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CHAPTER

# 21

# Antiviral drugs

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## Abbreviations

| | |
|---|---|
| **/c** | cobicistat |
| **/r** | ritonavir |
| **3TC** | lamivudine |
| **ABC** | abacavir |
| **AIDS** | acquired immunodeficiency syndrome |
| **AKI** | acute kidney injury |
| **ART** | antiretroviral therapy |
| **ATV** | atazanavir |
| **BIC** | bictegravir |
| **BMI** | body mass index |
| **CAB** | cabotegravir |
| **CHB** | chronic hepatitis B |
| **CPK** | creatinine phosphokinase |
| **CNS** | central nervous system |
| **DOR** | doravirine |
| **DRV** | darunavir |
| **DTG** | dolutegravir |
| **EFV** | efavirenz |
| **EVG** | elvitegravir |
| **FTC** | emtricitabine |
| **HIV** | human immunodeficiency virus |
| **ICC** | intrahepatic cholangiocarcinoma |
| **INSTIs** | integrase inhibitors |
| **LFTs** | liver function tests |
| **NNRTIs** | non-nucleoside/-tide reverse transcriptase inhibitors |
| **NRTIs** | nucleoside reverse transcriptase inhibitors |
| **PIs** | protease inhibitors |
| **PLWH** | people living with HIV |
| **PTSD** | post-traumatic stress disorder |
| **RAL** | raltegravir |
| **RPV** | rilpivirine |
| **RTV** | ritonavir |
| **TAF** | tenofovir alafenamide |
| **TDF** | tenofovir disoproxil fumarate |
| **WNL** | within normal limits |

## DRUGS ACTIVE AGAINST CORONAVIRUS DISEASE 2019 (COVID-2019)

### Molnupiravir

Molnupiravir is recommended in adults over 18 years of age for treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk for progression to severe COVID-19, including hospitalization or death, where alternative treatment options are not accessible or clinically appropriate.

In a study evaluating the effect of molnupiravir for the treatment of COVID-19 in 1433 non-hospitalized patients, only one death was reported in the molnupiravir group compared to three in the placebo group. The most common COVID-19 related complications reported in the molnupiravir vs placebo treatment groups were as follows: pneumonia (6.3% vs 9.6%), diarrhea (2.3% vs 3.0%), bacterial pneumonia (2.0% vs 1.6%), and worsening of COVID-19 (7.9% vs 9.8%) (Jayk Bernal et al., 2022) [R].

A decrease in hemoglobin was observed in molnupiravir trials, MOVe-OUT and MOVe-IN. Hemoglobin laboratory abnormalities were more common among molnupiravir participants than placebo in these studies. In the MOVe-IN study, hemoglobin abnormalities were reported in 22.4% and 8.3% of patients in molnupiravir 800 mg and placebo arms, respectively. In addition, hemoglobin abnormalities grade 1 and 2 were reported in 4% of patients in the molnupiravir group compared to 1% in the placebo group (8.5–10.4 g/dL in females and



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9.0–10.9 g/dL in males) (Singh et al., 2022) [R]. Authors concluded that molnupiravir appears to be a reasonably useful agent in reducing death in adult patients with high risk COVID-19.

### Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analog approved for treatment of mild to moderate COVID-19 in high-risk, non-hospitalized and hospitalized patients aged ≥12 years and weighing ≥40 kg. In a randomized double-blind placebo-controlled trial in 562 non-hospitalized patients with COVID-19 who underwent randomization and received at least one dose of remdesivir, or placebo were included in the analyses. The side effects observed in the remdesivir group were comparable to those in the placebo group (283 patients 42.3% vs 46.3%). The most common non-serious adverse events were nausea, headache, and cough, which occurred in at least 5% of patients in both groups. In addition, adverse effects related to the trial regimen occurred in 12.2% of patients in the remdesivir group compared to 8.8% in the placebo group. Patients in the remdesivir group had fewer serious adverse events than the placebo group, 1.8% vs 6.7%, respectively (Gottlieb et al., 2022) [R]. Authors concluded that patients who had a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo.

## DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS (CMV)

### Brincidofovir/cidofovir [SEDA-34, 447; SEDA-35, 503; SEDA-36, 401; SEDA-37, 329; SEDA-38, 261; SEDA-39, 269–270; SEDA-41, 301–302; SEDA-43, 323]

Brincidofovir is an oral analog of cidofovir which achieves high tissue levels of active metabolite and low systemic toxicity. A retrospective analysis of 44 adenovirus infections among 30 hematopoietic stem-cell transplant recipients (age range: 9 months to 19 years; 22 males and 8 females) reported one case of gastrointestinal (GI) toxicity related to brincidofovir (5%) and six cases of renal toxicity caused by cidofovir (27%) (Perruccio et al., 2021) [c]. Cidofovir is most commonly associated with drug-induced uveitis when administered intravenously and intravitreally. A recent narrative review explored the correlation between the drug formulation and the incidence of uveitis in human immunodeficiency virus (HIV) positive patients. Anterior uveitis was found in 14–26% of patients treated with intravitreal cidofovir compared to 26–59% in those treated intravenously (Testi et al., 2020) [R]. Patients with cidofovor-induced uveitis are either asymptomatic or experience photophobia and blurred vision. Therefore, in HIV patients presenting with uveitis obtaining a detailed medical history including use of all systemic/local medications is recommended.

