and week 144). A greater increase in high-density lipoprotein cholesterol for the EFV/TDF/FTC arm compared with the DTG + ABV/3TC arm was seen through week 144. Five participants presented with Grade 2 elevations in creatinine levels in the DTG + ABC/3TC arm. Six participants had Grade 3/4 alanine aminotransferase (ALT) elevations in the DTG + ABC/3TC arm [59r].

Elvitegravir

Observational Studies

A 96-week, phase 3, open-label, multicenter cohort study evaluated the safety and efficacy of Cobistat-containing regimens in HIV-1-infected adult patients

who are either treatment-naive (STB cohort) or treatment-experienced (COBI cohort: switch ritonavir to COBI) with stable, mild-to-moderate renal impairment. Thirty-three patients were enrolled and received at least one dose of STB elvitegravir/COBI/FTC/TDF (STB, $n=33$). Serious AEs were reported for 12% of patients ($n=4$), increased blood creatine phosphokinase ($n=1$), infected cyst ($n=1$), right ventricular failure and lymphoma (both in the same patient; $n=1$), and hepatitis C and Hodgkin's disease (both in the same patient; $n=1$). None of the AEs was considered related to study drug except for the serious AE of increased blood creatinine phosphokinase. The most frequent AEs were diarrhea (30%), insomnia (21%), and nausea and headache (each 18%). AEs considered related to study drug by the investigator were reported for 45% of patients (15/33 patients). The most frequently reported AEs considered related to study drug by the investigator were nausea (3 patients) and blurred vision, upper abdominal pain, vomiting, decreased eGFR, hyperglycemia, headache, and insomnia (each reported for 2 patients). Four patients (12%) discontinued study drug due to an AE. One patient discontinued due to HCV and Hodgkin's disease. The other 3 patients discontinued due to renal AEs, 2 of whom met the protocol-defined criterion for potential discontinuation. All 3 patients had baseline CrCl between 50 and 55 mL/min and developed CrCl <50 mL/min without evidence of PRT. Only 1 patient had cystatin C-based eGFR <50 mL/min·1.73 m^{-2} at the time of discontinuation, which was preexisting at baseline. CrCl returned to baseline after STB discontinuation in 2 patients. One patient had confirmed increase in serum creatinine >0.4 mg/dL and the study drug discontinued [60c].

Cobicistat

Observational Studies

The pharmacokinetics, pharmacodynamics, and safety of both pharmacoenhancers and the clinical utility of COBI in future HIV therapy is reviewed [61R].

Elvitegravir/Cobicistat/FTC/Tenofovir

A cross-sectional study was carried out between April and July 2014 at the Buea, Limbe and Kumba government Hospitals in South-Western Region of Cameroon on the efficacy of combination ARV therapy. Two hundred participants on HAART, DOTS were enrolled into the study. The ages ranged from 21–65 years with the mean age being 38.04 (±10.52) years. The 200 participants were divided into three treatment groups. Sixty (30%) participants were on HAART and DOTS combined treatment, 70 (35%) were on HAART and 70 (35%) were on DOTS. Out of 130 participants on HAART and HAART/DOTS, 80 (61.54%) were treated with the combination of AZT, 3TC, and NVP; 6 patients were on AZT, 3TC, and EFV while 44 patients were on TDF, 3TC, and EFV. Regarding the 130 participants on DOTS and HAART/DOTS, 63 (48.5%) were on the drug regimen rifamycin, isoniazid, ethambutol, pyrazinamide (intensive phase) and 67 (51.5%) were on rifamycin, isoniazid (continuation phase). The mean eGFR was significantly higher in patients on HAART than in the patients on HAART/DOTS with respect to AZT, 3TC, NVP combination [126.0 (±83.44) and 95.38 (±26.51), $p=0.039$]. In addition, the mean serum albumin was significantly higher in patients on HAART alone than those on HAART/DOTS with respect to AZT, 3TC, NVP combination [49.26 (±5.76) and 38.07 (±8.95), $p=0.001$]. No significant difference was found in mean serum creatinine between patients on HAART and those on HAART/DOTS with respect to TDF, 3TC, EFV combination. However, patients on HAART had abnormal higher value of mean serum creatinine compared to those on HAART/DOTS [2.06 (±4.16) and 0.97 (±0.28), $p=0.217$]. Authors concluded that the use of the HAART regimen (TNF, 3TC and EFV combination) among the HAART-treated adults was nephrotoxic. The other combined HAART and DOTS regimens had no nephrotoxic effect. Abnormal kidney function could be associated with HAART use [62C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) [SEDA-15, 2586; SEDA-32, 534; SEDA-33, 585; SEDA-34, 456; SEDA-35, 516; SEDA-36, 415; SEDA-37, 337]

Abacavir [SEDA-15, 3; SEDA-32, 534; SEDA-33, 585; SEDA-34, 456; SEDA-35, 516; SEDA-36, 415; SEDA-37, 337]

Observational Studies

A descriptive study of HIV-infected patients in Bangkok, Thailand was conducted in 103 patients with a median age of 46 (range 20–85) years during January 2011 to November 2014. Most of the participants (97%) were on ARV, and more than half of the patients had undetectable HIV RNA at the end of the study. The most common ARV regimen was TDF, 3TC, and EFV (25%). Two out of four patients who had positive HLA-B*5701 developed hypersensitivity after receiving ABC. One out of five patients who undergone HLA-B*4001 genotyping developed lipodystrophy after receiving d4T. One out of two patients who had positive HLA-B*3505 developed skin rash after receiving NVP. There were

45 ADRs reported that includes skin rashes, of which 18 were from TDF, 17 from EFV, four from AZT, two from ABC, and one each from NVP, raltegravir, ritonavir, and DDI. The most common ADRs of other types from each drug were AKI from TDF, dizziness from EFV, anemia from AZT, hypersensitivity reaction from ABC, and drug rash from NVP. ADRs, such as dizziness, insomnia, or depression from EFV or skin rash from ABC, EFV, or NVP, were improved in 96.4% of patients [63c].

SINGLE is an ongoing, phase 3, multicenter, randomized, double-blind, non-inferiority study involving treatment-naive HIV-infected participants. The safety profile of DTG + ABC/3TC through week 96 and week 144 was similar to week 48 and was generally favorable compared with the efavirenz/T DF/FTC arm throughout. The most common drug-related AEs in the EFV/TDF/FTC arm, which differed by more than 2% from the DTG + ABC/3TC arm, were dizziness [140 (33%) vs. 29 (7%)], abnormal dreams [67 (16%) vs. 27 (7%)], and rash [34 (8%) vs. 4 (<1%)]. The drug-related AE of insomnia was more commonly reported in the DTG + ABC/3TC arm ($n = 41$, 10%) than in the EFV/TDF/FTC arm ($n = 28$, 7%). The overall incidence of serious AEs was low and comparable across the DTG + ABC/3TC and efavirenz/TDF/FTC arms through week 96 [44 (11%) vs. 51 (12%), respectively] and week 144 [65 (16%) vs. 60 (14%), respectively]. Nine drug-related serious AEs occurred in the EFV/TDF/FTC arm compared with two in the DTG + ABC/3TC arm through week 144. During the double-blind phase, ABC hypersensitivity was reported in five participants in the EFV/TDF/FTC arm and in two (0.5%) participants in the DTG + ABC/3TC arm. Two fatalities were previously reported in the week 48 analysis 1; no additional fatalities occurred through week 144. Two new drug-related SAEs occurred, 1 in the EFV/TDF/FTC arm (renal failure between week 48 and week 96) and 1 in the DTG + ABC/3TC arm (osteonecrosis between week 96 and week 144). No clinically significant differences in laboratory parameters between the arms emerged from week 48. A greater increase in high-density lipoprotein cholesterol for the EFV/TDF/FTC arm compared with the DTG + ABC/3TC arm was seen through week 144; overall, both groups showed a small increase in the ratio of total cholesterol to high-density lipoprotein cholesterol. A comparable and modest rise in mean total triglycerides was seen through week 96 in both groups; however, the increase in triglycerides in the EFV/TDF/FTC arm was greater than in the DTG + ABC/3TC arm at week 144. Mean serum creatinine level in patients receiving DTG + ABC/3TC remained stable through week 144. Five participants presented with Grade 2 elevations in creatinine levels in the DTG + ABC/3TC arm on a single occasion through week 144. Overall, there was a low rate of elevated liver enzymes in both treatment groups across the study period. Six participants had Grade 3/4 ALT elevations in the DTG + ABC/3TC arm. Three were due to acute HCV infections, and 3 due to concurrent use of hepatotoxic drugs (anabolic steroids, naltrexone, and duloxetine). Three Grade 3/4 ALT elevations were observed in the EFV/TDF/FTC arm; two of these were due to acute HCV infections and one due to the use of anabolic steroids. Two participants (one in each study arm) with acute HCV infections were withdrawn from the study [64c].

