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Antiviral Drugs

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Key to abbreviations and alternative names of some antiviral drugs

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

DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS

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

Observational Studies

Topical cidofovir treatment in herpes simples virus infections resulted in irreversible acute kidney injury [1A]. A 58-year-old man underwent a matched unrelated donor (MUD) stem cell transplant for secondary myelodysplastic syndrome. His conditioning regimen consisted of busulfan, fludarabine, and antithymocyte globulin. The patient received oral valganciclovir during the peritransplantation phase at a dose of 900 mg twice daily for CMV prophylaxis, and prophylactic valacyclovir was initiated on day 1. The patient was readmitted within 2 weeks of his initial hospital discharge with neutropenic fever, worsening mucositis, and acute cutaneous graft-versus-host disease (GVHD). The patient was treated with intravenous (IV) acyclovir at 5 mg/kg followed by antiviral therapy containing 5% cidofovir administered as oral gel. The patient's creatinine had increased to 1.8 mg/dL prior to the initiation of topical cidofovir. The frequency of administration of topical cidofovir was increased to three times daily, and the dose of IV acyclovir was adjusted to 5 mg/kg every 12 hours. Despite 8 days of therapy with both topical cidofovir and IV acyclovir, the oral lesions persisted; both agents were discontinued, and dose-adjusted foscarnet was initiated, and he developed progressive oliguric acute kidney injury (AKI). While receiving cidofovir therapy, the patient developed glucosuria (≥1000 mg/dL), proteinuria and hypouricemia, an indication of proximal tubule injury. Intermittent hemodialysis began approximately 2 weeks after initial treatment with high-dose acyclovir and topical cidofovir. His post transplantation course was complicated by grade IV acute cutaneous GVHD, multiple infections, acute liver injury, and persistent oral herpes simplex virus (HSV) infection. Based on the Naranjo adverse drug reaction (ADR) probability scale, it is possible that topical cidofovir was the cause of AKI in this patient.

A 52-year-old man with a history of small lymphocytic lymphoma underwent an MUD stem cell transplant. His conditioning regimen included fludarabine, cyclophosphamide, rituximab, and antithymocyte globulin. The patient had normal renal function before undergoing transplantation. He was given oral valganciclovir (900 mg) twice daily during the peritransplantation phase for CMV prophylaxis, and prophylactic valacyclovir was initiated on day 1. Patient was readmitted with perianal lesions that were positive for HSV, and the valacyclovir oral dose was increased to 1 g three times daily. Later valacyclovir was discontinued, and 44 mg/kg of foscarnet was administered IV every 8 hours and the patient had improved kidney functions. On the basis of these case reports, the authors recommend caution when

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using topical cidofovir in patients who have the potential for high systemic absorption that could affect renal function.

A 67-year-old female was referred for ophthalmologic monitoring while receiving IV cidofovir treatment for extensive recurrent laryngotracheal papillomatosis. She underwent three laser excisions with intralesional injections of cidofovir (75 mg/mL). Due to the extension of the lesion, she was treated with IV cidofovir (dose: 4 mg/kg) every 2 weeks. The patient developed mild bilateral anterior uveitis without iridocapsular synechiae. The patient's vision decreased and the IV cidofovir was discontinued. The authors suspected that ocular hypotonia due to cidofovir was caused by lesion of the nonpigmented ciliary epithelium [2A].

The current therapy for the treatment of CMV retinitis including its limitation by drug toxicity and antiviral resistance has been reviewed [3r].

Respiratory papillomatosis patients were treated with 7.5 mg/mL of cidofovir in adjuvant therapy. Thirty one adult patients were treated with the drug and 26 (83.9%) patients showed good response and 19 cured of respiratory papillomatosis. Six patients developed dysplasia during the treatment with cidofovir [4c].

Dermatological Studies

Plantar warts are benign lesions produced by the human papillomavirus (HPV) [5c]. A retrospective observational study was reported in patients with plantar warts. Patients received treatment with cidofovir cream between July 2008 and July 2011. Patients used 1% or 3% cidofovir cream, with or without occlusion, and once or twice a day for 4–40 weeks. Study was conducted in 35 patients between the ages of 6 to 55 years. In 19 patients (54.3%), there was total disappearance of the lesions, in 9 (25.7%), the response was partial, with a reduction in the number and/or size of the warts but without complete disappearance, and seven patients showed no response. Only two patients (5.7%) reported local irritation.

A 55-year-old man with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection presented with new lesions on his scrotum and perianal area. He was treated with darunavir (DRV), ritonavir (RTV), FTC/tenofovir (TDF), and trimethoprim-sulfamethoxazole. The patient was treated for HSV with a high-dose of oral acyclovir, valacyclovir, and famciclovir. However, the lesions increased, and a biopsy confirmed the original diagnosis of verrucous HSV. Given concern for acyclovir-resistant HSV, oral therapy was discontinued, and IV cidofovir treatment was started. Cidofovir (IV) caused elevations in serum creatinine levels and IV was discontinued. Intralesional cidofovir was administered every other week, and the patients lesions improved with 6 treatments [6A].

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

Observational Study

A 42-year-old female solid organ transplant recipient underwent a double lung transplantation for cystic fibrosis. The recipient was CMV-seronegative and received a graft from a CMV-seropositive donor. Two months post-transplant, the patient developed CMV infection, while treatment with IV ganciclovir failed due to antiviral drug resistance, and her viral load increased. The treatment was then switched to foscarnet, followed by a second course of CMV-specific immune globulins. The viral load was reduced within 2 weeks of treatment. However, the patient developed side effect of hypokalemia, hypomagnesaemia, impaired renal function, weight gain occurred due to generalized edema, loss of appetite, nausea, and fever. Due to the severity of side effects, foscarnet was discontinued, and leflunomide administered. Consequently, symptoms and electrolyte disturbances disappeared and kidney function recovered [7A].

A case of foscarnet resistance arising from a UL54 mutation after a short duration of foscarnet exposure was reported [8A]. A 46-year-old Caucasian man with acute myelogenous leukemia, underwent conditioning chemotherapy with fludarabine and melphalan, followed by a MUD allogeneic hemaptopoetic stem cell transplantation (HSCT). Despite continued broad-spectrum antimicrobial therapy, the patient developed recurrent neutropenic fevers. He was later diagnosed with human herpes virus -6 (HHV) and antiviral therapy was initiated with foscarnet 90 mg/kg/day. During foscarnet treatment, the patient developed a diffuse, maculopapular skin rash as well as gastrointestinal symptoms, including bloating, diarrhea, and nausea.

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

Observational Study

18-year-old female, immune-compromised was diagnosed with lupus nephritis and treated with prednisolone and cellcept. After 7 months, she was re-admitted with acute renal failure and showed mild edema in her lower limb. Her laboratory investigations revealed hemoglobin: 9 g/dL, WBCs $3.6 \times 10/\mu L$ [9], plate-let count $163 \times 109/\mu L$, serum creatinine 160 μmol/L and 24-hour urine protein 600 mg/day with normal serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and serum albumin. Patient received 1 g methylprednisolone IV and cellcept orally. She was detected with CMV infection, and ganciclovir 200 mg IV infusion twice daily was administered, but, after 5 days, the patient developed acute liver injury. A chest radiograph showed right

lower lobe consolidation and abdominal sonar revealed ascites. Ganciclovir was then stopped and liver function subsequently improved. The authors conclude from the study that ganciclovir may induce acute liver injury, thus it is important to monitor liver function while treating with ganciclovir.

A meta-analysis was conducted in patients, with lung or heart transplant recipients having CMV genotypic resistance. Patients infected with resistant CMV received valganciclovir for a median of seven months. Twelve percent (2/16) of patients were seen to be infected with ganciclovir-resistant virus upon their initial CMV infection. The other 87% (14/16) of patients were diagnosed with ganciclovir-resistant infections a median of 88 days. Ganciclovir resistance was diagnosed at a median of 8.5 months (range 5–21) post-transplant. The median duration of treatment with foscarnet-containing regimens was 38 days (range 17–210). Twenty-nine percent (4/14) of patients treated with a foscarnet-containing regimen failed to achieve serum virologic suppression. This group included three patients who died from CMV pneumonitis and one patient who recovered from pneumonitis but had persistent viremia for over seven months. The remaining 71% (10/14) of patients treated with a foscarnet-containing regimen achieved virologic suppression after a median of 23 days. Twenty percent (2/10) of patients who had virologic suppression subsequently died; one patient died of persistent CMV pneumonitis, and one patient died of allograft failure without evidence of active CMV infection. The other 80% (8/10) of patients who had virologic suppression suffered relapsing infections. Seventy-eight percent (11/14) of patients treated with foscarnet experienced toxicity, including renal injury (71%, 10/14), electrolyte abnormalities (71%, 10/14), and GI disturbances (28%, 3/14) (9 patients had multiple toxicities). One patient required hemodialysis. Foscarnet was discontinued due to toxicity in 36% (5/14) of patients. One patient treated with ganciclovir developed drug-related neutropenia that required treatment with granulocyte colony-stimulating factor [9c].

