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EVALUATION OF ADVERSE DRUG REACTIONSON ANTIRETROVIRAL THERAPY ON HIV PATIENTS

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ABSTRACT

Antiretroviral therapy has transformed HIV into a manageable chronic disease, but antiretroviral medications have the potential to cause short-term and long-term adverse effects. Medication- related adverse effects may manifest in overt symptoms or initially only as laboratory abnormalities. The spectrum of potential antiretroviral drug toxicity is broad, including renal toxicity, mitochondrial and metabolic effects, gastrointestinal symptoms, weight gain, cardiovascular effects, hypersensitivity, skin reactions, insomnia, and neuropsychiatric manifestations. In general, newer antiretroviral medications have improved safety profiles compared with older antiretroviral medications, and this is reflected in the recommendations issued in the Adult and Adolescent ARV Guidelines. Clinicians who provide care to persons with HIV should have an understanding of the basic toxicity profile of antiretroviral medications,keeping in mind that the potential adverse effects of most antiretroviral medications are less toxicthan the effects of untreated HIV. This Topic Review will explore antiretroviral-associated adverse effects by drug class and by specific drug. Issues related to drug interactions with antiretroviral medications are addressed in the Topic Review Drug Interactions with Antiretroviral Therapy.

KEYWORDS: Pharmacovigilance, Antiretroviral Therapy, HAART, Adverse Drug Reeactions, Heptatoxicity, Osteonecrosis, Lactic Acidosis.

INTRODUCTION

Pharmacovigilance is defined as the detection, assessment, understanding and prevention of adverse drug reaction (ADRs) of any drugs or any drug related problems. ADR in patients can occur due to variety of medications and drugs and can occur mild to severe cases. All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient. Abetter understanding of the adverse effects of antiretroviral agents is of interest not only for HIV specialists as they try to optimize therapy, but also for other physicians who care for HIV- positive patients.

Antiretroviral Therapy

The treatment for HIV is called antiretroviral therapy (ART). ART involves taking a combination of HIV medicines (called an HIV treatment regimen) every day. ART is recommended for everyone who has HIV. People with HIV should start taking HIV medicines as soon as possible. ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives. ART also reduces the risk of HIV transmission. A main goal of HIV treatment is to reduce a person's viral load to an undetectable level. An undetectable viral load means that thelevel of HIV in the blood is too low to be detected by a viral load test. People with HIV who maintain an undetectable viral load have effectively no risk of transmitting HIV to their HIV- negative partners through sex. HIV attacks and destroys the infection-fighting CD4 cells of the immune system. Loss of CD4 cells makes it hard for the body to fight off infections and certain HIV-related cancers. HIV medicines prevent HIV from multiplying (making copies of itself), which reduces the amount of HIV in the body (called the viral load). Having less HIV inthe body gives the immune system a chance to recover and produce more CD4 cells. Even though there is still some HIV in the body, the immune system is strong enough to fight off infections and certain HIV-related cancers.

Approved Antiretroviral Medications & Their Combination-

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)- NRTIs force the HIV virus to use faulty versions of building blocks so infected cells can't make more HIV.

- Abacavir, or ABC (Ziagen)
- Didanosine, or ddl (Videx)

- Emtricitabine, or FTC (Emtriva)
- Lamivudine, or 3TC (Epivir)
- Stavudine, or d4T (Zerit)
- Tenofovir alafenamide, or TAF (Vemlidy)
- Tenofovir disoproxil fumarate, or TDF (Viread),
- Zidovudine or ZDV (Retrovir)

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)- These are also called "non-nukes." NNRTIs bind to a specific protein so the HIV virus can't make copies of itself, similar to jamming a zipper.

- Cabotegravir/rilpivirine (Cabenuva)
- Delavirdine or DLV (Rescripor)
- Doravirine, or DOR (Pifeltro)
- Efavirenz or EFV (Sustiva)
- Etravirine or ETR (Intelence)
- Nevirapine or NVP (Viramune)
- Rilpivirine or RPV (Edurant)

Protease Inhibitors (PIs)- These drugs block a protein that infected cells need to put together new HIV virus particles.