An overview compared the efficacy and safety of the combined DTG/ABC/3TC co-formulation to single tablet regimen (STR). The DTG/ABC/3TC regimen is highly effective in achieving sustained suppression of HIV-1 RNA in plasma. The STR has a favorable safety profile and a low potential for drug interactions, which will contribute to a prominent role in therapy with ABC as backbone component [65R].

Lamivudine [SED-15, 1989; SEDA-32, 531; SEDA-33, 587; SEDA-34, 456; SEDA-35, 517; SEDA-36, 416; SEDA-37, 338]

Observational Studies

A 48-week randomized, parallel, open-label, multicenter, non-inferiority trial to compare the efficacy and safety of three PI-based second-line antiretroviral combinations in three African countries has been reported. The patients (454) were randomized to three groups to receive LPV/r (co-formulated LPV 200 mg/ritonavir 50 mg two tablets twice daily) with TDF 300 mg/FTC 200 mg (one tablet daily with food) (control group); ABC (600 mg tablet) with ddI (enteric-coated capsule of 250 or 400 mg based on body weight) once daily fasting, and LPV/r twice daily (ABC/ddI group); or DRV 800 mg (two 400 mg tablets) boosted with ritonavir (100 mg tablet) and TDF/FTC, all taken with food once daily (DRV group). Participants in the ABC/ddI group with chronic HBV continued on 3TC 150 mg/day. Gastrointestinal complaints were common and significantly different between the DRV/r and the LPV/r groups [26 (17%) vs. 48 and 50 (33%)]. Twenty-four (5%) participants reported symptoms of neuropathy, mainly from baseline: 11 were in ABC/ddI group. No statistically significant differences were recorded across groups for liver and kidney toxicity: only one patient had increased alanine aminotransferase (>5 × upper limit of normal). Sixty-one (14%) participants experienced a 25% decrease in estimated eGFR between baseline and week 48, with a higher frequency in those taking TDF. Grade 3 or 4 AEs occurred in 58 (13%) patients, with no difference between groups. Only five patients stopped assigned treatment because of AEs: one for suspected ABC reaction, one in DRV group for severe kidney failure that was not related to the study

drug, two for progressive neuropathy in ddI in patients with pre-existent d4T-related neuropathic pain, and one patient requesting to reduce the pill burden (ABC/ddI group on TB treatment). The authors suggests that patients with high viral load at first-line failure may need special management to avoid early second-line failure [66C].

Stavudine [SED-15, 3180; SEDA-32, 535; SEDA-33, 587; SEDA-34, 456; SEDA-35, 517; SEDA-36, 417; SEDA-37, 338]

See also Section Zidovudine.

Observational Studies

The long-term side effects of d4T led to recommendations in 2009 to phase out the use of this drug. A prospective observational cohort study was conducted with 18786 HIV-1-infected patients from 107 clinics in 37 countries. Overall, 963 of 13246 (7.3%) EuroSIDA patients under follow-up during the study period received a d4T-based cART regimen. There were 392 patients taking d4T in 1 January 2006, of whom 381 (97.2%) discontinued before 1 January 2013. The majority of patients, 288 (75.6%), discontinued d4T together with at least one other ARV drug. The most frequent reason for discontinuation was indicated as physician's choice (26.5%), followed by unknown reasons (17.6%), abnormal fat distribution (15.8%), treatment failure (virological, immunological and/or clinical) (15.0%), other reasons (9.2%), patient's wish (6.0%) and toxicity (5.5%). Among those who discontinued d4T alone ($n=93$; 24.4%), d4T-related toxicities such as abnormal fat distribution, dyslipidaemia and nervous system toxicity were frequently indicated (24.7%, 4.3% and 3.2%, respectively) However, the proportions of d4T discontinuations were very high because of physician's decision, unknown and treatment failure (23.7%, 19.4% and 7.5% respectively). In authors opinion, all HIV clinicians should be aware of the potential harmful effects associated with d4T treatment and avoid the drug as much as possible [67M].

Zidovudine [SED-15, 3713; SEDA-32, 536; SEDA-33, 588; SEDA-34, 458; SEDA-35, 517; SEDA-36, 417, SEDA-37, 338]

Eight hundred and fifty-two patients received three different backbones of nucleoside reverse transcriptase inhibitor in a non-randomized manner. Of these 161 patients were on AZT, 628 on d4T, and 63 on TDF; all received lamvudine. Grade 4 anemia was higher for those receiving ZDV than the d4T group. The patients taking d4T had a higher increase in hemoglobin than those were on ZDV [68C].

A prospective cohort study was conducted in 211 adult patients (≥18 years of age) with HIV/AIDS who commenced ART. All ADRs in the first 12 months of therapy were recorded, and the severity, causality, and preventability were assessed. Of these, 181 (85.7%) experienced at least one ADR and 66 (31.3%) experienced at least one severe ADR within 12 months of commencing ART. The patients taking AZT-containing regimens experienced severe ADRs [69C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Tenofovir [SED-15, 3314; SEDA-32, 537; SEDA-33, 588; SEDA-34, 458; SEDA-35, 518; SEDA-36, 418; SEDA-37, 338]

The safety and efficacy of TDF in HIV-1-infected children has been evaluated in a randomized-controlled trial. Ninety-seven children were in the age group of 2 to <16 years were on a d4T (d4T) or AZT-containing regimen. They had HIV-1 RNA <400 copies/mL and were randomized to either switch d4T or ZDV to TDF or continue d4T or ZDV. No subjects discontinued the study drug because of an AE in the 48 weeks of treatment. Only four subjects discontinued TDF because of proximal renal tubulopathy in the extension phase [70c].

Renal Toxicity

A retrospective, longitudinal observational study was conducted in 451 adult HIV-1-infected patients treated with TDF to assess the incidence of renal damage and to identify the associated potential risk factors. Patients treated with TDF from January 2010 to December 2012 were included in the study. Patient follow-up started when initiating treatment with TDF until the end of the study period (July 31, 2013). Renal toxicity was classified as moderate eGFR < 60 mL/min or severe eGFR < 30 mL/min. The incidence rate for moderate and severe renal insufficiency was calculated as number of cases per 1000 patient-year. The incidence rate of moderate severe renal insufficiency (RI) was 29.2 cases per 1000 person-year (95%), whereas the incidence of severe RI was 2.2 cases per 1000 person-year (95%). Multivariate analysis confirmed an independent association with the risk of kidney damage for age (OR 1.08 95%), time on treatment with TDF (OR 1.16 95%), baseline creatinine (OR 49.80 95%) and treatment with NNRTIs (OR 0.45 95%). Mild to moderate renal failure is a frequent complication during treatment with TDF although severe renal

impairment is rare. Risk factors included age, duration of treatment with TDF, elevated baseline creatinine levels, and treatment with protease inhibitor boosted with ritonavir combinations [71C].