A 17-year-old boy diagnosed with CMV retinitis after chemotherapy for ALL had aggravated blurred vision, and CMV retinitis in both eyes. IV ganciclovir therapy (250 mg twice daily) was given, accompanied by intravitreous ganciclovir injection (0.1 mg twice weekly) and in 3 weeks the viral copies were reduced. Upon the completion of ganciclovir therapy, right retinal detachment developed, and surgery by vitrectomy and buckling with an encircling band procedure was performed. After surgery, the retinitis of the left eye improved without the retinal detachment [10A].

Neurological Studies

A 35-year-old woman infected with HIV received antiretroviral therapy for 7 weeks and ganciclovir for 3 months. She developed CMV retinitis with varied neurologic complaints. Addition of corticosteroids to anti-CMV therapy improved neurological complications [11c].

A retrospective cohort study was reported in CMV retinitis patients without HIV. Ten patients with a mean age of 33.7 years were included in the study. The patients received intravitreal ganciclovir injection (2 mg/0.1 mL) alone until quiescence. Thirteen eyes with active lesions (mean best-corrected visual acuity (BCVA) of 0.51 ± 0.41) received 5.54 ± 3.36 intravitreal ganciclovir injections and were healed in 1.81 ± 1.25 months. Immune recovery uveitis was observed in six eyes (33.33%) and retinal detachment developed in one eye. One eye had recurrence of uveitis 1 month after stopping ganciclovir injections. The rest of the patients had no recurrence follow-up for 12 months [12c].

A retrospective monocentric study was performed in 547 patients undergone allogeneic stem cell transplantation [13R]. One hundred and ninety patients were presented with CMV reactivation (35%). Eighty of 160 (50%) patients presented Ganciclovir-related neutropenia, 39 patients had grade III neutropenia and 41 patients had grade IV neutropenia. The average time between the introduction of ganciclovir and the occurrence of neutropenia was 35 days (range 2–216 days). All patients with grade III–IV neutropenia (80 patients in all) received granulocyte colony-stimulating factor. Twenty-seven patients (14%) developed a CMV disease (18 had disseminated gastrointestinal colitis, two pneumonitis and seven disseminated gastrointestinal and lung disease). In those 80 patients with ganciclovir-related neutropenia, 20 patients (25%) developed concomitant bacterial infections, and 16 patients (20%) developed concomitant fungal infections. Antiviral therapy may become a potentially life-threatening complication in patients with neutropenia and CMV activation because of the risk of bacterial or fungal infections.

Combination Study

A 51-year-old woman diagnosed with HIV-1 infection was under antiretroviral therapy (ART) with TDF 300 mg, FTC 200 mg, and efavirenz 600 mg, once daily. Ganciclovir 250 mg and fluconazole 150 mg were given 14 days prior to ART for loss of appetite and dysphagia. The patient underwent left nephrectomy, for unknown reasons. She was found to have pallor, with no signs of icterus, cyanosis, lymphadenopathy, clubbing and pedal edema. A drug interaction occurred between TDF and ganciclovir. TDF concentration increased and that led to acute kidney injury. Ganciclovir was discontinued and the patient's renal function recovered. In conclusion, patients who are on TDF-based ART should avoid co-administration of ganciclovir or valganciclovir. In case ganciclovir or valganciclovir are indicated for treatment of the co-infection, then TDF may be substituted with

any other appropriate antiretroviral drug, to preserve renal function [14c].

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

Acyclovir

Nervous System

A 69-year-old morbidly obese woman reported with mental status changes after she was treated with acyclovir for shingles. Acyclovir-induced acute renal injury induced her creatinine level to 7.4 mg/dL. Acyclovir was discontinued and the patient returned to the baseline [15A]. Neurotoxicity was reported in a 75-year-old lady on administration of acyclovir IV and on termination of acyclovir patient recovered from neurological abnormalities [16A].

Renal Function

A 45-year-old male with acute retinal necrosis treated with IV acyclovir developed nephrotoxicity. Switching to oral valacyclovir led to toxic hepatitis. Withdrawal of the drug resulted in return of renal and liver function to normal levels [17A].

A 58-year-old man with acquired immune deficiency syndrome on highly active antiretroviral therapy had severe thrombocytopenia when administered with acyclovir [18A].

Famciclovir

Renal Function

Efficacy and safety of famciclovir among herpes zoster patients with renal dysfunction has been reported [19c]. Fifty-three herpes zoster patients with a creatinine clearance (Ccr) of less than 90 mL/min, including nine patients treated with hemodialysis were included in the study. Famciclovir was administered to each individual according to their Ccr. No ADR were reported in the participants. Famciclovir did not alter the Ccr and did not have any AEs on renal function after herpes treatment.

Skin Lesions

Three cases of the use of famciclovir for recurrent herpes-associated erythema multiforme have been reported [20A]. A 50-year-old Caucasian woman with HSV 2 reported with herpes-associated erythema multiforme (HAEM). Mycophenolate mofetil, cyclosporine, methotrexate, adalimumab, IV immunoglobulin (IVIg), valacyclovir, acyclovir, doxycycline, hydroxychloroquine, oxycodone, hydroxyzine, and long-term prednisone were tried, but were unsuccessful. She had red, targetoid, confluent plaques, some eroded, on her face, trunk, and extremities without mucosal involvement. The patient was given methylprednisolone 125 mg IV followed by prednisone 60 mg and famciclovir 500 mg three times daily. Patient completely recovered in 19 months.

Patient 2 was a 65-year-old Caucasian woman treated for erythematous targetoid lesions on her right lower extremity. She was treated with doxycycline 100 mg twice daily for 2 weeks, but had no effect. She failed to recover even after treating with valaciclovir 1 g daily and desoximetasone 0.25% ointment twice daily for 5 days. The patient was free of the lesions after switching to famciclovir 500 mg daily.

Patient 3, a 27-year-old Latina woman with serologically proven HSV 1 and 2 had targetoid macules and bullae of her hands and elbows and erosions of her hard palate. After valacyclovir treatment failed she was put on prednisone, but her lesions recurred. She was Cushingoid with erythematous targetoid lesions with central bullae on her fingers and erosions on her hard palate. Biopsy confirmed she had HAEM. Following treatment with famciclovir 500 mg orally twice daily, her palatal and cutaneous erosions resolved completely.

Neurological

A 67-year-old man's control of trigeminal neuralgia with botulinum toxin A injections was lost after herpes labialis and herpes zoster infection. Famciclovir treatment improved patient's trigeminal neuralgia [21].

Valaciclovir

Sixty HIV type 1 (HIV-1)/HSV-2-coinfected adults on suppressive ART were included in the study, had placebo, low-dose valaciclovir (500 mg twice daily), or high-dose valaciclovir (1 g twice daily). Valaciclovir did not decrease systemic immune activation or inflammatory biomarkers in HIV-1/HSV-2-coinfected adults on suppressive ART. One of the low dose valaciclovir administered patients showed nausea (1/20) and in high dose reported with 1 episode of nausea, headache and diarrhea. Eight patients had adverse events related to the study drug (5 placebo, 1 low-dose, 2 high-dose) [22c]. Maternal valaciclovir did not show any effect on infant CMV acquisition or breast milk CMV viral loads [23C].

Comparative Studies

A randomized trial was conducted to compare the efficiency of valganciclovir and valaciclovir prophylaxis for prevention of CMV in renal transplantation. One hundred nineteen recipients with renal transplants (recipient or donor CMV-seropositive) were randomly allocated (1:1)

with valaciclovir (2 g, four times daily) or valganciclovir (900 mg daily) for 3 months. The incidence of CMV disease was 2% with valaciclovir and 5% with valganciclovir prophylaxis and more patients with valaciclovir prophylaxis developed biopsy-proven acute rejection of the renal transplant [24C].

Neurological

A 58-year-old female patient diagnosed with herpetic skin lesion treated with valaciclovir 500 mg daily. After 4 days she developed confusion, drowsiness, restless and talked irrelevantly. Electroencephalography (EEG) showed generalized slowing of brain wave activity but no epileptic discharges. Valaciclovir discontinued and she underwent dialysis. She regained normal sensorium on day 5 [25A].