### Foscarnet [SEDA-35, 504; SEDA-36, 403; SEDA-37, 329; SEDA-38, 262; SEDA-39, 270; SEDA-41, 301; SEDA-43, 301]

Nephrotoxicity is the most common adverse effect seen with foscarnet. In a retrospective, single-center, observational study of 91 patients, compared intermittent administration and a 24-h infusion, nephrotoxicity remained the most frequently seen adverse effect regardless of the administration method (Domingo et al., 2021) [c]. Twenty-eight of 45 patients (62.2%) who received continuous-infusion foscarnet experienced an acute kidney injury (AKI), compared with 39 of 62 patients (62.9%) who received conventional infusion ($P = 0.94$). The average duration of outpatient antiviral days for the continuous infusion group was 9 days (range, 0–121 days), compared with 6.3 days (range, 0–70 days) in the intermittent infusion group ($P = 0.54$) (Domingo et al., 2021). In another retrospective study of 90 hematopoietic stem cell transplantation (HSCT) patients, 32 met the selection criteria. This study showed that in HSCT patients who received foscarnet, renal dysfunction was found to be closely related to electrolyte abnormalities of potassium, calcium, and magnesium (Ota & Hirata, 2021) [c]. In patients receiving foscarnet, close monitoring of renal function and electrolytes is warranted.

### Ganciclovir/valganciclovir [SEDA-34, 449; SEDA-35, 504; SEDA-36, 404; SEDA-37, 330; SEDA-38, 262; SEDA-39, 270–271; SEDA-41, 301; SEDA-43, 323]

Ganciclovir and valganciclovir share a similar side effect profile because valganciclovir is the prodrug of ganciclovir. The most common side effect associated with both ganciclovir and valganciclovir is leukopenia. A recent systemic review of 102 studies (25 human and 77 animal) assessing the long-term effects in subjects receiving a prophylactic dose of ganciclovir observed a correlation with spermatic toxic effects in those patients (Jensen et al., 2021) [M]. Hu and colleagues describe a case report of a 39-year-old female where intravitreal ganciclovir was associated with photoreceptor damage which can lead to abnormal retinal function (Hu et al., 2021) [A].

A meta-analysis of 23 studies involving 3478 participants evaluated the efficacy and safety of valganciclovir

in cytomegalovirus (CMV) prophylaxis identified leukopenia as a dose-related adverse effect. Patients receiving high dose (900 mg) valganciclovir were 2.9 times more likely to develop leukopenia than low dose (450 mg) treatment (95% CI: 1.9–4.7) (Lee et al., 2021) [M].

Patients receiving ganciclovir or valganciclovir should be closely monitored for leukopenia, retinal function, and spermatic effects.

## DRUGS ACTIVE AGAINST HEPATITIS B VIRUS (HBV)

### Entecavir [SEDA-35, 512; SEDA-36, 411; SEDA-37, 335; SEDA-39, 273; SEDA-41, 303; SEDA-43, 324]

It is well-documented that patients infected with chronic hepatitis B (CHB) are at risk of cirrhosis and/or hepatocellular carcinoma (HCC). These risk factors increase proportionally to serum hepatitis B virus (HBV) DNA levels (Chen et al., 2006) [C].

Studies have shown reduced risk of HCC in patients infected with HBV treated with nucleoside analogues (NAs) such as lamivudine (3TC), entecavir (ETV), or tenofovir disoproxil fumarate (TDF). However, a different outcome was observed in patients with CHB infection. Currently, both ETV and TDF are equally recommended as first-line NAs for treatment of CHB. Both ETV and TDF are potent drugs utilized in the treatment of both CHB infections, hepatitis B e antigen (HBeAg) positive or negative. In a nationwide population cohort study involving patients with CHB who were either started on entecavir ($n = 11\,464$) or TDF ($n = 12\,692$) between 2012 and 2014 using data from the Korean National Health Insurance Services database treatment with TDF has been shown to be more effective in lowering the risk of HCC compared to ETV (Choi et al., 2019) [C].

Chang et al. conducted a study to compare the long-term risk of ETV versus TDF on HCC and intrahepatic cholangiocarcinoma (ICC) in CHB patients from a large multi-institutional database in Taiwan. This was a retrospective study for CHB patients undergoing ETV or TDF treatment from 2011 to 2018. These patients were then linked to the National Cancer Registry database for development of HCC or ICC. The HCC incidence was not different between two groups. However, among decompensated cirrhotic patients, a lower risk of HCC was observed in the TDF group compared to the ETV group. Also, there were no differences between ETV and TDF groups in the ICC incidence. Hence, the authors concluded treatment with ETV and TDF showed a comparable long-term risk of HCC in CHB patients (Chang et al., 2021) [C].