Renal overload of TDF in patients with a pre-existing kidney impairment resulting in worsening renal function has been reviewed [72R].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) [SEDA-15, 2553; SEDA-31, 486; SEDA-32, 537; SEDA-33, 590; SED-34, 459; SEDA-35, 519; SEDA-36, 420; SEDA-37, 339]

Efavirenz [SEDA-15, 1204; SEDA-32, 537; SEDA-33, 590; SEDA-34, 459; SEDA-35, 519; SEDA-36, 420; SEDA-37, 339]

A systematic review and meta-analysis of randomized-controlled trials on EFV-based regimens in antiretroviral-naive HIV-infected patients was conducted [73R]. The authors are of the opinion that there is good efficacy and beneficial safety profile of drugs from new classes of antiretroviral agents (integrase inhibitors, CCR5 antagonists) compared with other initial regimens used in clinical practice for the treatment of HIV-infected patients.

Observational Studies

A retrospective cohort study was reported using clinical data from HIV-1 infected adults (aged ≥15 years), who received EFV as part of their initial antiretroviral therapy between January 2004 and December 2011. HIV-positive patients (2920) were on non-nucleoside reverse-transcriptase inhibitors, NVP or EFV plus two nucleoside reverse-transcriptase inhibitors (NRTIs), often d4T, DDI, AZT, TDF, or ABC plus 3TC. Three hundred fifty-eight ADRs were reported during 8834 person-years of follow-up, with an incidence rate (IR) of 40.5 ADRs per 1000 person-years on EFV-based regimens. ADRs were reported in 195 patients (55%) within 12 months of treatment initiation, 50 patients (14%) within 13–24 months, 36 (10.1%) within 25–36 months, and 77 (21.5%) more than 36 months after commencement of treatment. The majority (55%) of the ADRs were Grade 3 in terms of severity while Grade 2 and Grade 1 ADRs accounted for 31.3% and 12.3%, respectively. The proportion of life-threatening (Grade 4) ADRs was 1.4%. The incidence of ADRs varied across the NRTIs, and was 151 per 1000 person-year (31 events) for d4T-containing regimens, 51.7 (6 events) for ABC, 40.2 (176 events) for TDF, 34.7 (128 events) for AZT and 33.8 (15 events) for DDI. Of those that experienced an ADR, 48.9% (n=175) had EFV substituted with NVP. The most common ADR was lipodystrophy, with an incidence of 63.1 per 1000 person-year (184 events) followed by neuropsychiatric symptoms with an incidence of 29.9 per 1000 person (88 events). More than one-third (33 out of 88) of the neuropsychiatric AEs occurred within 12 months of starting ART, while 12 (13.6%), 13 (14.8%) and 30 (34.1%) were within 13–24, 25 to 36 and more than 36 months of treatment. Lipo-accumulation was the most common lipodystrophy syndrome reported, while nightmares were the most frequently reported neuropsychiatric symptom (incidence of 6.8 per 1000). Twenty-four incidents of gynecomastia were recorded, mainly in patients who received regimens containing d4T (incidence 107 per 1000 person-year), while seizures were rare, with only two incidents reported among patients on AZT-based NRTI. Neuropsychiatric ADRs associated with EFV-based ART had both early and late onset patients on chronic EFV therapy [74C].

Twelve patients with R5-tropic virus and suppressed viral load on two NRTIs plus EFV switched to MVC 600 mg twice daily for 14 days, and then to MVC 300 mg twice daily. MVC was well-tolerated with no Grade 3/4 adverse events; all subjects maintained viral suppression to the end of the study. One subject experienced a transient Grade 1 aspartate transaminase (AST) elevation during the 600 mg twice daily in MVC treatment. The authors suggests that when switching from EFV to MVC, increasing the dose of MVC from 300 mg twice daily to 600 mg twice daily for 1 week would be sufficient to compensate for the prolonged induction effect of EFV [75c].

A study compared semen characteristics across 378 HIV-1-infected patients receiving different antiretroviral regimens or never treated by antiretroviral drugs. This study was done between 2001 and 2007. Sperm motility was the only semen parameter that significantly varied. The median percentage of rapid spermatozoa was 5% in the group of patients receiving a regimen including EFV vs. 20% in the other groups and the sperm velocity was reduced by about 30% in this group [76C].

A review describes the epidemiology, severity and management of neuropsychiatric side effects of EFV [77R].

Etravirine [SEDA-33, 592; SEDA-34, 459; SEDA-35, 520; SEDA-36, 421; SEDA-37, 339]

Observational Studies

The successful use of a TMC125-based regimen in a patient treated with chemotherapy for advanced Hodgkin's lymphoma has been reported. TMC125 constitutes a valuable option for concomitant use with chemotherapy due to its moderate inducing effect on drug-metabolizing enzymes [78c].

Data from cohorts of the EuroSIDA and EUResist Network in France, Italy, Spain, Switzerland and UK collected in 2007 to 2012 from HIV-1-infected patients undergone antiretroviral treatment showed the efficacy of TMC125 plus darunavir/ritonavir (DRV group; $n=999$) vs. TMC125 plus an alternative boosted protease inhibitor (other PI group; $n=116$) were evaluated. The drug responses measured for 24 weeks and the DRV group and PI group showed no significant difference in antiretroviral treatment efficiency. These data do not indicate a difference in response between the DRV and other PI groups [79C].

A prospective study evaluated 25 virologically suppressed patients, largely pretreated (15.6 years on therapy) with antiretroviral drug toxicity ($n=19$) or interactions ($n=9$, mainly with chemotherapy against non-Hodgkin lymphoma or anti-HCV therapy), who switched to a dual therapy with TMC125 plus RAL. Patients were not required have prior virological failure or resistance to both drugs. After a median follow-up of 722 days (473–1088: 53.3 patients-year), there were no cases of transient virological replication or failure. Only 1 patient left therapy at day 10 due to a Grade 2 rash. There were no cases of Grade 3-4 liver toxicity and total cholesterol and triglycerides levels decrease significantly after initiation [80c].

Nevirapine [SEDA-33, 593; SEDA-34, 460; SEDA-35, 521; SEDA-36, 421; SEDA-37, 339]

Observational Study

A prospective, observational study was conducted in the outpatient department of skin and venereal disease reported with cutaneous adverse drug reactions (CADRs). Ninety patients were enrolled in the study. Male to female ratio for CADRs was 1:2. The most commonly encountered CADR was maculopapular rash in 76.67% cases followed by urticaria (8.89%), Stevens-Johnson syndrome (4.4%) and fixed dose eruptions (3.33%). NVP was suspected in 52 out of 90 (57.77%) cases of CADRs which included 39 cases of maculopapular rash, five cases of urticaria, four cases of Stevens-Johnson syndrome, and two cases each of pustular rash and angioedema, respectively [81c].

Tuberculosis and HIV co-infected patients having the NVP concentrations <3000 ng/mL were found to be a risk factor for virological failure [82C].

A retrospective study showed the incidence of NVP toxicity in children who were switched from EFV to NVP compared with that of children who had started NVP-based antiretroviral therapy directly. Children in the switched group who developed NVP toxicity had higher mean CD4 cell counts than children in treatment naïve group with NVP [83c].

Rilpivirine [SEDA-35, 521; SEDA-36, 423; SEDA-37, 340]

A phase 3, 96-week, randomized, open-label, international, non-inferiority study was conducted in 799 patients who received RPV/FTC/TDF or EFV/FTC/TDF. At week 96, trial completion RPV/FTC/TDF was non-inferior to EFV/FTC/TDF [HIV-1 RNA <50 copies/mL: 77.9% vs. 72.4%, respectively]. Compared with EFV/FTC/TDF, RPV/FTC/TDF group had fewer AE-related discontinuations (3.0% vs. 11.0%), significantly fewer AEs. Overall, the 96-week RPV/FTC/TDF treatment demonstrated non-inferior in efficacy and tolerability than EFV/FTC/TDF [84C].