Chronic fatigue syndrome presents with fatigue, low motivation, diminished mood, and reduced activity, with depression have been reported in a retrospective study in 15 adolescents and preteens treated with valaciclovir for viral disease [26c].

DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

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

A 64-year-old woman with chronic hepatitis B was given 3TC and adefovir, even-though her serum creatinine level was normal (<1.01 mg/dL). She developed bone pain due to Fanconi syndrome and osteomalacia and subsequently adefovir was discontinued. The patient medication was switched to entecavir, and she recovered from the syndrome [27c].

Urinary Tract

A 64-year-old man suffering polyarthralgia and bone pain had renal dysfunction, hypophosphatemia and increased levels of bone alkaline phosphatase. The patient was taking oral adefovir 10 mg/day and 3TC 100 mg/day. The patient's serum creatinine level had gradually increased after the initiation of adefovir dipivoxil administration for hepatitis B. An iliac bone biopsy revealed an abnormal increase in osteoid tissues. Reducing the dose of adefovir 10 mg to 5 mg and initiating the administration of eldecalcitol were effective for reducing proteinuria and glucosuria, and for ameliorated bone pain. This case reported to be a clinical course of hypophosphatemic osteomalacia caused by secondary Fanconi's syndrome for 8 years after administration of adefovir [28c].

A retrospective study was reported of 292 patients with Hepatitis B infection. Patients were on treatment with adefovir (10 mg/day) and 3TC (100 mg/day) for 6 months. During the duration of treatments, 28 (9.6%) patients developed renal impairment (defined as eGFR < 50 mL/min/1.73 m^2), and 73 (27.1%) developed hypophosphatemia, including 14 with persistent hypophosphatemia. Three of the 14 patients with persistent hypophosphatemia developed Fanconi's syndrome; their serum creatinine level was normal, but eGFR was lower. According to author's long-term treatment of hepatitis B with low-dose adefovir and 3TC could potentially cause renal impairment and hypophosphatemia [29c].

Adefovir dipivoxil and entecavir carry significant risks for the development of lactic acidosis and hepatic dysfunction, as discussed in this report [30A].

Antiviral therapy could lead to the emergence of mutant strains in chronic hepatitis B patients. In 147 patients, the antiviral resistance rate was 17% (25/147) for 3TC 5.44% (8/147) for adefovir, and 0.68% (1/147) for 3TC and adefovir. The change in nucleotide sequence in a particular (YMDD, YVDD, or YIDD) portion of the gene was responsible for the generation of resistant strains [31c].

Comparative Study

A phase 3, multicentred, randomized, double-blind, controlled trial compared the efficacy and safety of tenofovir disoproxil fumarate (TDF) with adefovir dipivoxil (ADV) in Chinese patients with chronic hepatitis B. A total of 509 patients, 202 hepatitis B e antigen (HBeAg) were received TDF 300 mg once daily with ADV 10 mg once daily for 48 weeks. The most common side effect reported was upper respiratory tract infection (8.2% in TDF group vs 6.7% in ADV group). Grade 3/4 ALT abnormalities were reported in TDF group (8.9%) compared with the ADV group (7.1%). The study is still continuing for 192 weeks with TDF 300 mg/daily to generate more safety data [32C].

A 50-year-old Chinese man with chronic hepatitis B and kidney transplantation received nucleos(t)ide analog therapy with sequential monotherapy and combination therapy. Patient received entecavir plus adefovir that resulted in decreased hepatitis B virus load, normal hepatic function, and stabilized CCr but resulted in multidrug resistance, subsequently the patient was administered with TDF plus entecavir for 8 weeks, which improved the hepatic function and Ccr. Compared with combination therapy with adefovir plus entecavir, TDF plus entecavir showed a potent antiviral effect for multidrug resistance and minimized renal injury [33A].

Nucleos(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease have been reviewed [34R].

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

Boceprevir

Acute Pancreatitis

A 43-year-old white man with hepatitis was treated for 17 weeks with peg-interferon, ribavirin and 13 weeks on boceprevir. The patient was hospitalized with epigastric pain that radiated to his back, along with nausea, and vomiting. The patient's hemoglobin level was 14 g/L, hematocrit was 43, leukocytes were 5700 mm^3, platelets 163 000 mm^3, amylase was 1209 IU/mL, lipase was 6462 IU/mL, aspartate aminotransferase was 34 IU/mL, alanine aminotransferase was 42 IU/mL, total Ca 9.0 mg/dL, ionized Ca 4.5 mg/dL, and triglycerides were 195 mg/dL. Peg-interferon, ribavirin and boceprevir were discontinued and the patient was placed under supportive care. In the author's opinion acute pancreatitis was associated with boceprevir [35c].

Patients with chronic hepatitis C when treated with boceprevir and telaprevir to peg-interferon α and ribavirin developed seizures [36c].

A case of red cell aplasia in a patient treated with ribavirin, peg-interferon alpha and telaprevir has been reported [37c].

HCV causing complexities in using boceprevir and other antiviral agents were also reviewed [38R].

Drug–Drug Interactions

A randomized, open-label study reported the pharmacokinetic interactions between boceprevir and RTV-boosted protease inhibitors (PI/r). The patients received boceprevir (800 mg, three times daily) for 6 days and then atazanavir (ATV) 300 mg once daily, lopinavir (LPV) 400 mg twice daily, or DRV 600 mg twice daily, each with RTV 100 mg on days 10–31, plus concomitant boceprevir on days 25–31. Boceprevir decreased the exposure of all RTV-boosted protease inhibitors with no unexpected AEs. The authors note that these drug–drug interactions may reduce the effectiveness of boceprevir co-administered with protease inhibitors [39c].

Telaprevir

Combination

Hepatitis C virus (HCV) reinfection occurs universally after liver transplantation, with accelerated cirrhosis rates of up to 30% within 5 years after liver transplantation. Dual antiviral therapy with pegylated interferon-2a (peg-IFN) and ribavirin (RBV) only reached sustained virological response rates of ~30% after liver transplantation. Telaprevir (TVR), boceprevir, and simeprevir and the NS5B polymerase inhibitor SOF, combination therapy offers a new therapeutic option for HCV-infected patients. Three cases were reported of TVR-based triple antiviral therapy in HCV genotype 1 reinfected patients after liver transplantation, a 57-year-old Caucasian female and a 43-year-old Caucasian male were therapy naïve, whereas, a 49-year-old Caucasian male patient was pretreated ineffectively. TVR of 750 mg thrice daily were administered over 12 weeks. Initial peg-IFN and RBV doses ranged from 135–180 μg/week and 800–1200 mg/day depending on the patient's body weight. Doses of peg-IFN and RBV were adapted to 90–135 μg/week and 400–800 mg/day after 2–12 weeks of protease inhibitor therapy. Dual therapy was continued for 36 weeks with total treatment duration of 48 weeks in the therapy naïve patients. After 4 weeks of TVR based therapy, viral load decreased and became negative in naïve patients in 6–8 weeks. The pretreated patient showed a negative viral load in week 4. In the pretreated patient a breakthrough was detected in week 24 and therapy was discontinued. Side effects reported were dysgeusia and anemia leading to erythropoietin application and blood transfusions [40c].

Severe anemia occurred in one-third of patients who received telaprevir-based triple therapy. Risk was greater in patients with diabetes and advanced liver fibrosis [41C].

A 65-year-old man developed a *Mycobacterium abscessus* pulmonary infection during treatment with telaprevir, peginterferon and ribavirin [42c].

Liver Function

Three patients were treated with telaprevir 750 mg/daily for 12 weeks after liver transplantation. Side effects with telaprevir treatment reported included dysgeusia and anemia leading to erythropoietin application and blood transfusions [40c].

A 50-year-old woman was presented with diffuse, intensely pruritic pink-red combination therapy with papules on her trunk and extremities 3 weeks after starting ribavirin, telaprevir, and interferon. She also had cervical lymphadenopathy, fever, eosinophilia, and transaminitis consistent with a severe drug reaction to telaprevir. Severe cutaneous eruptions secondary to telaprevir have resulted in fatal skin reactions, including drug reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [43c].

Skin

A case study reported in a 50-year-old woman with diffuse, intensely pruritic pink-red papules on her trunk and extremities 3 weeks after combination therapy with ribavirin, telaprevir, and interferon [43c].