## DRUGS ACTIVE AGAINST HEPATITIS C VIRUS (HCV)

### Glecaprevir/pibrentasvir [SEDA-41, 304; SEDA-43, 325]

A phase 3, open-label, multicenter study evaluating the efficacy and safety of glecaprevir/pibrentasvir for treatment of chronic hepatitis C virus (HCV) reported headache (18%), pruritus (7%), nausea (6%), and fatigue (5%) as the most common treatment-related adverse effects. Out of 100 patients (64 males and 16 females, ages 28–79), four experienced six serious treatment-emergent adverse events which were not related to glecaprevir/pibrentasvir and did not lead to treatment discontinuation (Peribañez-Gonzalez et al., 2021) [C]. In Korea, a similar study evaluated the effectiveness and safety of glecaprevir/pibrentasvir in in 267 patients being treated for HCV found that gastrointestinal discomfort (9.7%), upper respiratory infection (9.4%) and pruritus (6.4%) were the most common adverse events among these patients (Park et al., 2021) [C]. The authors concluded that the 8- to 12-week G/P regimen had high efficacy and was well-tolerated in most Korean patients who had chronic HCV infections regardless of HCV GT and patient comorbidities.

### Ledipasvir/sofosbuvir [SEDA-41, 304; SEDA-43, 325]

In a multi-centered prospective observation study to evaluate the safety and efficacy of ledipasvir/sofosbuvir with or without ribavirin was evaluated in a trial by Lim and colleagues. Authors collected data from 667 patients from 2011 to 2016. Adverse events were lower in the patient group that did not receive ribavirin. In this trial, fatigue, headache, and infections/infestations were the most common adverse events associated with ledipasvir/sofosbuvir with ribavirin (≥10%). Anemia was observed in both groups; however, it was significantly less common in patients who were treated with ledipasvir/sofosbuvir alone (7/495, 1.4%) compared with patients with treatment of ledipasvir/sofosbuvir/ribavirin (42/139, 30.6%) (Lim et al., 2018) [M].

### Ribavirin + sofusbuvir [SEDA-41, 304; SEDA-43, 325]

In a randomized open label efficacy and safety study, a novel formulation, composed of epigallocatechin gallate + sofosbuvir + ribavirin was compared to sofosbuvir + ribavirin treatment in patients with CHC genotype 4. Treatment-naïve and treatment-experienced patients

($n = 80$) were randomly assigned to receive a one daily fixed dose of Catvira or sofosbuvir + ribavirin for 12 or 24 weeks. Both Catvira and sofosbuvir + ribavirin yielded similar outcomes of viral load ($P < 0.001$). However, patients who received sofosbuvir + ribavirin showed significant decline in hemoglobin levels after 24 weeks ($P < 0.05$) (Shiha et al., 2021) [c]. Adverse effects in the Catvira group were reported in 4 patients (5%) in the 24-week group and were predominantly mild or moderate in severity. The most common adverse events in both groups were headache and epigastric pain. All these adverse events resolved and no severe adverse events were reported.

### Sofosbuvir [SEDA-41, 304, 305; SEDA-43, 325]

Sofosbuvir is a NS5B polymerase inhibitor that is commonly associated with an array of adverse effects. Some of these adverse effects include but are not limited to itching, rash, anemia, decreased appetite, headache, chills, and insomnia. A recent phase 3 trial a total of 205 patients with genotype 1 HCV infection without cirrhosis were enrolled out of them, 202 completed the full treatment and post-treatment course and 3 discontinued follow-up. SVR12 was achieved in 98% of patients and in 100.0% and 98% of patients with genotype 1a, and 1b. In the other exploratory study, SVR 12 was achieved by 100% patients with genotype 2 ($n = 21$), genotype 3 ($n = 7$), and genotype 6 ($n = 8$). Leukopenia, neutropenia, dizziness, increased creatine phosphokinase (CPK), proteinuria, and hypercholesterolemia were reported as the main adverse effects while being treated with the antiviral therapy (Kong et al., 2021) [C]. A prospective study on the effectiveness and side effect profile of treatment with sofosbuvir and daclatasvir. Out of 229 patients in the study 66% patients were females and 34% males with a median age of $42.2 \pm 10.6$ SD. At the end of week 12, 93% of the patients accomplished SVR. Whereas the highest efficacy rate of 93% was achieved among the combined therapy of SOF/DAC (92.6%) among the different HCV genotype 3 patients. Minor adverse effects reported were lethargy, headache, nausea, insomnia, fever, and diarrhea (Younas et al., 2021) [C]. Overall, the use of sofosbuvir is well-tolerated by most patients but should still be closely monitored when utilized.