An open-label, single-arm study at two public sexual health clinics and two hospital emergency departments in urban Australia reported the safety of co-formulated FTC, RPV, and TDF as a 3-drug, single-tablet regimen for post-exposure prophylaxis (PEP) in men who have sex with men (MSM). Single-tablet FTC-RPV-TDF once daily for 28 days were given to 100 HIV-uninfected PEP in MSM. PEP completion was 92%; premature cessation resulted from loss to follow-up (6%), AEs (1%), or study burden (1%). No participant was found to acquire HIV through week 12. Eighty-eight participants experienced at least one clinical AE; 4 patients had Grade 3 AEs or higher, possibly attributable to study drug. Fifty-six participants experienced at least one laboratory AE; 4 had AEs of Grade 3 or higher, due to the single tablet [85c].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: PROTEASE INHIBITORS [SED-15, 2586; SEDA-32, 541; SEDA-33, 593; SEDA-34, 461, SEDA-35, 522; SEDA-36, 423; SEDA-37, 340]

Atazanavir

Observational Study

Ritonavir-boosted atazanavir (ATV/r) is a relatively well-tolerated antiretroviral drug. A retrospective analysis of routine TDM of ATV carried out as day-by-day clinical practice for the optimization of drug dosing in HIV-infected 240 adult patients between January 2010 and May 2013 participated in the study. HIV-infected patients treated with ATV for at least 3 months and with one assessment of ATV plasma were included in the study. Patients were at 901 ± 870 days of therapy with ATV, mainly treated at the conventional ATV/r dosage 300/100 mg q.d. (68%), given concomitantly with tenofovir-based antiretroviral regimens. One hundred forty-seven (61%) out of the 240 HIV-positive patients enrolled in the present study experienced hyperbilirubinemia of Grade ≥1. Overall,

55 out of the 240 HIV-positive patients developed dyslipidemia, namely hypercholesterolemia ($n=26$) or hypertriglyceridemia ($n=45$). Patients with dyslipidemia had ATV concentrations significantly higher as compared with patients with no ATV-related complications [86C].

An international phase 3 double-blind and double-dummy study was conducted in 692 HIV-1-infected adults. Patients had estimated eGFR of at least 70 mL/min and genotypic sensitivity to ATV, FTC, and TDF. Eligible patients were randomized 1:1 to receive either COBI ($n=344$) or RTV ($n=348$) and matching placebo, each administered once daily with ATV plus FTC/TDF. After week 48, study visits occurred every 12 weeks until week 144. At week 144, a small increase in serum creatinine (median change from baseline +0.13 vs. +0.07 mg/dL) and a corresponding decrease in eGFR (median change −15.1 vs. −7.5 mL/min) were observed in both groups. Seven patients (2.0%) in each group developed proximal renal tubulopathy (PRT). In 5 of the 7 patients in the COBI group and 6 of the 7 patients in the RTV group, PRT occurred after week 48. In the COBI-containing regimen, reversibility of renal laboratory abnormalities was seen in 6 of the 7 patients after discontinuation of the study drug [87C].

An open-label, single-center, single-dose, crossover study, randomized study reported in 64 healthy subjects to one of eight treatment sequences, in a single center in the United States between 25 April 2013 and 20 June 2013. Subjects were randomized equally to one of eight treatment sequences in which treatments were administered over four or five study periods. Subjects received a 300 mg ATV capsule co-administered with a 150 mg COBI tablet or an FDC tablet of ATV/COBI (300/150 mg) following a light meal (treatment A or B, respectively), according to the assigned treatment sequences on day 1 (period 1) and day 8 (period 2). On day 15 (period 3) and day 22 (period 4), subjects received a 300 mg ATV capsule co-administered with a 150 mg COBI tablet or an FDC tablet of ATV/COBI (300/150 mg) under fasted conditions (treatment C or D, respectively). Thirty-two subjects were assigned to receive the ATV/COBI (300/150 mg) FDC tablet following a high-fat meal (treatment E) on day 29 (period 5). Study drugs were administered in the morning within approximately 5 min after a meal in periods 1, 2 and 5, or after fasting for approximately 10 h in periods 3 and 4. Overall, the most common AEs were dizziness (6.3%), abdominal discomfort (4.7%), musculoskeletal chest pain (4.7%) and nasopharyngitis (4.7%); all were mild to moderate in severity and had resolved by study completion. For laboratory abnormalities, 6 subjects (9.4%) experienced elevations in total bilirubin, with the highest observed in the subject who received duplicate doses of study drugs on study day 1. Other laboratory abnormalities that occurred in two or more subjects included: creatine kinase ($n=2$, 3.1%), low leukocytes ($n=4$, 6.3%), low neutrophils ($n=5$, 7.8%), urinary red blood cells ($n=2$, 3.1%) and urinary white blood cells ($n=7$, 10.9%) [88c].

Norethindrone-based progestin-only contraceptives exhibited greater drug exposure, when co-administered with RTV-boosted ATV regimen in women infected with HIV [89c].

Ritonavir (r)

In Nigeria, atazanavir/ritonavir (ATV/r) is the preferred protease inhibitor (PI) as it cause fewer side effects than lopinavir/ritonavir (LPV/r). A recent study evaluated the immunologic and virologic effects of switching 400 patients to an ATV/r-containing regimen from LPV/r at the Lagos University Teaching Hospital in Nigeria. Two hundred and fifty-five patients were virologically suppressed on LPV/r prior to switch, 107 patients were switched due to failure on a first-line line of treatment, 28 were on saquinavir/ritonavir (SQV/r)-based regimen, and 10 were unintentionally switched. Ninety-nine patients evaluated for 12 months after ATV/r switch and only two showed detectable viral load. Twenty-six patients from this group did not show any viral load after 24 months of treatment. In a comparison group of 576 patients who were maintained on LPV/r-based regimens, 359 patients had undetectable viral loads after 24 months of treatment. The study concluded that there was no significant difference between LPV/r and ATV/r in virologic failure [90C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INHIBITORS OF HIV FUSION [SEDA-33, 598; SEDA-34, 464; SEDA-35, 525; SEDA-36, 428; SEDA-37, 341]

Enfuvirtide

Participants were enrolled between March 2008 and May 2011 at 62 centers in the United States, with follow-up through 48 weeks. Of 720 potential participants screened for resistance testing, 360 patients were randomly assigned and 337 participants completed the study. Patients received 600 mg of darunavir with 100 mg of RTV, 90 mg of enfuvirtide (ENF) by subcutaneous injection, 200 mg of TMC125 (ETR), 400 mg of RAL, and 500 mg of tipranavir with 200 mg of RTV. The most common antiretroviral regimen was RAL plus RTV-boosted darunavir with ENF, ETR (56%); in the add-NRTIs group, 81% of participants used TDF plus FTC (or 3TC), Thirty-seven (21%) and 44 (24%) participants in the omit- and add-NRTIs groups, respectively, had a

serious AE. Three serious AEs in the omit-NRTIs group and 13 in the add-NRTIs group were related to antiretroviral therapy. After treatment initiation, there were no deaths in the omit-NRTIs group and 6 deaths in the add-NRTIs group. The causes of death were as follows: heart failure in a participant with lymphoma (9 weeks on study treatment), Listeria meningitis (17 weeks), renal failure (21 weeks), sepsis with liver failure (25 weeks), progressive multifocal leukoencephalopathy (30 weeks), and abdominal bleeding in a participant with HCV and cirrhosis (52 weeks). Three deaths occurred during the pre-randomization screening period [91C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INTEGRASE INHIBITORS [SEDA-33, 599; SEDA-34, 465; SEDA-35, 525; SEDA-36, 428; SEDA-37, 342]

Dolutegravir

The side effect profiles of DTG are similar to RTV and have been found to be well tolerated. DTG has a long plasma half-life and is suitable for once daily use without the need for a boosting agent. The clinical effectiveness of DTG is reviewed here [92R]. Clinical effectiveness of DTG in the treatment of HIV was also reviewed [92R]. Clinical effectiveness of DTG in the treatment of HIV/AIDS has been reviewed and the side effect profiles of DTG are similar to RTG [93R].