Dermatological side effects in hepatitis C infected patients treated with a triple regimen PEG-interferon, ribavirin and telaprevir have also been reported [44c].

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

Observational Study

A 44-year-old man presented with a 3-month history of myalgia and progressive weakness. He received entecavir for 5 years for hepatitis B. Serum creatine kinase levels were elevated and muscle histopathology showed abundant T-lymphocyte infiltration of muscle fibers, symptoms reduced after withdrawing entecavir [45A].

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

Anemia is a well-known ribavirin (RBV)-related event in HCV therapy which is exacerbated by the addition of telaprevir and boceprevir. This retrospective study evaluated and compared RBV exposure and parameters able to influence decreased hemoglobin in a large population of patients treated with dual or triple therapy. Patients on triple therapy had higher RBV concentrations (3460ng/mL vs 1843 ng/mL). The proportion of patients with a >20 mL/min/1.73 m^2 decreased in eGFR at 12 weeks of treatment and was higher in patients on triple therapy, whereas it was 32%, 14%, and 5% for boceprevir, telaprevir, and dual therapy, respectively. There was no correlation between boceprevir and telaprevir concentrations and hemoglobin or eGFR decrease. Exacerbation of anemia in patients on triple therapy was related to higher RBV concentrations [46c].

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

Potential benefit of telbivudine on renal function as well as AEs were reviewed [47R].

A systematic review and meta-analysis showed that telbivudine was effective and safe for preventing intrauterine transmission of HBV [48R].

Neurological

Myopathy or neuropathy were associated with 3TC/telbivudine therapy in hepatitis B patients. A retrospective study was reported in six patients diagnosed with nucleotide analogues-associated myopathy or neuropathy and depletion of mitochondrial DNA that was responsible for the mitochondrial dysfunction in the 3TC/telbivudine-associated neuromyopathy [49c].

A long-term efficacy and safety study in a Chinese population showed that telbivudine as a monotherapy or as a combination therapy with adefovir dipivoxil in chronic hepatitis B patients had the same safety and efficacy [50C].

Faldaprevir

Faldaprevir, a first generation, second-wave protease inhibitor, in combination with a peg-interferon/RBV regimen, has been shown to increase treatment success and reduce the treatment duration [51R].

Sofosbuvir

The first global approval of SOF was granted by the US FDA on December 6, 2013 [52R]. SOF, is a potent first-in-class nucleoside inhibitor for treatment of HCV. The drug has low toxicity, a high resistance barrier, and minimal drug interactions with other HCV direct-acting antiviral agents, such as protease inhibitors or anti-NS5A agents. SOF is safe and can be used across different viral genotypes, disease stages, and special patient groups, such as those coinfected with HIV. When used in combination with ribavirin or another direct-acting antiviral agent, SOF has improved the HCV treatment spectrum for universal HCV antiviral therapy.

A multicenter, open-label, nonrandomized, uncontrolled phase 3 trial study was conducted in patients chronically infected with HCV receiving 400 mg of SOF administered orally once daily along with ribavirin orally twice daily for 24 weeks. Patients treated with SOF plus ribavirin had a rapid decrease in serum HCV within 2 weeks. Of the 223 patients who received at least 1 dose of the study drug, 7 (3%) discontinued treatment due to an adverse event. Fourteen patients (6%) experienced serious ADs. The grade 1 or 2 AEs were mostly fatigue, insomnia, nausea, and headache. Thirty-four patients (15%) had decreased hemoglobin less than 10 mg/dL with three patients reported with less than 8.5 mg/dL hemoglobin. Forty-three patients (19%) required dose reduction of ribavirin due to AEs. Overall, 32 patients (14%) experienced elevations of total bilirubin greater than 3.0 mg/dL [53C].

Simeprevir

A randomized, double-blind multicenter trial undertaken in 394 patients (aged $\geq$18 years) with chronic HCV genotype 1 infection and no history of HCV treatment, were randomly treated with simeprevir (150 mg once daily, orally) plus peg-interferon alpha-2a plus RBV for 12 weeks, followed by peg-interferon alfa-2a plus RBV (simeprevir group), or placebo orally plus

peg-interferon alpha-2a plus ribavirin for 12 weeks, followed by peg-interferon alpha-2a plus RBV (placebo group). Treatment lasted for 24–48 weeks in the simeprevir group and 48 weeks in the placebo group. AEs in the first 12 weeks of treatment led to discontinuation of simeprevir in two (<1%) patients and one placebo patient discontinued. Fatigue and headache were the most common AEs reported in both groups. The prevalence of anemia (42 [16%] vs 14 [11%], respectively) and rash (72 [27%] vs 33 [25%]) were similar in the simeprevir and placebo groups [54C].

An open-label, phase 3 study conducted in 39 sites in 7 Europe and North America countries from September 20, 2011–August 28, 2013. One hundred and six patients with chronic HCV genotype 1 infection and documented HIV-1 co-infection were enrolled in the study. Patients received simeprevir (150 mg once daily) with peg-IFN/RBV (peg-IFN alfa-2a 180 μg/week plus RBV 1000 or 1200 mg/day depending on body weight) for 12 weeks. During the simeprevir plus peg-interferon/RBV treatment phase, 63.2% of the worst recorded AEs were grade 1/2, and 33.0% were grade 3/4. The most frequent AEs (>25% of patients) were fatigue, headache, and nausea. Six (5.7%) patients were reported with angina pectoris, increased aspartate aminotransferase, dyspnea, general physical health deterioration, hyperbilirubinemia, intervertebral disc protrusion, mental status changes, pneumothorax, and thoracic vertebral fracture. Four (3.8%) patients discontinued simeprevir due to AEs. Rash was reported in 16.0% of patients, photosensitivity reactions in 1.9%, and sunburn in 2.8%. Grade 3 hyperbilirubinemia was reported in two patients (1.9%). Grade 3 neutropenia was reported in 18 (17.0%), grade 4 neutropenia in 4 (3.8%) patients, and grade 3 anemia reported in 3 (2.8%) patients [55C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: COMBINATIONS

Fixed Dose Combination Antiretrovirals

Abacavir/Lamivudine

OBSERVATIONAL STUDY

A retrospective, multicenter, cohort study with ABC/3TC/NVP in 78 HIV-infected, ARV-naïve patients for 96 weeks were reported. One or more drugs of the regimen were discontinued in 33 (42.3%) patients. In 15 (19.2%) patients (13 NVP, 2 ABC/3TC), therapy was stopped due to toxicity. Eighty percent of them had rash/liver toxicity. Six (7.7%) patients discontinued ART due to virologic failure. The authors conclude that the toxicity was mostly associated with NVP [56c].

A retrospective, multicenter cohort study was conducted in 183 patients. Patients received 600 mg of ABC 300 mg of 3TC (fixed-dose combination) plus DRV/RTV; in >90% of patients, DRV/RTV was given in a once-daily dose of 900/100 mg for 48 weeks. After 48 weeks the regimen was DRV/RTV 800/100 mg. Of these, nine patients had dyslipidaemia, three had gastrointestinal symptoms, and two had suspected hypersensitivity due to ABC. One patient of each had the following conditions: renal failure, neutropenia, arthralgia, lipodystrophy and osteoporosis. Authors suggests that ABC/3TCplus DRV/RTV may be an effective and well-tolerated alternative regimen for naive and experienced HIV-1-infected patients [57C].

Abacavir/Lamivudine/ZDV

A systematic review and meta-analysis on virological efficacy of ABC has been reported [58R].

OBSERVATIONAL STUDY

An open-label, noninferiority study in ART-naïve patients treated with AZT/3TC and lopinavir/RTV for 96 weeks was reported. One hundred and twenty patients were randomized to receive ABC/3TC/ZDV ($n=61$) or to continue the PI-based ART ($n=59$). Switching to ABC/3TC/ZDV was not inferior compared with continuing the PI regimen; the difference in failure rate (ABC/3TC/ZDV) was −4.4% and +0.4% respectively. AEs leading to discontinuation of these drugs occurred in seven patients in the PI arm and in six patients in the ABC/3TC/ZDV arm. Five patients developed lipodystrophy or dyslipidemia, and one patient developed Hodgkin's lymphoma. In the ABC/3TC/ZDV arm two patients experienced hypersensitivity to ABC, one patient developed anemia, and one patient reported myopathy on ZDV, without any myocardial infarctions in either group [59C].

New Component Drugs

ELVITEGRAVIR (FORMERLY GS-9137)

6-[(3-chloro-2-fluorophenyl) methyl]-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxoquinoline-3-carboxylic acid) is a potent inhibitor of HIV-1 integrase.