- Atazanavir or ATV (Reyataz)
- Darunavir or DRV (Prezista)
- Fosamprenavir or FPV (Lexiva)
- Indinavir or IDV (Crixivan)
- Lopinavir + ritonavir, or LPV/r (Kaletra)
- Nelfinavir or NFV (Viracept)
- Ritonavir or RTV (Norvir)
- Saquinavir or SQV (Invirase, Fortovase)
- Tipranavir or TPV (Aptivus)

Integrase Inhibitors- These stop HIV from making copies of itself by blocking a key protein thatallows the virus to put its DNA into the healthy cell's DNA. They're also called integrase strand transfer inhibitors (INSTIs).

- Bictegravir or BIC (combined with other drugs as Biktarvy)
- Dolutegravir or DTG (Tivicay)
- Elvitegravir or EVG (Vitekta)
- Raltegravir or RAL (Isentress)

Fusion Inhibitors - Unlike NRTIs, NNRTIs, PIs, and INSTIs -- which work on infected cells -- these drugs help block HIV from getting inside healthy cells in the first place.

Enfuvirtide, or ENF or T-20 (Fuzeon) gp120 Attachment Inhibitor - This is a new class of drug with currently just one medication, fostemsavir (Rukobia). It is for adults who have tried multiple HIV medications and whose HIV has been resistant to current available therapies. It targets the glycoprotein 120 on the surface of the virus, stopping it from being able to attach itself to the CD4 T-cells of your body'simmune system.

CCR5 Antagonist - Maraviroc, or MVC (Selzentry), also stops HIV before it gets inside a healthy cell, but in a different way than fusion inhibitors. It blocks a specific kind of "hook" onthe outside of certain cells so the virus can't plug in.

Post-Attachment Inhibitor or Monoclonal Antibody - This is a new class of antiviral medication specifically for adults living with HIV who have tried multiple HIV medications and whose HIVhas been resistant to current available therapies. Ibalizumab-uiyk (Trogarzo) blocks your body's HIV infected cells from spreading the virus into those which are uninfected. It is administered byIV.

Pharmacologic enhancers, or "Drug Boosters" - Ritonavir (RTV), taken in a low dose, increases blood levels of lopinavir (LPV) and the drug LPV/r (Kaletra). Cobicistat (Tybost) does the same thing in combination with atazanavir, darunavir, elvitegravir.

- Atazanavir + cobicistat, or ATV/c (Evotaz)
- Darunavir + cobicistat, or DRV/c (Prezcobix)
- Elvitegravir + TDF + FTC + cobicistat, or EVG/c/TDF/FTC (Stribild)
- Elvitegravir + TAF + FTC + cobicistat, or EVG/c/TAF/FTC (Genvoya)

Fixed-Dose Combinations

Some drug manufacturers put together specific medicines into a single pill so they're easier totake, including:

Integrase strand transfer inhibitor (INSTI)-based

- Bictegravir + tenofovir alafenamide + emtricitabine, or BIC/TAF/FTC (Biktarvy)
- Dolutegravir + abacavir + lamivudine, or DTG/ABC/3TC (Triumeq)
- Dolutegravir + rilpivirine, or DTG/RPV (Juluca)
- Dolutegravir + lamivudine, or DTG/3TC (Dovato)
- Elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine or EVG/c/TAF/FTC(Genvoya)
- Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine, or EVG/c/TDF/FTC (Stribild)

Protease inhibitor (PI)-based

- Atazanavir + cobicistat, or ATV/c (Evotaz)
- Darunavir + cobicistat, or DRV/c (Prezcobix)
- Darunavir + cobicistat + tenofovir alafenamide + emtricitabine, or DRV/c/TAF/FTC)(Symtuza)

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based

- Doravirine + tenofovir disoproxil fumarate + lamivudine, or DOR/TDF/3TC (Delstrigo)
- Efavirenz + tenofovir disoproxil fumarate + emtricitabine, or EFV/TDF/FTC (Atripla)
- Rilpivirine + tenofovir alafenamide + emtricitabine , or RPV/TAF/FTC (Odefsey)
- Rilpivirine + tenofovir disoproxil fumarate + emtricitabine or RPV/TDF/FTC (Complera)

Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-based

- Abacavir + lamivudine, or ABC/3TC (Epzicom)