Observational Studies

An open-label, non-randomized, multicenter phase I/II study of HIV-infected, treatment-experienced children between 4 weeks and <18 years in age was conducted. DTG dose was prescribed using the weight of the patients: 50 mg for children >=40 kg, 35 mg for children between 30 and 40 kg, and DTG was available as 50, 25 and 10 mg tablets. Most frequent reported events were as follows: gastrointestinal diarrhea in 8 (35%), decrease appetite in 7 (30%), abdominal pain in 5 (21%) and nausea in 3 (13%); respiratory cough in 13 (56%), pharyngeal pain in 8 (35%), nasal congestion in 7 (30%) and sinus congestion in 4 (17%); musculoskeletal extremity pain in 6 (26%), arthralgia in 3 (13%) and back pain in 3 (13%) and general fever in 7 (30%), lymphadenopathy in 6 (26%), headache in 6 (26%) and dizziness in 4 (17%). None of these were considered related to DTG and are common events among adolescents with other illnesses. There were two Grade 3 clinical events: gastritis and deep vein thrombosis, not considered related to DTG that resolved without DTG discontinuation. Two subjects experienced Grade 3 laboratory abnormalities; one patient developed unconjugated bilirubin elevation while on ATV [94c].

Raltegravir (RTG)

Observational Study

This review provide an overview of RTG role in the management of HIV-1 infection, highlighting its key pharmacokinetic and pharmacodynamic properties. Due to RTGs' tolerability, efficacy, few drug-to-drug interactions and its weak genetic barrier to resistance, the authors' are of the opinion that RTG should be administered twice daily and with fully active companion antiretrovirals [95R].

RTG is the first human immunodeficiency virus (HIV) integrase strand transfer inhibitor approved by the US FDA and the European Medicines Agency (EMA) for treatment of HIV infection in children. A new pediatric formulation of RTG has been introduced with 25-mg and 100-mg tablets that can be chewed or swallowed whole [96L].

A 23-year-old man was admitted with severe thrombocytopaenia. He was diagnosed with acute HIV infection and HIV-associated thrombocytopaenia. Although his thrombocytopaenia improved immediately with short-term dexamethasone therapy, this effect was not sustained after cessation of therapy. Antiretroviral therapy including RTG was initiated, and the patient recovered from severe thrombocytopaenia within several days. No significant AES reported [97c].

The data on efficacy and safety of integrase strand transfer inhibitors in antiretroviral-naive HIV patients and the strengths and weaknesses of drugs within this class are reviewed here. Integrase strand transfer inhibitors cause a rapid drop in viral load, exhibit very low drug interactions (except elvitegravir/ COBI), and have low pill burden and convenient dosing frequency. RTG was also superior to atazanavir/ritonavir and darunavir/ritonavir in the ACTG 5257 study for the combined virologic/tolerability endpoint. Elvitegravir/COBI/FTC/TDF was non-inferior to efavirenz/FTC/TDF and to atazanavir/ritonavir plus FTC/TDF in terms of confirmed virologic response in the GS-US-236-0102 and GS-US-236-0103 studies, respectively. DTG showed non-inferiority compared to RTG in the SPRING-2 study and was superior to efavirenz and darunavir/ritonavir in the SINGLE and FLAMINGO trials, respectively [98R].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: CHEMOKINE RECEPTOR CCR5 ANTAGONISTS [SEDA-33, 600; SEDA-34, 465; SEDA-35, 528; SEDA-36, 430; SEDA-37, 343]

Maraviroc

Observational Study

An open-label safety study of MVC was conducted at 262 sites worldwide in 1032 R5 HIV-positive treatment-experienced patients. Safety data were analyzed overall

and by subgroup based on ARV combination [MVC+ optimized background therapy (OBT), MVC±OBT + DRV/r, MVC±OBT+RAL, MVC±OBT+RAL+DRV/r, MVC±OBT+RAL+ETV±DRV/r]. Most (90.3%) AEs (AEs) were of mild or moderate severity with few Grade 3/4 events, discontinuations, or temporary discontinuations/dose reductions due to AEs or serious AEs [99C].

The role of CCR5 in HIV-1 infection, the development of the CCR5 antagonist MVC, its pharmacokinetics, pharmacodynamics, drug–drug interactions, and the implications of these interactions on treatment outcomes, including viral mutations and drug resistance, and the mechanisms associated with the development of resistance to MVC are reviewed [100R].

DRUGS ACTIVE AGAINST INFLUENZA VIRUSES: ION CHANNEL INHIBITORS [SED-15, 105, 3051; SEDA-32, 544; SEDA-33, 269, 602; SEDA-34, 467; SEDA-35, 529; SEDA-36, 430; SEDA-37, 344]

Amantadine

A meta-analysis was performed in palliative care patients with fatigue that is common in patients with an incurable disease (terminal illness) such as advanced cancer, HIV/AIDS, multiple sclerosis, amyotrophic lateral sclerosis, or cardiac, lung or kidney failure. Data from 18 drugs and 4696 participants were included in the study. Treatment results pointed to weak and inconclusive evidence for the efficacy of amantadine, pemoline and modafinil in multiple sclerosis and for carnitine and donepezil in cancer-related fatigue. Adverse reactions were mild and had little or no impact [101M].

Study reported the effect of amantadine on irritability in persons in the post-acute period after traumatic brain injury (TBI) [102c].

DRUGS ACTIVE AGAINST INFLUENZA VIRUSES: NEURAMINIDASE INHIBITORS [SED-15, 2436; SEDA-32, 544; SEDA-33, 601; SEDA-34, 466; SEDA-35, 528; SEDA-36, 431; SEDA-37, 344]

Oseltamivir (Tamiflu)

Influenza is a seasonal disease affecting both adults and children. Influenza, if untreated could lead to severe lower respiratory tract infections, acute otitis media, rhinosinusitis, febrile seizures, dehydration or encephalopathy. Oseltamivir is a well-studied drug for the treatment of the influenza virus for both the treatment and prevention of infection. Oseltamivir treatment should only be recommended in severe influenza cases where it is confirmed by reliable laboratory tests [103c].

A 15-year-old Japanese female with influenza infection developed abnormal psychiatric symptoms after administration of standard doses of oseltamivir. She had no history of neurological illness, had never previously taken oseltamivir, and had not developed psychiatric reactions during previous influenza infection. Her delirium-like symptoms, including insomnia, visual hallucinations, and a long-term memory deficit, disappeared after cessation of oseltamivir and administration of benzodiazepine. A detailed assessment was performed, including neurological examination (electroencephalogram, brain magnetic resonance imaging, single photon emission computed tomography with 99mTc-ethyl cysteinate dimer and with 123I-iomazenil, cerebrospinal fluid analysis and glutamate receptor autoantibodies), drug level determination and simulation, and genetic assessment (OAT1, OAT3, CES1, Neu2). Abnormal slowing in the electroencephalogram, which is characteristic of influenza-associated encephalopathy, was not observed in repeated recordings. The serum level determination of active metabolite Ro 64-0802 determined at 154 h after final dosing of oseltamivir was higher than the expected value, suggesting delayed elimination of Ro 64-0802. Thus, abnormal exposure to Ro 64-0802 might have contributed, at least in part, to the development of neuropsychiatric symptoms in this patient. The score on Naranjo's ADR probability scale was 6. Mutation of c.122G>A (R41Q) in the sialidase Neu2 gene, increased CSF glutamate receptor autoantibodies, and limbic GABAergic dysfunction indicated by SPECT with 123I-iomazenil were found as possible contributory factors to the CNS side effects [104S].