COBICISTAT (FORMERLY GS-9350)

Thiazol-5-ylmethyl *N*-[1-benzyl-4-[[2-[[(2-isopropylthiazol-4-yl) methyl-methyl-carbamoyl]amino]-4-morpholino-butanoyl]amino]-5-phenyl-pentyl]carbamate is an inhibitor of cytochrome P450 3A.

OBSERVATIONAL STUDY

A phase 3, non-comparative, open-label study was conducted in 73 patients to evaluate the efficacy and safety of switching RTV to COBI in patients with CCr 50–89 mL/min, who are virologically suppressed on a stable regimen containing RTV-boosted ATV or DRV. Serious AEs occurred in 7% patients treated with ATV or DRV and were discontinued in 10% of the patients. There were two cases of renal discontinuations and no cases of proximal renal tubulopathy reported [60c].

Elvitegravir

The pharmacokinetics (PK) and safety of COBI boosted elvitegravir (EVG/COBI) were evaluated in subjects with impaired liver function [61c]. A phase 1, open-label, parallel-group study evaluated the steady-state pharmacokinetics of EVG and COBI in HIV-infected subjects with moderate hepatic impairment versus control subjects with normal hepatic function. Twenty subjects were enrolled and 10 subjects received EVG (150 mg) plus COBI (150 mg) once daily for 10 days, followed by an 11-day follow-up period and 10 were the control group. Subjects in the hepatic impairment group reported three grade 1 AEs (mild) and one grade 2 AE (moderate), while subjects in the normal control group reported five grade 1 AEs. In summary, the study suggested no clinically relevant changes in EVG or COBI PK following multiple dose administration.

A review examined the safety data of the three FDA-approved INSTIs: RAL, EVG and DTG, and reported that the most common clinical AEs for these drugs were diarrhea, nausea and headache. DTG and COBI, a component of Stribild™, increase serum creatinine and decrease estimated CCr [62R].

The potential use of EVG for the treatment of HIV infection has been reviewed [63R].

Cobicistat

OBSERVATIONAL STUDIES

Pharmacokinetic [64R], and uses in combination with COBI [65H], have been reported.

Elvitegravir/Cobicistat/FTC/Tenofovir

A randomized double-blinded study compared the first integrase inhibitor–based single-tablet regimen combined EVG/COBI/FTC/TDF vs RTV-boosted ATV plus FTC/TDF showed AEs after 144 weeks of treatment. Twenty one subjects (5.9%) discontinued the study drug because of an AE with EVG/COBI/FTC/TDF and 30 subjects (8.5%) in ATV + RTV + FTC/TDF in 144 weeks of treatment. From weeks 96 to 144, 6 and 9 patients from each group, respectively discontinued the study due to AE. Rates of study drug discontinuation because of renal events remained low through week 144 [5 (1.4%) vs 8 (2.3%)], including 2 subjects in EVG/COBI/FTC/TDF group and 6 subjects in the ATV + RTV + FTC/TDF group since week 96. There were no cases of PRT among EVG/COBI/FTC/TDF subjects and three cases among ATV + RTV + FTC/TDF subjects. Through 144 weeks, fractures occurred in 10 EVG/COBI/FTC/TDF subjects (2.8%) vs 19 ATV + RTV + FTC/TDF subjects (5.4%) [66r].

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

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

An open-label, randomized study conducted for 96-week compared the safety and efficacy of ABC/3TC and TDF/FTC plus EFV in HLA-B 5701-negative antiretroviral-naive adults A total of 385 subjects were enrolled. AEs reported were decreased hip bone mineral density in both arms, with a greater decline with TDF/FTC (ABC/3TC 2.2% and TDF/FTC 3.5%; $p < 0.001$) at week 96. Patients in the ABC/3TC arm reported increased total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides [67C].

Didanosine [SED-15, 1113; SEDA 32, 535; SEDA-33, 587; SEDA-35, 516; SEDA-36, 416]

A systematic review analyzed the diagnosis, pathogenesis, natural history, and management of nodular regenerative hyperplasia (NRH) in patients with HIV. The authors conclude that the NRH vary from patients being completely asymptomatic to the development of portal hypertension. There was a strong association between the occurrence of NRH and the use of antiviral therapies such as DDI [68R].

Emtricitabine [SEDA-35, 517; SEDA-36, 416]

A study conducted in 161 patients in Spain on the safety, efficacy, and persistence of emtricitabine/TDF versus other nucleoside analogues [69c]. Patients were in the age group of 50 to 55 years. One hundred and

twelve patients were on emtricitabine and TDF and 49 with other nucleotide reverse transcriptase inhibitors. Followed-up for 19 months and 21.9% of subjects developed at least one laboratory adverse event of grade 3, 5.6% interrupted cART due to adverse events, and 19.3% had virologic failure. There was no significant differences between emtricitabine and TDF and nucleotide reverse transcriptase inhibitor users for any output except for longer persistence.

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

Observational Studies

Safety and effectiveness of antiretrovirals (300 mg of 3TC and 600 mg of ABC) marketed in Japan was studied between January 2005 and March 2009 (final follow-up in December 2010). Six hundred and twenty four patients were enrolled in the study. Age group were 10–81 years, the adults (15≤ and ≤64 years) being 96.0% (599 cases) and the elderly patients (over 65 years) were 3.7% (23 cases). Two hundred and two of the 624 patients had ADRs 32.4% (202/624). The highest incidence of ADR was the metabolism and nutrition disorders (13.9%, 87/624 patients), followed by gastrointestinal disorders (4.3%, 27/624), skin and subcutaneous tissue disorders (4.0%, 25/624), hepatobiliary disorders (3.7%, 23/624), psychiatric disorders (1.3%, 8/624) and nervous system disorders (1.3%, 8/624). Serious AEs were reported on 19 patients (30 events), including two cases each of pancreatitis acute, fever, liver disorder and drug eruption. Of these serious AEs, two events (hepatic dysfunction and immune reconstitution inflammatory syndrome) reported in two patients were associated with 3TC/ABC interactions [70C].

A case report of a man with HIV infection and acquired immune deficiency syndrome was diagnosed with drug-induced pure red cell aplasia due to 3TC treatment [71A]. The patient had a hemoglobin level of 7.6 g/dL and a hematocrit proportion of 21.2%, with normal leukocyte and platelet counts. ART consist of 3TC (300 mg), EFV (600 mg) and ABC (600 mg). 3TC treatment was discontinued and D4T was added in the ART. Subsequently the patient's hemoglobin concentration and hematocrit level returned to normal. This case indicated that 3TC can induce severe anemia without the influence of AZT.

A meta-analysis of randomized trials comparing the efficacy of 3TC and FTC reported that the two drugs are clinically equivalent [72R].

Stavudine (D4T) [SED-15, 3180; SEDA-32, 535; SEDA-33, 587; SEDA-34, 456, SEDA-35, 517; SEDA-36, 417]

Metabolic complication [73R], and neurological and psychiatric AEs from D4T were reviewed [74R].

Observational Studies

In a cross sectional study, 203 HIV-infected Malawian adult patients on D4T-containing ART and 64 healthy controls, on standard first-line D4T containing ART, for at least 6 months, were recruited. The D4T related AEs reported were peripheral neuropathy in 21% (43/203), lipodystrophy in 18% (20/112) and elevated lactate level (>2.5 mmol/L) in 17% (19/113). They studied mitochondrial DNA as a biomarker for the toxicity of D4T, and suggested the use of peripheral blood mtDNA/nDNA ratio as a marker of mitochondrial toxicities of D4T [75c].

A cross sectional study in India was conducted on 80 HIV infected children aged 2–18 years of age who were on D4T based HAART (protease inhibitors, D4T and NVP) for ≥2 years. Lipodystrophy was observed in 33.7% of children followed by lipohypertrophy was the result of long duration HAART [76c].

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

In an experimental study, AZT-induced oxidative stress selectively down regulated mitochondrial thymidine kinase 2 and deoxyguanosine kinase, leading to decreased mitochondrial DNA precursor pools. The authors suggests that these enzymes have significant implications for the regulation of mitochondrial nucleotide biosynthesis and antiviral therapy [77E].

A study in 195 HIV patients from China were switched from AZT/D4T+DDI+NVP to 3TC+TDF and LPV+RTV resulted in less multidrug resistant mutation [78c].

Anemia appeared to be marginally increased among children ($p=0.05$) treated with AZT [79c].