## DRUGS ACTIVE AGAINST HERPES SIMPLEX VIRUS-1, -2 (HSV-1, HSV-2)

### Acyclovir [SEDA-39, 271–272; SEDA-41, 310; SEDA-43, 323]

Acyclovir and valacyclovir are commonly associated with neurotoxicity, especially in patients with renal dysfunction. In a systematic case review, 119 cases of neurotoxicity were observed: 73.9% of cases were in patients taking acyclovir and 29.4% in patients taking valacyclovir. Of the 119 patients, 49.6% were men with a mean age of 59.6 years old. Additionally, 83.3% of these cases found documentation of renal impairment to support the increased risk of neurotoxicity in patients with renal dysfunction (Brandariz-Nunez et al., 2021) [M]. A more recent finding highlighted polyuria as another complication secondary to renal dysfunction. A 53-year-old man admitted for severe hypoxemic varicella-zoster virus (VZV) pneumonia developed a rare case of severe polyuria associated with acyclovir 2 days after discharge and was associated with symptomatic orthostatic hypotensive episodes. Acyclovir-induced nephrotoxicity manifested as a delayed result of polyuria (Yvin et al., 2021) [r]. Neurotoxicity and nephrotoxicity remain the most common adverse effects associated with acyclovir and valacyclovir.

### Interferon [SEDA-41, 303; SEDA-43, 324]

In a retrospective study of 316 children (ages 1–18), receiving interferon treatment for chronic hepatitis B, the following adverse effects were observed: fever (85.76%), neutropenia (74.68%), decreased appetite (45.89%), tiredness (33.23%), hair loss (20.75%), and thyroid dysfunction (13.29%). (Scheinin et al., 2022; Wang et al., 2021) [c]. Furthermore, interferon has been linked to psychological effects. One large multicenter, double blind, prospective, randomized, placebo-controlled trial sought to find any gender differences in interferon-induced depression with pre-emptive antidepressant treatment. The study showed significantly more women without pre-emptive antidepressant therapy suffered from clinically relevant depression (MADRS values $\geq 13$, $P = 0.041$) and self-rated symptoms (BDI $\geq 17$, $P = 0.024$) while on interferon (Sarkar et al., 2021) [C]. Additionally, a case report involving a 17-year-old female found rapid onset of psychotic symptoms after interferon therapy was used for her multiple sclerosis patient (Huang et al., 2020) [A]. A retrospective case series in Thailand involving 34 patients including 26 male patients, showed interferon can exacerbate psoriasis in patients being treated for Hepatitis C (20%) (Chularojanamontri et al., 2021) [c]. Another literature search identified one multiple sclerosis patient, a 39-year-old male, who reported rare findings of atypical hemolytic uremic syndrome (aHUS) due to interferon treatment, even though he had been receiving it for almost 20 years. This case represented the latest onset of -interferon related aHUS (Parisi et al., 2021) [A]. A case report involving a 57-year-old-man described a unique case of necrotizing fasciitis due to intramuscular injection of interferon-beta-1a (Avonex®) that he had been receiving for multiple sclerosis. Interferon administration can leave room for potential adverse effects of necrotizing fasciitis if not

administered correctly described in this case report. (McDaniel & Trankiem, 2020) [A]. Interferon is associated with multiple different adverse effects and providers should continue to closely monitor patients on this medication.

# DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS (HIV): INTEGRASE INHIBITORS (INSTIS)

## Bictegravir [SEDA-41, 305; SEDA-43, 325]

Bictegravir (BIC) is most commonly associated with nausea, diarrhea, and fatigue. It is usually well-tolerated, making it first-line therapy in antiretroviral therapy (ART) naive patients. In a retrospective study, bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) was compared against darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF) to determine the effects on body mass index (BMI) in people living with HIV (PLWH) who were being initiated on single-tablet therapy for the first time. Baseline characteristics for the (BIC/FTC/TAF) cohort $N = 1134$ (female 324, male 810 with an average age of 48.9 years while the (DRV/c/FTC/TAF) cohort $N = 1116$ female 311 and male 805 with an average age of 49.2 years. Individuals taking BIC/FTC/TAF experienced a mean difference weight gain of about 2.84 kg and a mean difference BMI increase of 1.23 kg/m$^2$ more than patients taking DRV/c/FTC/TAF. As it could be a class effect of INSTIs, clinicians should be aware of this adverse effect and follow-up with patients (Emond et al., 2022) [C].

## Cabotegravir

Cabotegravir (CBG) is a newer INSTI, which is an injectable formulation and is dosed once a month after a 28-day oral lead-in period. It has been well-tolerated by most patients and is commonly associated with injection site reactions. Both ATLAS and FLAIR trials were randomized, multicenter phase 3 noninferiority trials. The ATLAS trial included 1045 patients, 280 of whom were females while the FLAIR trial included 809 patients, 237 of whom were females. During the ATLAS and FLAIR trials, it was found that approximately 85% of patients receiving CBG experienced injection site reactions at higher rates than any other adverse effect (Jaeger et al., 2021 [MC]; Orkin et al., 2021 [MC]). These adverse effects include but are not limited to, pain, swelling, nodule formation, and induration. Other common adverse effects experienced by participants included headache (~10%), nasopharyngitis (~18%), and upper respiratory infection (~16%) (Durham & Chahine, 2021) [R].