In an in vivo animal study, mice were infected with influenza A virus. The infected mice were then orally administered with polyphylla saponin I and oseltamivir twice a day for 5 days. In vitro studies in MDCK cells have shown that polyphylla saponin I (6.25, 12.5, 25 and 50 μg/mL) and oseltamivir (40 μg/mL) could inactivate the influenza virus. Studies in mice showed that polyphylla saponin I (5 and 10 mg/kg), and oseltamivir (3 mg/kg) reduced viral hemagglutination titer, improved the pathology of lung, and increased the survival time from 8.5±0.3 to 13.2±0.5 days. The experimental data suggests that the polyphylla saponin I may have antiviral activity on influenza A virus [105E].

OTHER DRUGS

Imiquimod [SED-15, 1718; SEDA-35, 530; SEDA-36, 431; SEDA-37, 344]

Dermatological Studies

A 38-year-old HIV-1-positive African woman established on cART presented with a 3-week history of a

large, tender hypertrophic ulcer on the left labium majus. She was commenced on acyclovir (400 mg TDS for 2 weeks), and a PCR swab of the ulcer was positive for HSV-2. The treatment was switched to valaciclovir 500 mg BD (for 3 weeks) and then 1 g BD (for 4 weeks). The ulcer persisted (still PCR positive for HSV-2) and a biopsy showed extensive ulceration with non-specific inflammatory changes. Further treatment with valganciclovir and topical foscarnet led to minimal improvement for 12 months. Topical imiquimod (three times a week) was commenced and within 2 months the ulcer had completely resolved without any noticeable side effects.

A 44-year-old man of West African origin presented with genital ulceration. The ulcers resolved after empirical acyclovir treatment. He was also diagnosed with HIV-2 and hepatitis B co-infection (CD4 60 cells/mm^3) but then defaulted care prior to starting cART. Three years later, he re-presented with a 6-month history of intermittently recurring genital ulceration of HSV. He had three painless hypertrophic ulcers on his scrotum and one on his penile shaft. Acyclovir 800 mg TDS, PCP and MAI prophylaxis and cART (Truvada, darunavir and ritonavir) were commenced. The ulcers were positive on PCR testing. After 4 weeks, the ulcers had fully healed and the acyclovir dose was reduced to 400 mg BD. Seven months later the genital ulceration recurred and acyclovir was increased (400 mg TDS). He was on cART with good adherence, CD4 200 cells/mm^3 and HIV-VL <50 copies/mL. The ulcers were again HSV-2 positive on PCR testing and showed no improvement after 4 weeks of acyclovir. Tests for other STIs including syphilis were negative. The drugs were switched to valaciclovir for 2 weeks, followed by topical foscarnet cream for 3 months. However, there was no improvement and the ulcer remained positive for HSV-2. A biopsy showed a nonspecific inflammatory infiltrate with no viral inclusions seen and no pathogens identified on staining. Administration of valganciclovir and topical foscarnet cream did not show any improvement in ulceration. Three times weekly topical imiquimod therapy healed the ulcers completely within 8 weeks of treatment. He suffered a recurrence several months later which also fully responded to a 2-week course of imiquimod [106c].

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References

[1] Caruso Brown AE, et al. Pharmacokinetics and safety of intravenous cidofovir for life-threatening viral infections in pediatric hematopoietic stem cell transplant recipients. Antimicrob Agents Chemother. 2015;59(7):3718–25 [c].

[2] Romani D, Brandán SA. Effect of the side chain on the properties from cidofovir to brincidofovir, an experimental antiviral drug against to Ebola virus disease. Arab J Chem. 2015; http://dx.doi.org/10.1016/j.arabjc.2015.06.030, in press [c].

[3] Melendez DP, Razonable RR. Letermovir and inhibitors of the terminase complex: a promising new class of investigational antiviral drugs against human cytomegalovirus. Infect Drug Resist. 2015;8:269–77 [r].

[4] Sano T. Safety and efficacy of foscarnet for preemptive therapy against cytomegalovirus reactivation following unrelated bone marrow transplantation. Jpn J Chemother. 2015;63(6):568–75 [c].

[5] Hu Y, Liu Y, Liu S, et al. Analysis of foscarnet-induced adverse drug reaction in Beijing area from 2008 to 2014. Chin Pharm J. 2015;50(18):1634–8 [C].

[6] Timperley A, Taha H, Das S. Management of cytomegalovirus retinitis in HIV infection in the era of highly active antiretroviral therapy. Int J STD AIDS. 2015;26(10):757–8 [A].

[7] Boeckh M, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. Ann Intern Med. 2015;162(1):1–10 [C].

[8] Chon WJ, et al. Use of leflunomide in renal transplant recipients with ganciclovir-resistant/refractory cytomegalovirus infection: a case series from the University of Chicago. Case Rep Nephrol Dial. 2015;5(1):96–105 [c].

[9] Mattioni S, et al. Assessment of the efficacy and safety of pre-emptive anti-cytomegalovirus (CMV) therapy in HIV-infected patients with CMV viraemia. Int J STD AIDS. 2015;26(5):306–12 [C].

[10] Mareri A, et al. Anti-viral therapy for congenital cytomegalovirus infection: pharmacokinetics, efficacy and side effects. Journal Matern Fetal Neonatal Med. 2016;29(10):1657–64 [R].

[11] Rao S, et al. Intravenous acyclovir and renal dysfunction in children: a matched case control study. J Pediatr. 2015;166(6). 1462–1468.e4, [C].

[12] Noska A, et al. The role of antiviral therapy in immunocompromised patients with herpes simplex virus meningitis. Clin Infect Dis. 2015;60(2):237–42 [c].

[13] Ueno S, et al. Good's syndrome with opportunistic infection of the central nervous system: a case report. BMC Neurol. 2015;15(1):1–4 [A].

[14] Gentry Iii JL, Peterson C. Death delusions and myoclonus: acyclovir toxicity. Am J Med. 2015;128(7):692–4 [A].

[15] Pachnio A, et al. Acyclovir therapy reduces the CD4+ T cell response against the immunodominant pp65 protein from cytomegalovirus in immune competent individuals. PLoS One. 2015;10(4):e0125287 [c].

[16] Ide N. An elderly patient presenting with abnormal penciclovir blood concentration increased by famciclovir at the usual dose: a case report. Jpn J Chemother. 2015;63(5):469–72 [A].

[17] Shen XJ. Effect of famciclovir combined with oxymatrine on T lymphocyte subsets in patients with chronic severe viral hepatitis B. World Chin J Digestol. 2015;23(18):2961–5 [c].

[18] Shah SA, Gulbis A, Wilhelm K. A case series using famciclovir in stem cell transplant recipients with valacyclovir hypersensitivity reactions. J Oncol Pharm Pract. 2015;21(4):305–9 [A].

[19] Wang G, et al. Cost-effectiveness analysis of lamivudine, telbivudine, and entecavir in treatment of chronic hepatitis B with adefovir dipivoxil resistance. Drug Des Devel Ther. 2015;9:2839–46 [c].

[20] Yang DH, et al. Tenofovir disoproxil fumarate is superior to lamivudine plus adefovir in lamivudine-resistant chronic hepatitis B patients. World J Gastroenterol. 2015;21(9): 2746–53 [c].

[21] Li BX, et al. Clinical effects of entecavir and adefovir dipivoxil in treatment of hepatitis B associated decompensated cirrhosis. World Chin J Digestol. 2015;23(21):3460–3 [c].