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]

A Phase 2, double-blind, double-dummy, multicenter, active-controlled study in antiretroviral naive adults with

HIV-1 (RNA 5000 copies per milliliter and a CD4 count 50 cells per microliter) were randomized, 2:1 to receive an STR of EVG/COBI/FTC/tenofovir alafenamide (EVG/COBI/FTC/TAF) or EVG/COBI/FTC/TDF, plus placebo for 48 weeks. Mild to moderate AEs reported in both treatments. Patients on EVG/COBI/FTC/TAF had higher increases in total cholesterol, low-density lipoprotein, and high-density lipoprotein [80c].

Over a 9-year period (2001–2010), a total of 407 category II Yellow Card reports (Medicines and Healthcare Products Regulatory Agency) of patients with suspected kidney related ADRs due to TDF were reviewed. Among the 106 reports analyzed, 53 (50%) had features of kidney tubular dysfunction, 35 (33%) had glomerular dysfunction and 18 (17%) had Fanconi syndrome. Of the 106 patients, 33 (31.4%) patients required hospitalization due to TDF-related kidney effects with a mortality of 18.2% (6 out of 33 patients) [81M].

Long-term kidney toxicity as a modest but significant risk for TDF-containing regimens [82R].

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

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

Observational Studies

In a retrospective cohort study, 3089 adults received a fixed dose combination of D4T, 3TC and NVP. A total of 180 (5.8%) individuals discontinued efavirenz or NVP due to severe liver toxicity. The risk was highest in co-infected patients treated with NVP (11.3% for HBV and 15.2% for HCV), compared to 8.0% for HBV and 6.9% for HCV co-infected individuals treated with efavirenz. One hundred and eighty two patients discontinued ART due to skin rash [83C].

Genetic Variation

Inter-individual variability in plasma efavirenz concentrations has been reported in 800 patients from Ghana with confirmed HIV infection. Efavirenz was administered orally as a single fixed dose of 600 mg daily for 24 months. Five hundred and seventy-eight (72.3%) patients were on antiretroviral therapy, while 222 (27.8%) were antiretroviral therapy naive at the time of sampling. Genotyping for the allelic discrimination was done from the genomic DNA isolated from patient's serum. Plasma concentration of efavirenz was depends on the variation in allele CYP2B6 gene. In conclusion, CYP2B6 and CYP2A6 SNPs were associated with higher plasma efavirenz concentrations due to reduction in major and minor phase I routes of elimination [84C].

A prospective study reported on the use of ART containing efavirenz in pregnant women in Rio de Janeiro, Brazil and the incidence of ADR were discussed [85C].

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

A combination of TMC125 plus RAL treatment in 24 patients for 48 weeks did not cause any drug interactions and no liver toxicity [86c].

A 46-year-old HIV-positive patient with BEACOPP chemotherapy for advanced Hodgkin's lymphoma, switched from DRV, TDF and FTC to TMC125 (200 mg BID) + RAL (400 mg BID) + FTC (200 mg QD) + TDF (300 mg QD) showed less drug–drug interactions [87c].

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

Pharmacokinetics and pharmacodynamics of the antiviral drugs affecting the nervous system was discussed in this review [88R].

Comparative Study

A systematic review and meta-analysis on the use of nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis has been reported [89R]. This meta-analysis compared five randomized clinical trials and four retrospective clinical trials. Eight hundred and thirty three patients received nevirapine, and 1424 received efavirenz, including patients co-infected with HIV and TB. NVP-based regimens showed higher AEs and were discontinued more frequently than efavirenz.

Observational Study

A longitudinal prospective cohort study was conducted in Rwandan children infected with HIV. HIV-infected 183 cART-naïve children below 15 years of age initiated cART between March 2008 and December 2009 were included in the study and monitored for 18 months. cART regimen was NVP, efavirenz, or protease-inhibitor based. The most common side effects reported were nausea and vomiting (14.8%), NVP-associated skin rash and hypersensitivity (13.2%), anemia

(7%), diarrhea (6%), and dizziness and fatigue (5%). Most of the symptoms were reversed after discontinuation of NVP [90C].

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

The effectiveness and safety of TMC 278 in treatment-naive adults infected with HIV-1 has been reported. Randomized controlled trials from multiple databases on the effectiveness and safety of TMC 278 in treatment-naive adults infected with HIV-1 was collected. The data analysis included the four randomized controlled trials with a total of 2522 patients. TMC 278 demonstrated noninferior antiviral efficacy in viral load and baseline CD4 count. TMC 278 showed significantly higher difference in virological failure rates compared with the efavirenz group. The most commonly reported AEs were rash and neurological events, which were lower with TMC 278 than efavirenz (RR, 0.11; 95% CI, 0.03–0.33; RR, 0.52; 95% CI, 0.45–0.60, respectively) [91C].

Liver toxicity in HIV-infected patients receiving TMC125 and TMC 278 has been reported in this review [92R]. According to the authors both TMC125 and TMC 278 are safe to be used in patients with liver abnormalities.

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]

Fosamprenavir/Amprenavir

An open-label study reported on the drug–drug interaction of fosamprenavir (FPV)-RTV on DTG PK parameters, in 12 healthy subjects with a mean age of 33.4 years. All patients received 50 mg DTG daily for 5 days and were on a regimen of 50 mg DTG every 24 hours in combination with 700/100 mg FPV-RTV every 12 hours for 10 days. No deaths or serious AEs occurred. Abnormal dreams were reported by 2 subjects. Rash was reported by 2 subjects (17%) who were receiving both DTG and FPV-RTV [93c].

Experimental Study

Chronic effects of antiretrovirals (3TC, D4T, delavirdine, nelfinavir, amprenavir and LPV/RTV) of 3 or 9 times doses were given to pregnant albino rats. D4T increased maternal weight ($p = 0.001$), while 3TC at 3 and 9-time doses reduced maternal weight. Higher rates of maternal death were reported with amprenavir at all of the doses, and LPV/RTV at 3- and 9-times doses. None of the antiretroviral drugs studied were harmful to the fetuses with regard to implantation, reabsorption, teratogenity and mortality. D4T at all doses reduced the litter weights ($p < 0.001$); however, 3TC, delavirdine, and amprenavir all at 3-times dose increased the litter weight [94E].

Atazanavir

A phase 3, randomized, open-label study reported the efficacy and tolerability of 3 non-nucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1 in a 1:1:1 ratio. Follow-up were done for at least 96 weeks. Of the three inhibitor studies, RAL treatment was superior to the other two inhibitors [95c].

The efficacy of abacavir/3TC + ATV (ABC/3TC + ATV) to TDF/FTC + ATV/RTV in a population, HIV-1 infected patients over a period of 24 weeks were reported [96C]. After 24 weeks, ABC/3TC + ATV ($n = 199$) was found to be noninferior to TDF/FTC + ATV/RTV ($n = 97$) by both the primary analyses (87% in both groups) and all secondary efficacy analysis. Fasting HDL was increased from the baseline levels for the ABC/3TC + ATV group compared to the TDF/3TC + ATV/RTV group. Rates of AEs were of moderate or greater severity (grade 2–4) between the two groups (40% [79/199] for ABC/3TC + ATV and 37% [36/97] for TDF/FTC + ATV/RTV), with only upper respiratory tract infection observed in $\geq$5% of patients in either treatment group (4% [5/199] for ABC/3TC + ATV and 6% [6/97] for TDF/FTC + ATV/RTV). There were few grade 2–4 treatment-related AEs in either group (8% [16/199] for ABC/3TC + ATV and 5% [6/97] for TDF/FTC + ATV/r). In the TDF/FTC + ATV/RTV group, one patient had grade 2 palpitations. In the ABC/3TC + ATV group, two patients had grade 2 cardiomyopathy, one patient had grade 2 coronary artery disease, and one patient had a grade 4 acute inferior myocardial infarction.

A drug interaction study showed that RTV was responsible for the adverse interactions that occurred when telaprevir and ATV were administered together [97A].

A systematic review suggests that RTV-boosted ATV appears to be a safe, effective and durable option for treatment-naive and early treatment-experienced HIV-1 patients, including non-pregnant and pregnant women [98R].

Another study indicates that some of the AEs associated with ARV use may be mediated through 'off-target' effects involving nuclear receptor activation. ARV drugs activate pregnane X receptors and constitutive androstane receptors, increasing the risk of drug interactions due to altered drug metabolism and disposition. The

closely related liver X receptors (LXRα/β), estrogen receptors (ERα/β) and glucocorticoid receptor (GR) regulate many endogenous processes such as lipid/cholesterol homeostasis, cellular differentiation and inflammation. ATV and RTV activated LXRα/β, while tipranavir enhanced transcriptional activity of ERα. Direct ligand-binding domains interact with LXRα and/or LXRβ were confirmed in vitro studies for DRV, efavirenz, flavopiridol, maraviroc and tipranavir. Likewise, efavirenz was also predicted and confirmed as a ligand of ERα-LBD [99E].