## Dolutegravir [SEDA-41, 312; SEDA-43, 326]

Dolutegravir (DTG) is most commonly associated with insomnia and small increases in serum creatinine similar to cobicistat. For some time, it was thought the use of dolutegravir in pregnant patients resulted in birth defects, limiting its use in this population. A recent retrospective cohort study of 1427 women in Brazil showed newborns exposed to dolutegravir throughout pregnancy had no incidences of neural tube defects. DTG is usually well tolerated in most patients; however, recent studies are showing that the use of DTG may be associated with increases in BMI (Pereira et al., 2021) [C]. A retrospective cohort study of 211 female and 249 male who were virally suppressed adolescents showed increases in BMI from approximately 0.3 kg/m$^2$ per year to 1.2 kg/m$^2$ per year upon transition to DTG, with the biggest increase seen in female patients. Medical professionals should be cognizant of these potential changes when prescribing DTG (Thivalapill & Simelane, 2021) [C].

## Elvitegravir [SEDA-41, 307; SEDA-43, 326]

Integrase inhibitors (INSTIs) are recommended as first-line therapy in ART regimens due to their low barriers to resistance in addition to their ease of tolerability. Elvitegravir (EVG) is found in single-tablet combination therapies EVG/c/FTC/TDF and EVG/c/FTC/TAF and is usually associated with gastrointestinal effects. A recent case report in Barcelona described a 57-year-old male with a past medical history of HIV, HBV, and HCV on a regimen of EFV/FTC/TDF who was found to have a serious case of cholestasis after switching to EVG/c/FTC/TAF. At baseline, the patient's labs were within normal limits (WNL) and had already achieved viral suppression. Due to a possible drug-drug interaction with HCV treatment, the ART regimen was changed to EVG/c/FTC/TAF. Approximately 3 months later, the patient was found to have elevated liver function tests (LFTs) but was asymptomatic. The EVG/c/FTC/TAF was discontinued and RPV/FTC/TAF was initiated which saw a normalization of the patient's LFTs (Ugarte et al., 2021) [A]. Despite advantages of therapy, elvitegravir can cause rare but serious side effect of cholestasis.

## Raltegravir [SEDA-41, 313]

Raltegravir (RAL) is generally well tolerated, but can be associated with myopathies, CPK elevations, and rhabdomyolysis similar to HMG-CoA reductase inhibitors (statins). RAL is rarely correlated with neuropsychiatric effects, but a recent study utilizing data from the Women's Interagency HIV Study (WIHS) may be possible. A total of 551 women from the original study met the inclusion criteria which included completion of >1 WIHS study visit prior to either starting or switching to

an INSTI-based regimen. Investigators analyzed subscale scores from the PTSD Civilian Checklist. Women with post-traumatic stress disorder (PTSD) who were starting a RAL-based regimen were found to have experienced improvement in arousal subscale symptoms ($P = 0.03$), but those who switched to a RAL-based regimen had deterioration of their re-experiencing subscale symptoms ($P < 0.005$). Clinician should take into consideration the results from this study when switching to ART regimens containing RAL in patients with PTSD (O'Halloran et al., 2021) [C].

## DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS (HIV): NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

### Doravirine [SEDA-41, 306]

Even though doravirine (DOR) is overall well tolerated, it is commonly associated with dizziness, nausea, and headaches. In a recent review article on the effects of second-generation NRTIs such as DOR on neuropsychiatric adverse effects (NPAE), DOR was associated with NPAE such as headache, sleep disturbances, dizziness, and mood changes. Data on DOR was derived from two Phase-III studies: DRIVE-AHEAD and DRIVE-FORWARD. In the DRIVE-AHEAD study, overall rates of NPAE observed in the DOR group was 26% compared to 59% in the efavirenz group. In the DRIVE-FORWARD study, treatment experienced patients that switched from an NNRTI or boosted protease inhibitor, elvitegravir, only 1.6% of the patients experienced NPAE mainly headache. DOR has less NPAE compared to efavirenz, but similar NPAE as rilpivirine (RPV) which can be cause for concern when used in patients with pre-existing disorders as RPV has warnings and precautions against its use in these populations (Senneker & Tseng, 2021) [R].