[22] Kim J, et al. Efficacy and safety of tenofovir in nucleos(t)ide-naïve patients with genotype C chronic hepatitis B in real-life practice. Int J Clin Pharm. 2015;37(6):1228–34 [C].
[23] Lu J, et al. Effect of Peg-interferon α-2a combined with adefovir in HBV postpartum women with normal levels of ALT and high levels of HBV DNA. Liver Int. 2015;35(6):1692–9 [c].
[24] Ilyas F, et al. Intraocular pressure rise in the course of peginterferon alpha-2a, ribavirin, and boceprevir therapy for hepatitis C. Can J Ophthalmol. 2015;50(6):e112–4 [c].
[25] Coilly A, et al. Multicenter experience with boceprevir or telaprevir to treat hepatitis C recurrence after liver transplantation: when present becomes past, what lessons for future? PLoS One. 2015;10(9):e0138091 [c].
[26] Shiraishi M, et al. Postmarketing surveillance of telaprevir-based triple therapy for chronic hepatitis C in Japan. Hepatol Res. 2015;45(13):1267–75 [c].
[27] Neukam K, Munteanu DI, Rivero-Juarez A, et al. Boceprevir or telaprevir based triple therapy against chronic hepatitis C in HIV coinfection: real-life safety and efficacy. PLoS One. 2015;10(4): e0125080 [C].
[28] Oze T, et al. The real impact of telaprevir dosage on the antiviral and side effects of telaprevir, pegylated interferon and ribavirin therapy for chronic hepatitis C patients with HCV genotype 1. J Viral Hepat. 2015;22(3):254–62 [c].
[29] Matsui K, et al. Does elevation of serum creatinine in patients with chronic hepatitis C under therapy of telaprevir mean renal impairment? Nephrology. 2015;20(11):843–8 [c].
[30] Morihara D, et al. Adjusting the starting dose of telaprevir according to renal function decreases adverse effects and affects the sustained virological response rate. Eur J Gastroenterol Hepatol. 2015;27(1):55–64.
[31] Kawano A, et al. Bacterial infection as an adverse effect of telaprevir-based triple therapy for chronic hepatitis C infection. Intern Med. 2015;54(6):567–72 [c].
[32] Verna EC, et al. Telaprevir- and boceprevir-based triple therapy for hepatitis C in liver transplant recipients with advanced recurrent disease: a multicenter study. Transplantation. 2015;99(8):1644–51 [c].
[33] Falcaõ EMM, et al. Cutaneous eruption due to telaprevir. Case Rep Dermatol. 2015;7(3):253–62 [A].
[34] Federico A, et al. Telaprevir may induce adverse cutaneous reactions by a T cell immune-mediated mechanism. Ann Hepatol. 2015;14(3):420–4 [c].
[35] Kawaguchi Y, et al. Efficacy and safety of telaprevir, pegylated interferon α-2b and ribavirin triple therapy in Japanese patients infected with hepatitis C virus genotype 1b. Intern Med. 2015;54(20):2551–60 [C].
[36] Zhou L, et al. Changes in mitochondrial toxicity in peripheral blood mononuclear cells during four-year administration of entecavir monotherapy in Chinese patients with chronic hepatitis B. Med Sci Monit. 2015;21:2058–63 [E].
[37] Hung CH, et al. Tenofovir versus entecavir in treatment of chronic hepatitis B virus with severe acute exacerbation. Antimicrob Agents Chemother. 2015;59(6):3168–73 [C].
[38] Huang M, et al. Comparison of the efficacy of tenofovir disoproxil fumarate and entecavir for initial treatment of patient with chronic hepatitis B in China. Int J Clin Exp Med. 2015;8(1):666–73 [c].
[39] Buti M, et al. Entecavir has high efficacy and safety in white patients with chronic hepatitis B and comorbidities. Eur J Gastroenterol Hepatol. 2015;27(1):46–54 [C].
[40] Masip M, et al. Prevalence and detection of neuropsychiatric adverse effects during hepatitis C treatment. Int J Clin Pharm. 2015;37(6):1143–51 [C].
[41] Saadoun D, et al. PegIFNα/ribavirin/protease inhibitor combination in severe hepatitis C virus-associated mixed cryoglobulinemia vasculitis. J Hepatol. 2015;62(1):24–30 [c].
[42] Jung E, et al. Tenofovir monotherapy versus tenofovir plus lamivudine or telbivudine combination therapy in treatment of lamivudine-resistant chronic hepatitis B. Antimicrob Agents Chemother. 2015;59(2):972–8 [C].
[43] Wu Q, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. Clin Gastroenterol Hepatol. 2015;13(6):1170–6 [C].
[44] Marcellin P, et al. Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. J Hepatol. 2015;62(1):41–7 [C].
[45] Zeuzem S. Efficacy and safety of faldaprevir, deleobuvir, and ribavirin in treatment-naive patients with chronic hepatitis C virus infection and advanced liver fibrosis or cirrhosis. Antimicrob Agents Chemother. 2015;59(2): 1282–91 [c].
[46] Noell BC, Besur SV, deLemos AS. Changing the face of hepatitis C management—the design and development of sofosbuvir. Drug Des Devel Ther. 2015;9:2367–74 [R].
[47] Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's Class A cirrhosis. Gastroenterology. 2015;148(4). 762–770. e2, [C].
[48] Kohli A, Kattakuzhy S, Sidharthan S, et al. Four-week direct-acting antiviral regimens in noncirrhotic patients with hepatitis C virus genotype 1 infection: an open-label, nonrandomized trial. Ann Intern Med. 2015;163(12):899–907 [C].
[49] Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir with velpatasvir in treatment-naive noncirrhotic patients with genotype 1 to 6 hepatitis C virus infection: a randomized trial. Ann Intern Med. 2015;163(11):818–26 [C].
[50] Leroy V, et al. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. Clin Gastroenterol Hepatol. 2015;13(11). 1993-2001.e2, [C].
[51] Wyles DL, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373(8):714–25 [C].
[52] Bourlière M, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15(4):397–404 [C].
[53] Gane EJ, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology. 2015;149(6). 1454–1461.e1, [C].
[54] Ruane PJ, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. J Hepatol. 2015;62(5):1040–6 [c].
[55] Majumdar A, Kitson MT, Roberts SK. Treatment of hepatitis C in patients with cirrhosis: remaining challenges for direct-acting antiviral therapy. Drugs. 2015;75(8):823–34 [R].
[56] Jafari A, et al. Safely treating hepatitis C in patients with HIV or hepatitis B virus coinfection. Expert Opin Drug Saf. 2015;14(5):713–31 [R].
[57] Sanford M. Simeprevir: a review of its use in patients with chronic hepatitis C virus infection. Drugs. 2015;75(2):183–96 [R].
[58] Smit C, et al. Effect of abacavir on sustained virologic response to HCV treatment in HIV/HCV co-infected patients, Cohere in Eurocoord. BMC Infect Dis. 2015;15(1):1–10 [C].
[59] Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr. 2015;70(5):515–9 [R].