Darunavir

In a randomized clinical trial, 178 patients received once-daily ATV/RTV ($n=90$) or DRV/RTV ($n=88$) plus TDF/FTC. After 24 weeks, the mean cholesterol levels had increased (7.26 and 11.47 mg/dL in the ATV/RTV and DRV/RTV arms). However, the ratio of total to HDL cholesterol decreased in patients treated with ATV/RTV compared to DRV/RTV [100C].

In another study, sixteen HIV-1-infected pregnant women were enrolled and received DRV/RTV 600/100 mg. The pharmacokinetic plasma concentration of total DRV during the second and third trimesters in the pregnant woman was 28% and 19% lower than the postpartum, and the total RTV plasma concentrations were higher during the postpartum period compared with the second and third trimesters of pregnancy. The most common AEs, were infections and infestations (44%), gastrointestinal disorders (25%) and premature labor (25%). Of 12 infants, four were born prematurely (at weeks 30, 36, 36 and 37) [101c].

The efficacy and safety of DRV/ritonavir compared with LPV/RTV in HIV-1-infected treatment-naïve patients has been reported [102]. Six hundred and eighty-nine patients were involved in the study. Patients received DRV/RTV 800/100 mg or LPV/r 800/200 mg total daily dose (either once or twice daily) plus TDF/FTC. In the DRV/RTV and LPV/RTV arms, 85/343 and 114/346, respectively, had discontinued by week 192. No protease inhibitor (PI) primary mutations developed and only low levels of nucleoside reverse transcriptase inhibitor resistance developed in virological failures in both groups. AEs reported were treatment-related diarrhea, increases in total cholesterol and triglyceride mostly in LPV/RTV group. DRV (once-daily) was found to be non-inferior and statistically superior in virological response to LPV/RTV.

A prospective, observational, multicenter, cohort study assessed the incidence of AEs in patients receiving DRV. Four hundred and twenty-nine patients were enrolled in the study and were given DVR once or twice daily. The authors were of the opinion that DRV administrated both once daily or twice daily was safe and well tolerated [103C].

Nelfinavir

Drug–Drug Interactions

The interactions between nelfinavir and rifabutin have been reported in a case of bilateral uveitis associated with co-administration of rifabutin and nelfinavir. Uveitis did not subside until rifabutin was discontinued. The study showed that drug–drug interaction and AEs led to the discontinuation of rifabutin [104A].

Ritonavir

A retrospective study reported on HIV-infected patients treated with double-dose of lopinavir-ritonavir (LPV/RTV) based ART during concomitant rifampicin-containing antituberculosis treatment for 2 months. Optimal treatment for tuberculosis (TB) in HIV infected was treated with lopinavir-ritonavir (LPV/RTV 800 mg/200 mg) twice daily. During co-administration, gastrointestinal toxicity occurred in 9/25 patients and increased aspartate aminotransferase or alanine aminotransferase of any grade in three patients (12%). AEs reported were gastro-intestinal toxicity in 9/25 (36%) patients and diarrhea in 7 (28%) patients, and vomiting in five patients. Treatment discontinued in three patients due to AEs [105c].

Saquinavir

The Polish Observational Cohort of HIV/AIDS Patients (POLCA) study group assessed the efficacy and side effects of saquinavir in 259 naive patients, of these 56.1% continued the drug for 24 months. Twenty three percentage of patients discontinued saquinavir containing regimen due to gastrointestinal side effects. A gradual decrease in proteinuria (44.4–26%), and increase in HDL was also reported [106c].

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

Enfuvirtide

The effectiveness of Enfuvirtide (ENF) was studied in a cohort of 40 HIV-1-infected patients in Mexico. The median age was 44.8%, and 90% of the patients were men. Twenty-seven of those patients were followed

through the 48-week analyses. Significant reduction in viral copy numbers were reported in 81% patients. Pain at the site of injection was the main adverse event in 100% of patients. Another AE was the presence of subcutaneous nodules at the injection site in 45.4% of the patients and 19% of patients developed instant side reactions, but none of the patients discontinued the treatment [107c].

Drugs Active Against Human Immunodeficiency Virus: Integrase Inhibitors [SEDA-33, 599, SEDA-34, 465, SEDA-35, 525; SEDA-36, 428]

Dolutegravir

A systematic review and meta-analysis on relative efficacy and safety of DTG are reported [108r], [109R].

DTG was reported to caused headache and insomnia [110R], [111R].

DTG administration showed hypersensitivity reactions in <1% of patients and elevations in liver transaminases were reported in patients co-infected with HBV and HCV [112r].

OBSERVATIONAL STUDIES

A 96-week, phase 3b, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study was conducted at 64 research centers with 484 patients. The patients were randomly assigned (1:1) to receive DTG 50 mg once daily or DRV 800 mg plus RTV 100 mg once daily. The most frequently reported AEs with grade 1 and grade 2 were diarrhea, nausea, headache, and nasopharyngitis. Serious AEs were reported in the DTG group (11%) than in the DRV plus RTV group (5%). Creatinine toxic effects were reported infrequently (DRV, 10 patients (4%); DRV plus RTV two patients (<1%); two (<1%) patients in the DTG group had grade 2 toxic effects [113C].

Raltegravir

OBSERVATIONAL STUDY

Extensive pulmonary involvement with RAL-induced DRESS syndrome in a postpartum woman with HIV was reported. An 18-year-old postpartum woman with HIV, was treated with 3TC–AZT, LPV–RTV and RAL, for 1-week had developed rash and fevers. She had high fever, respiratory distress, hypotension and tachycardia. She also had febrile (102°F) with cervical and submandibular lymphadenopathy, diffuse morbilliform rash, generalized pruritus, facial edema, and oedematous hands and feet. After discontinuing RAL and starting prednisone, her DRESS symptoms completely resolved [114c].

An open-label, randomized, multicenter study was reported in patients with 3 age groups in 4 cohorts. Cohort I, ≥12 to <19 years and cohort IIA, ≥6 to <12 years, were assigned to receive film-coated tablets, as used in the adult formulation. In all, 126 subjects were treated with RAL of these, 96 received the final selected dose. AEs reported were rash and drug-induced liver injury [115C].

A 39-year-old man positive for HIV had CD4+ T-lymphocyte count 3 cells/μL, and HIV RNA was 4.5×106 copies/mL, but urine analysis showed a heavy proteinuria (3 g/day). He was treated for atypical mycobacteriosis with ethambutol, azytromycin, and rifabutin for a total of 6 months, and highly active antiretroviral therapy (AZT/3TC + DRV/RTV), along with cotrimoxazole prophylaxis. The patient developed a symptomatic muscular toxicity (creatine phosphokinase increased to 5000 UI/L, n.v. <186 UI/L) and AZT/3TC was replaced by RAL. The patient subsequently developed fever with an itchy rash on the limbs and scalp, and painful oral aphthae. The patient was then treated with prednisone (1 mg/kg), and the symptoms subsided [116A].

A non-randomized, Phase I, parallel-assignment, open-label pharmacokinetic study in HIV/HCV-coinfected patients with advanced liver cirrhosis (Child-Pugh C), were given RAL (400 mg twice daily) showed no AEs even with the highest dose of RAL [117c].

MUSCULOSKELETAL

A prospective, observational, multicenter study (Surveillance Cohort Long-Term Toxicity of Antiretrovirals) was reported in a cohort of HIV-infected patients receiving RAL-based ART. A total of 496 HIV-infected patients were included in the study [333 (67.1%) male]. The mean age at enrolment was 45.9 ± 9.3 years, the mean CD4 cell count was 386 ± 277 cells/μL and the mean HIV-RNA level was 2.99 ± 1.56 log10 copies/mL. Of these, 192 patients (38.7%) were positive for hepatitis C antibody, 196 (39.5%) had lipodystrophy and 29 patients (5.8%) were antiretroviral therapy naïve. A total of 26 patients (5.2%) reported muscle symptoms; 16 of them had muscle pain and 17 had muscle weakness (7 had both). Seven patients (1.4%) discontinued RAL because of muscular events (three for muscle pain/weakness and four for creatinine phosphokinase increases). No cases of rhabdomyolysis were reported. Authors suggest that monitoring of muscle symptoms and creatinine phosphokinase levels should be considered in patients receiving RAL co-administered with ATV and in those with CNS symptoms [118C].