### Efavirenz [SEDA-41, 310]

Efavirienz (EFV) is commonly associated with central nervous system CNS psychiatric effects such as depression, vivid dreams, insomnia, and metabolic effects such as hypertriglyceridemia. More studies have been carried out to explore the cognitive effects of EFV use. A recent study in C57BL/6 mice showed that long-term use can be associated with dose-dependent cognitive deficits due to neuroinflammation. Mice who were given 40 mg/kg experienced impairment of short-term memory and those given 80 mg/kg experienced significant impairment of short-term memory and spatial learning (Zhang et al., 2021) [E]. In rare cases, EFV may result in hepatic impairment which can be seen when monitoring LFTs. A recent prospective study substantiated a relationship between EFV use and liver injury. 75% of the patients had liver biopsies conducted with 60% experiencing submassive necrosis, 35% with nonspecific hepatitis, and 5% with mixed cholestatic hepatitis (Maughan et al., 2021) [R]. Patients receiving efavirenz should be monitored for neuropsychiatric and hepatic adverse effects.

### Etravirine

Etravirine (ETR) is a second-generation NNRTI which has a higher barrier to resistance than first-generation NNRTIs. It is commonly associated with rash and increases in liver enzymes. In a recent Phase I/II multicenter study including 26 children (46.2% girls) aged 1 year to <6 years from South Africa, Brazil, and the United States, approximately 20% experienced adverse effects which included rash, cough, nasal congestion, rhinorrhea, pharyngitis, diarrhea, and vomiting. Two children experienced elevated lipase levels, which is a rare adverse effect of ETR use, and resulted in one leaving the study (MacBrayne et al., 2021) [M]. Another study aimed to determine the long-term effects of ETR on the reproductive system, liver, kidneys, and bones in mature 8-week-old male Wistar rats. ETR was administered at a dose of 40 mg/kg for 16 weeks. At the end of the study, the authors concluded that ETR interfered with vitamin D metabolism and oxidative stress which could potentiate infertility, however, no effects on bones in growing rats was reported. In conclusion, monitoring of vitamin D levels may be essential in patients on ETR (Matuszewska et al., 2021) [E].

### Nevirapine [SEDA-41, 310]

Nevirapine (NVP) is also a second-generation NNRTI, which is commonly associated with lipid panel increases, hepatotoxicity, and neutropenia. In a multinational phase I/II proof-of-concept study on the pharmacokinetics of NPV was studied in 438 neonates at least 34 weeks gestational age. A NPV dose of 6 mg/kg twice daily for full-term neonates, and 4 mg/kg then 6 mg/kg twice daily for those considered preterm was most commonly associated with adverse effects such as neutropenia (25%) and anemia (6%) (Ruel et al., 2021) [MC]. In a pharmacovigilance study of 352 notifications, adverse effects reported by 272 males and 80 females were observed in Cuban patients living with HIV/AIDS utilizing a database. This study found approximately 30% of reported adverse effects were associated with the use with NVP. The main adverse effects reported were hypersensitivity reactions (24.4%), anemia (15.6%), and gastrointestinal effects (15.9%) (Morales-Pérez, 2021) [R]. Although NVP is tolerated well overall, patients should be observed for serious side effects of granulocytopenia.

### Rilpivirine [SEDA-41]

Rilpivirine (RPV) is commonly associated with CNS psychiatric effects such as depression/mood changes, metabolic effects, gastrointestinal effects, and in rare cases hepatic injury. In a systematic review/meta-analysis of 20 studies that included a total of 10988 patients (majority male), the authors found the combination of DTG/RPV was associated with an increase in depressive symptoms when compared with DTG and RPV used alone (Allen Reeves et al., 2021) [M]. In a United Kingdom case report, a 27-year-old Mediterranean male who had been switched from RAL to RPV saw an increase in his LFTs approximately 14 weeks later. The patient was switched to RAL on week 66, which showed an improvement in his liver function, however, that was changed to DRV/r on week 71 due to changes in the patient's mood. The patient was able to see a normalization of his LFTs and resolution of his nausea by week 92 (Lee et al., 2020) [A]. Patients on RPV should be monitored for changes in mood/behavior as well as liver function tests.

## DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS (HIV): NUCLEOSIDE/-TIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

### Abacavir (ABC) [SEDA-35, 516; SEDA-36, 415; SEDA-37, 337; SEDA-38, 270; SEDA-39, 276; SEDA-41, 307; SEDA-43, 326]

Abacavir (ABC) is a NRTI, which has been commonly associated with headache, fatigue, and nausea. Moreover, it has some warnings and precautions due to its association with an increased risk of cardiovascular disease in some patients. In a recent review on the use of antiretroviral therapy in older people with HIV, it was discussed that ABC can be associated with increased risk of myocardial infarction when compared to the other NRTIs. The study also mentioned the NA-ACCORD study, which found that persons with recent ABC exposure had an 84% increase in MI risk compared with those without recent ABC exposure [adjusted hazard ratio = 1.84 (1.17–2.91). The findings of these studies warrant caution when using ABC in older populations (Richterman & Sax, 2020) [M].