[60] Post FA, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF in HIV-infected patients with mild-to-moderate renal impairment. J Acquir Immune Defic Syndr. 2015;68(3):310–3 [c].
[61] von Hentig N. Clinical use of cobicistat as a pharmacoenhancer of human immunodeficiency virus therapy. HIV/AIDS. 2015;8:1–16 [R].
[62] Nsagha DS, Pokam BT, Assob JC. HAART, DOTS and renal disease of patients co-infected with HIV/AIDS and TB in the South West Region of Cameroon. BMC Public Health. 2015;15(1):1040 [C].
[63] Kiertiburanakul S, et al. The use of pharmacogenetics in clinical practice for the treatment of individuals with HIV infection in Thailand. Pharm Pers Med. 2015;8:163–70 [c].
[64] Walmsley S, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr. 2015;70(5):515–9 [c].
[65] Bollen P, et al. Clinical pharmacokinetics and pharmacodynamics of dolutegravir used as a single tablet regimen for the treatment of HIV-1 infection. Expert Opin Drug Saf. 2015;14(9):1457–72 [R].
[66] Ciaffi L, et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. AIDS. 2015;29(12):1473–81 [C].
[67] Podlekareva D, et al. Changing utilization of stavudine (d4T) in HIV-positive people in 2006–2013 in the EuroSIDA study. HIV Med. 2015;16(9):533–43 [M].
[68] Parkes Ratanshi R, et al. Development of severe anemia and changes in hemoglobin in a cohort of HIV-infected Ugandan adults receiving zidovudine-, stavudine-, and tenofovir-containing antiretroviral regimens. J Int Assoc Provid AIDS Care (JIAPAC). 2015;14(5):455–62 [C].
[69] Bezabhe WM, et al. Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: a prospective cohort study from Ethiopia. Drug Saf. 2015;38(7):629–39 [C].
[70] Saez-Llorens X, et al. A randomized, open-label study of the safety and efficacy of switching stavudine or zidovudine to tenofovir disoproxil fumarate in HIV-1-infected children with virologic suppression. Pediatr Infect Dis J. 2015;34(4):376–82 [c].
[71] Quesada PR, et al. Incidence and risk factors for tenofovir-associated renal toxicity in HIV-infected patients. Int J Clin Pharm. 2015;37(5):865–72 [C].
[72] Coppolino G, et al. The case of chronic hepatitis B treatment with tenofovir: an update for nephrologists. J Nephrol. 2015;28(4):393–402 [R].
[73] Kryst J, et al. Efavirenz-based regimens in antiretroviral-naive HIV-infected patients: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2015;10(5):e0124279 [R].
[74] Abah IO, et al. Incidence and predictors of adverse drug events in an African cohort of HIV-infected adults treated with efavirenz. Germs. 2015;5(3):83–91 [C].
[75] Waters L, et al. Switching safely: pharmacokinetics, efficacy and safety of switching efavirenz to maraviroc twice-daily in patients on suppressive antiretroviral therapy. Antivir Ther. 2014;20(2):157–63 [c].
[76] Frapsauce C, et al. Impaired sperm motility in HIV-infected men: an unexpected adverse effect of efavirenz? Hum Reprod. 2015;30(8):1797–806 [C].
[77] Gaida R, Truter I, Grobler C. Efavirenz: a review of the epidemiology, severity and management of neuropsychiatric side-effects. S Afr J Psychiatr. 2015;21(3):94–7 [R].
[78] Kurz M, et al. Etravirine: a good option for concomitant use with chemotherapy for Hodgkin's lymphoma. Int J STD AIDS. 2015;26(3):212–4 [c].
[79] Vingerhoets J, et al. Efficacy of etravirine combined with darunavir or other ritonavir-boosted protease inhibitors in HIV-1-infected patients: an observational study using pooled European cohort data. HIV Med. 2015;16(5):297–306 [C].
[80] Casado JL, et al. Efficacy and pharmacokinetics of the combination of etravirine plus raltegravir as novel dual antiretroviral maintenance regimen in HIV-infected patients. Antiviral Res. 2015;113:103–6 [c].
[81] Pawar MP, et al. Nevirapine: most common cause of cutaneous adverse drug reactions in an outpatient department of a tertiary care hospital. J Clin Diagn Res. 2015;9(11):FC17–20 [c].
[82] Bhatt NB, et al. Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship. J Antimicrob Chemother. 2015;70(1):225–32 [C].
[83] Sanjeeva GN, et al. Nevirapine-related adverse events among children switched from efavirenz to nevirapine as compared to children who were started on nevirapine-based antiretroviral therapy directly. AIDS Care. 2015;27(5):655–9 [c].
[84] van Lunzen J, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS. 2016;30(2):251–9 [C].
[85] Foster R, et al. Single-tablet emtricitabine-rilpivirine-tenofovir as HIV postexposure prophylaxis in men who have sex with men. Clin Infect Dis. 2015;61(8):1336–41 [c].
[86] Gervasoni C, Meraviglia P, Minisci D, et al. Metabolic and kidney disorders correlate with high atazanavir concentrations in HIV-infected patients: is it time to revise atazanavir dosages? PLoS One. 2015;10(4):e0123670 [C].
[87] Gallant JE, et al. Cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results. J Acquir Immune Defic Syndr. 2015;69(3):338–40 [C].
[88] Sevinsky H, et al. A randomized trial in healthy subjects to assess the bioequivalence of an atazanavir/cobicistat fixed-dose combination tablet versus administration as separate agents. Antivir Ther. 2015;20(5):493–500 [c].
[89] DuBois BN, et al. Increased exposure of norethindrone in HIV+ women treated with ritonavir-boosted atazanavir therapy. Contraception. 2015;91(1):71–5 [c].
[90] Akanmu AS, et al. Immunological and virological outcomes of patients switched from LPV/r to ATV/r-containing second-line regimens. Curr HIV Res. 2015;13(3):176–83 [C].
[91] Tashima KT, et al. HIV salvage therapy does not require nucleoside reverse transcriptase inhibitors a randomized, controlled trial. Ann Intern Med. 2015;163(12):908–17 [C].
[92] Das S, Taha H, Das A. Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS. Infect Drug Resist. 2015;8:339–52 [R].
[93] Taha H, Das A, Das S. Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS. Infect Drug Resist. 2015;8:339–52 [R].
[94] Viani R, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents. Pediatr Infect Dis J. 2015;34(11):1207–13 [c].
[95] Calcagno A, D'Avolio A, Bonora S. Pharmacokinetic and pharmacodynamic evaluation of raltegravir and experience from clinical trials in HIV-positive patients. Expert Opin Drug Metab Toxicol. 2015;11(7):1167–76 [R].
[96] Blonk MI, et al. Dose optimization of raltegravir chewable tablets in a 4-year-old HIV-infected child. Clin Infect Dis. 2015;61(2):294–5 [L].
[97] Aoki A, et al. A case of severe thrombocytopaenia associated with acute HIV-1 infection. Int J STD AIDS. 2015;26(3):209–11 [c].
[98] D'Abbraccio M, et al. Efficacy and tolerability of integrase inhibitors in antiretroviral-naive patients. AIDS Rev. 2015;17(3):171–85 [R].
[99] Lazzarin A, et al. The maraviroc expanded access program—safety and efficacy data from an open-label study. HIV Clin Trials. 2015;16(1):10–21 [C].

[100] Kanmogne G, Woollard S. Maraviroc: a review of its use in HIV infection and beyond. Drug Des Devel Ther. 2015;9:5447–68 [R].
[101] Mücke M, et al. Pharmacological treatments for fatigue associated with palliative care cochrane database of systematic reviews. Cochrane Database Syst Rev. 1996;5: CD006788 [M].
[102] Hammond FM, et al. Amantadine effect on perceptions of irritability after traumatic brain injury: results of the amantadine irritability multisite study. J Neurotrauma. 2015;32(16):1230–8 [c].
[103] Esposito S, Principi N. Oseltamivir for influenza infection in children: risks and benefits. Expert Rev Respir Med. 2016;10:79–87 [c].
[104] Morimoto K, et al. Analysis of a child who developed abnormal neuropsychiatric symptoms after administration of oseltamivir: a case report. BMC Neurol. 2015;15(1):1–5 [S].
[105] Pu X, et al. Polyphylla saponin I has antiviral activity against influenza A virus. Int J Clin Exp Med. 2015;8(10):18963–71 [E].
[106] McKendry A, Narayana S, Browne R. Atypical presentations of genital herpes simplex virus in HIV-1 and HIV-2 effectively treated by imiquimod. Int J STD AIDS. 2015;26(6):441–3 [c].