A retrospective, cohort study in adult patients with HIV-1 infection were treated with RAL-containing antiretroviral therapy from May 2009 to May 2013. The study contained 155 subjects, 117 (75.5%) were men, 141 (91%) were white, and the mean (±SD) age was 49.2 (±9.2) years. The median duration of the RAL-containing

regimen at the end of follow-up was 30.7 months. Other antiretroviral drugs taken in association with RAL, 84 (54.2%) patients received TDF/FTC, 39 (25.2%) ABC/3TC, 53 (34.2%) DRV/RTV, 32 (20.6%) lopinavir/RTV, and 14 (9%) efavirenz. AEs reported were skeletal muscle toxicity in 37 (23.9%) patients during the RAL-containing treatment. Creatinine kinase elevation was observed in 33 (21.3%) patients, diffuse myalgia without weakness in three (2%) patients, and proximal muscle weakness in one (0.6%) subject, while no cases of rhabdomyolysis were reported. A creatinine kinase elevation prior to RAL treatment was observed in 18 (48.6%) out of 37 patients with skeletal muscle toxicity. AZT was included in the previous antiretroviral regimen in 15 (40.5%) out of 37 patients who developed skeletal muscle toxicity. According to the authors, the major factors associated with skeletal muscle toxicity were previous use of AZT, higher baseline creatinine kinase levels, previous increase of the creatinine kinase levels, and a higher body mass index [119C].

A retrospective observational study reported on HIV-1-positive ART-experienced adults was switched to an RAL/ATV or RAL/ATV/RTV regimen between July 2008 and June 2013, in France. Twenty-seven patients (69%) experienced at least one adverse event. A total bilirubin elevation occurred in 64% of patients (grade 1, $n=13$; grade 2, $n=12$), and raised CPK in 13% of patients (grade 1, $n=5$). There was elevation in total bilirubin levels, with a mean increase of 18 μmol/L at week 24 (95% CI, 8–29, $p<0.005$). Other grade 1 AEs related or possibly related to dual therapy included: muscle pain ($n=8$), asthenia ($n=6$), scleral icterus ($n=6$), jaundice ($n=5$), nausea and diarrhea ($n=4$), pain ($n=3$), headache ($n=3$), sleep disturbances ($n=3$), raised alanine aminotransferase ($n=2$), and loss of libido ($n=1$) [120c].

The safety and efficacy of RAL as an alternative to efavirenz for patients co-infected with HIV and TB has also been reported [121C]. A multicentre, phase 2, non-comparative, open-label, randomised trial at eight sites in Brazil and France in patients co-infected with HIV and tuberculosis. Participants in the efavirenz group received 600 mg per day of efavirenz (one tablet), 300 mg per day of 3TC (one 300 mg tablet in France, two 150 mg tablets in Brazil), and 245 mg per day of TDF (one tablet). RAL 400 mg twice daily given as an alternative to efavirenz for the treatment of patients co-infected with HIV and TB. One patient in the RAL 800 mg group had liver failure, Serious AEs reported with efavirenz in 19 patients (37%) and 17 (33%) patients in RAL group. Hepatotoxicity was reported in two patients with RAL that lead to discontinuation of treatment. Cutaneous rash reported in one patient in each efavirenz and RAL group.

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

Maraviroc

A long-term randomized, double-blind, multicenter phase IIb/III study (5 years) on the efficacy and safety of maraviroc (MVC) vs efavirenz in treatment-naive HIV-1 patients was reported. Naive patients with CCR5-tropic HIV-1 infection received MVC 300 mg twice daily or efavirenz 600 mg once daily, and AZT/3TC 300 mg/150 mg twice daily. Fewer patients on MVC vs efavirenz experienced treatment-related AEs (68.9% vs 81.7%) and discontinued on any adverse event (10.6 vs 21.3%). Nausea (MVC 38.6% vs EFV 36.6%) was the most common adverse event in both treatment arms observed. Other AEs (≥20% of patients, either arm) included dizziness (MVC 17.2% vs EFV 32.1%) and headache (MVC 30.3% vs EFV 29.1%). The other AEs (≥10% of patients, either arm) were nausea (MVC 30.8% vs EFV 28.5%), headache (MVC 19.4% vs EFV 18.0%), dizziness (MVC 11.9% vs EFV 28.0%), fatigue (MVC 10.6% vs EFV 9.1%), diarrhea (MVC 8.9% vs EFV 14.7%), vomiting (MVC 7.8% vs EFV 10.5%), and abnormal dreams (MVC 5.8% vs EFV 12.5%). Dizziness, rash and pregnancy each led to the discontinuation of eight patients (2.2%) in the EFV treatment arm [122c].

Selective and dual targeting of CCR2 and CCR5 receptors, including MVC for the treatment of HIV-1 infections, has been reviewed [123A].

An in vitro experimental study showed antagonistic effects with the combination of CCR5 inhibitors [124E].

The efficacy and safety of changes in highly active antiretroviral therapy regimens for HIV-infected patients has been evaluated [125c].

A retrospective cohort study was also conducted to evaluate the efficacy and safety of MVC plus RTV-boosted DRV-r once-daily in HIV-infected pretreated patients [126c]. Changing the treatment regimen reduced the AEs in 38 patients and improved viral clearance.

In an open-label, fixed-sequence, phase I study, 14 volunteers received MVC 150 mg BID (every 12 hours) for 5 days, followed by MVC 150 mg BID plus BOC 800 mg TID (every 8 hours) for 10 days, then MVC 150 mg BID plus TVR 750 mg TID (every 8 hours) for subsequent 10 days. AEs were higher with MVC + BOC and MVC + TVR versus MVC alone. Dysgeusia (50%) and pruritus (29%) occurred most commonly with MVC + BOC, and fatigue (46%) and headache (31%) with MVC + TVR. There were no serious AEs reported [127c].

Regulatory T cells play a key role in HIV-associated immunopathology, and the regulatory T cells in MVC-treated peripheral blood mononuclear cells (PBMCs) were reduced significantly [128E].

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]

Amantadine

Amantadine, at high dose (10 mg/kg), did not prevent dopamine depletion but exacerbated the behavioral manifestations of methamphetamine toxicity such as akinesia and catalepsy. Lower dose of amantadine (1 mg/kg) produced significant scavenging of the reactive oxygen species induced by methamphetamine. The authors suggests that amantadine should not be used concomitantly with methamphetamine as it may results in excessive neurotoxicity [129E].

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]

Oseltamivir (Tamiflu)

A meta-analysis by Dobson and colleagues was performed that includes all available data from randomized, double-masked, placebo-controlled adult trials, including trials that did not reach recruitment targets and had not been published (nine trials including 4328 patients). Oseltamivir treatment with 75 mg twice daily for 5 days resulted in a significant 21% (95% CI, 15–26) reduction, from 123 to 98 hours, in reported symptom duration in adult and adolescent patients with laboratory-confirmed influenza (the intention-to-treat infected with influenza group). The oseltamivir treatment resulted in an increased risk of nausea (6.2%) in the placebo group as compared with 9.9% and an increased risk of vomiting (3.3% vs 8.0%) [130M].

A retrospective analysis was reported of oseltamivir and zanamivir in 150 randomly-selected confirmed H1N1 patients between July 2009 and December 2009, where patients were in the age group of 18–65 years received oseltamivir alone or along with zanamivir. Oseltamivir alone treated patients (48%) developed gastrointestinal intolerance [131C].

OTHER DRUGS

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

Dermatological Studies

In a multicenter, open label, randomized, phase 2 study, the feasibility of cidofovir and imiquimod for treatment of vulval intraepithelial neoplasia was reported. One hundred and eighty patients with vulval intraepithelial neoplasia grade 3 were included in the study. Eighty nine patients were treated with 1% cidofovir (supplied as a gel in a 10 g tube, to last 6 weeks) and 91 patients were treated with 5% imiquimod (one 250 mg sachet for every application), self-applied three times a week for a maximum of 24 weeks. A complete response was reported in 41 (46%; 90% CI, 37.0–55.3) patients allocated cidofovir and by 42 (46%; 37.2–55.3) patients assigned imiquimod. AEs of grade 3 or higher were reported in 31 (37%) of 84 patients allocated cidofovir and 39 (46%) of 84 patients assigned imiquimod. The most frequent grade 3 and 4 AEs were pain in the vulva, pruritus, fatigue, and headache [132C].

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