### Emtricitabine (FTC) [SEDA-43, 327]

Emtricitabine (FTC) is another NRTI that is commonly used in various ART regimens. It is most commonly associated with headache, dizziness, gastrointestinal (GI) hyperpigmentation, and rash. A post hoc analysis of the phase III AMBER and phase III EMERALD trials aimed at investigating the incidence and prevalence of adverse effects of an ART regimen containing DRV/c/FTC/TAF. The analysis included 725 patients from the AMBER trial and 1141 patients in the EMERALD trial followed through week 96. Patients experienced GI side effects such as nausea and diarrhea, however, they resolved in a few weeks for most patients (median duration 8–16 weeks). However, 10 patients in the AMBER trial required treatment for a GI side effect; two patients discontinued treatment due to medication related diarrhea. While six patients required treatment for a GI adverse effect; two patients stopped treatment due to medication related adverse effects of diarrhea and abdominal pain (Dunn et al., 2022) [M]. GI intolerance is considered a barrier to the use of this regimen; however, as these adverse effects resolved shortly after treatment initiation, patient should be educated to increase compliance.

### Lamivudine (3TC) [SEDA-35, 517; SEDA-36, 416; SEDA-37, 338; SEDA-39, 276; SEDA-41, 308; SEDA-43, 326]

The NRTI Lamivudine (3TC) is often used as the backbone of several ART regimens. Lamivudine is usually well-tolerated in patients with minimal adverse effects such as headache and nausea. NRTIs have a black box warning of lactic acidosis, which is very rare. A case report from 2021 found a special case of lethal metabolic acidosis in a 70-year-old man in Switzerland on long-term NRTI-based antiretroviral therapy (ART) who had developed atypical necrotizing fasciitis approximately 1 month after kidney transplantation. A biopsy of the fasciitis areas was completed and then the patient was placed on supportive therapy with 2–4 μg/min of norepinephrine. In the following days, the patient's hemodynamic status slowly declined, and he was empirically placed on broad-spectrum antibiotics and norepinephrine had to be increased to 12 μg/min. Five days after admission into the ICU, medical staff noticed a steep increase in lactate from 1.2 to 6.3 mmol/L, which resulted in metabolic acidosis. The medical staff discontinued ABC/3TC and initiated intermittent high-flux hemodialysis. Plasma lamivudine levels were observed at 2035 ng, approximately 52 times the normal level in patients with normal renal function (Hollinger et al., 2021) [A]. NRTI sparing regimens can be a potential solution in patients presenting with sepsis to prevent hyperlactatemia.

### Tenofovir disoproxil fumarate (TDF) [SEDA-35, 518; SEDA-36, 418; SEDA-37, 338; SEDA-38, 272; SEDA-39, 276–277; SEDA-41, 308–309; SEDA-43, 326]

Tenofovir disoproxil fumarate (TDF) is commonly associated with gastrointestinal effects, headache, depression, decreased bone mineral density, and nephrotoxicity.

A very rare side effect of TDF use is Fanconi syndrome, which can manifest itself as hypokalemic periodic paralysis (HPP). In a case study, a 28-year-old South Korean man who had been on tenofovir for hepatitis B infection was suspected to have HPP with hypophosphatemia (phosphorus level of 1.1 mg/dL) as a result of receiving one dose of injected betamethasone for a herpes outbreak on the lips. Symptoms started the same night after receiving betamethasone. Patient's symptoms dramatically improved after treatment with intravenous phosphorus and potassium supplementation, and he was fully recovered in 12 h. It was hypothesized that TDF may have served as a risk factor for glucocorticoid-induced HPP in this patient (Shin et al., 2021) [A]. Although glucocorticoid-induced HPP is rare, clinicians should be aware of this serious adverse effect.

### Tenofovir alafenamide (TAF) [SEDA-41, 309; SEDA-43, 326]

Similar to TDF, Tenofovir alafenamide (TAF) is commonly associated with headache, decreased bone mineral density, and sometimes nephrotoxicity. In a recent case study, it was suspected that a 49-year-old Thai woman experienced worsening in renal function approximately 3 months after switching ART regimen from TDF/FTC/LPV/r to TAF/FTC/DTG. At her 6-month follow-up appointment, her serum creatinine was still worsening, prompting a renal biopsy which showed renal toxicity. Discontinuation of the TAF/FTC/DTG resulted in an improvement in the patient's renal function (Ueaphongsukkit et al., 2021) [A]. In a retrospective cohort study that included 74 males and 28 females aged 30–82 years old, it was found that switching from TDF to TAF resulted in no changes to the phosphate homeostasis in patients with isolated hypophosphatemia. The lack of change in phosphate levels can be cause for concern in patients with decreased bone density. Medical professionals should be mindful of these adverse effects when prescribing TAF (Sandmann et al., 2021) [c].

## DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS (HIV): PROTEASE INHIBITORS (PIS)

### Atazanavir (ATV) [SEDA-41, 311]

Atazanavir (ATV) is commonly associated with an array of adverse effects, which include rash, lipid panel changes, gastrointestinal upset, hepatic effects, and an increase in CPK, and is rarely associated with osteoporosis. In an in vivo live cell imaging clinical study reviewing the effects of ATV on human mesenchymal stem cells (hMSC), it was found that ATV impaired osteogenesis, leading to decreased bone health. (Cazzaniga et al., 2021) [E]. In an in vitro study, the effects of ATV on calcium homeostasis resulted in inhibition of the sarcoplasmic reticulum's ability to transport calcium, which can lead to muscle weakness, fatigue, and even pain in some instances. (Alomar et al., 2021) [E]. More research is warranted in this area to determine which ART drugs induce similar effects on the skeletal muscle.

### Darunavir (DRV) [SEDA-41, 311; SEDA-43, 327]

Darunavir (DRV) is commonly associated with rash, lipid panel changes, and gastrointestinal effects. A pharmacovigilance study of DRV safety profile using data-mining of FDA Adverse Event Reporting System (FAERS) included 10756 reports and 27234 adverse effects of DRV. The results showed a higher rate of male patients (54.5%) and 49.31% of the adverse effects were seen in ages 18–60. The study found statistically significant adverse effects related to DRV in various organs including the liver, kidney, metabolic and nutritional system, endocrine system, eye, cardiac system, musculoskeletal system, nervous system, skin, and gastrointestinal tract as well as mitrochondrial toxicity and safety concerns in pregnancy (Tian et al., 2021) [MC]. Further clinical trials and real-world data is required to confirm these findings. It has also been hypothesized that DRV may be associated with disturbances in the endocrine system. A recent case report on a 62-year-old female taking DRV/r with chronic back pain experienced Cushing syndrome after receiving 80 mg of triamcinolone injections. The patient initially reported to the emergency department 2 weeks after receiving the injections with an acute episode of anxiety/depression and was discharged with instructions for follow-up with a psychiatrist. Another 2 weeks had passed, and the patient presented to the outpatient HIV clinic with complaints of worsening depression/anxiety and with classic symptoms of Cushing's such as the moon face and buffalo hump The mechanism by which the Cushing's syndrome arose from a drug-drug interaction between the two medications. Discontinuation of the offending agent resulted in the resolution of the patient's symptoms (Mohan et al., 2021) [A].

## DRUGS ACTIVE AGAINST INFLUENZA VIRUS: NEURAMINIDASE INHIBITOR

### Oseltamivir [SEDA-41, 314; SEDA-43, 327]

Oseltamivir: Oseltamivir has been recently under surveillance for drug-induced neuropsychiatric effects in patients. An analysis of adverse events using the Japanese Adverse Drug Event Report database showed that neuraminidase inhibitors, especially oseltamivir, were associated with reports of abnormal behavior in pediatric patients (Wakabayashi et al., 2022) [MC] A retrospective

audit of 203 critically ill patients (96 males and 107 females, median age 56.9 years) showed that oseltamivir has also been associated with clinically relevant bradycardia in critically ill patients (MacLaren et al., 2021) [C]. Clinicians should be aware of the adverse effects associated with oseltamivir and educate patients and family members to monitor closely.

### Zanamivir [SEDA-41, 315]

Zanamivir has been available through a global compassionate use program (CUP) by GlaxoSmithKline (GSK) since 2009. Data was collected prospectively for this program and reporting of serious adverse events (SAEs) was mandatory and recorded in the GSK safety database. In total, 4033 requests for zanamivir treatment were received in hospitalized patients. Drug-related SAEs were reported in 41 (11%) patients, including hepatic failure in 2% and acute kidney injury in 1% of the patients (Wang-Jairaj et al., 2021) [MC]. Although rare, zanamavir can lead to serious side effects and providers should be aware and monitor as appropriate.

## DRUGS ACTIVE AGAINST INFLUENZA VIRUS: ENDONUCLEASE INHIBITOR

### Baloxavir marboxil [SEDA-41, 315; SEDA-43, 327]

Baloxavir marboxil, although a fairly new drug, has been associated with an increased risk of bleeding in patients treated for influenza. In 2019, bleeding symptoms were added to the package insert after 13 patients were identified with bleeding symptoms. In a retrospective cohort study based on a large-scale Japanese employment-based health insurance claims database, 498 237 patients (271 997 males and 226 240 females) were treated with anti-influenza drugs, with which 207 630 patients (207 630 males and 91 796 females) received baloxavir marboxil. In the baloxavir group, 397 bleeding events occurred (19%), which was similar to oseltamivir, zanamivir, and laninamivir (Hara et al., 2021) [MC]. Patients receiving antiviral medications for influenze should be monitored for signs and symptoms of bleeding.

## CONCLUSION

Our immune system is good in keeping majority of viral infections at bay but some viral infections like HBV, HCV, CMV, HIV, HSV, and influenza virus are frequently treated using antiviral drugs. Given the severity of certain side effects associated with antivirals, it is pertinent that monitoring parameters and careful considerations are taken during treatment with antivirals.

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