- Abacavir + lamivudine + zidovudine, or ABC/3TC/ZDV (Trizivir)
- Tenofovir alafenamide + emtricitabine, or TAF/FTC (Descovy)
- Tenofovir disoproxil fumarate + emtricitabine, or TDF/FTC (Truvada)
- Tenofovir disoproxil fumarate + lamivudine, or TDF/3TC (Cimduo)
- Zidovudine + Lamivudine or ZDV/3TC (Combivir)

Adverse Effects of Antiretroviral Agents

Adverse effects have been reported with all antiretroviral (ARV) drugs and, in the earlier era of combination antiretroviral therapy (ART), adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence. Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated because most clinical trials use highly specific inclusion criteria which exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, bone loss, and weight gain. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and managed. When selecting an ARV regimen, clinicians must consider potential adverse effects, as well as the individual's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of adverse effects. For example, underlying liver disease from alcohol use, coinfection with viral hepatitis, and/or liver steatosis mayincrease the risk of hepatotoxicity when efavirenz (EFV) or protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Certain ARVs may exacerbate pre-existing conditions, for example, psychiatric disordersmay be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors.
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications, for example, when pharmacokinetic boosters such as ritonavir or cobicistatare used, or when isoniazid is used with EFV.
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction, EFV neuropsychiatric toxicity and QTc prolongation, and atazanavir (ATV)-associated hyperbilirubinemia.

Table-1: Common and/or Severe Adverse Effects Associated with AntiretroviralTherapy

In this article we review the adverse effects of HAART therapy, with specific attention to the metabolic abnormalities associated with HIV treatment, including dyslipidemias, diabetes mellitus, insulin resistance, and the lipodystrophy syndrome and lactic acidosis associated with NRTI mitochondrial toxicity. Our aim is to help physicians gain a working knowledge of these adverse effects, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, promoting the early recognition and reversal of potentially serious adverse effects, and reducing the potential for adverse drug interactions.

Antiretroviral therapy can have a wide range of adverse effects on the human body (Fig. 1). Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy.[6] Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV. Several uncommon but more serious adverse effects associated with antiretroviral therapy, including AZT-associated anemia, d4T- associated peripheral neuropathy, PI-associated retinoid toxicity (exemplified by pruritus and ingrown toenails) and NNRTI-associated hypersensitivity reactions, are treated according to accepted therapy for these conditions in patients not receiving HAART. However, the subtle and serious nature of other adverse effects — lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash.

Adverse effects for ARV drugs that are no longer commonly used in clinical practice (ddI, d4T, FPV/r, IDV, NFV, SQV/r, and TPV/r) have been removed from this table, with the exception of lipodystrophy and peripheral neuropathy associated with ddI and d4T. Because these effects may persist long after discontinuation of ddI or d4T, and patients may still present with these long- lasting toxicities, the drugs remain listed among the ARVs associated with these two effects.

This table focuses on ARV-associated adverse effects that a patient may experience as a result of taking an ARV regimen. In this table, N/A indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bone Density Effects	**TDF**: Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. **TAF**: Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	**ZDV**: Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	**RPV, EFV**: QTc prolongation	**ATV/r and LPV/r**: PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A	N/A
Cardiovascular Disease	**ABC**: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	**Boosted DRV and LPV/r**: Associated with cardiovascular events in some cohorts	N/A	N/A

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Cholelithiasis	N/A	N/A	**ATV**: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A
Dyslipidemia	**ZDV > ABC**: ↑ TG and ↑ LDL **TAF**: ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	**EFV**: ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-Boosted PIs**: ↑ TG, ↑ LDL, ↑ HDL **LPV/r > DRV/r and ATV/r**: ↑ TG	**EVG/c**: ↑ TG, ↑ LDL, ↑ HDLL	N/A
Gastrointestinal Effects	**ZDV > Other NRTIs**: Nausea and vomiting	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) **LPV/r > DRV/r and ATV/r**: Diarrhea	**EVG/c**: Nausea and diarrhea	**IBA**: In a study of 40 people, 8% of patients reported diarrhea.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in Patients with HBV/HIV Coinfection or when HBV Resistance Develops**: Patients with HBV/HIV coinfection may develop severe hepatic flares. **ZDV**: Steatosis	**EFV**: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **NVP**: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	**All PIs**: Drug-induced hepatitis and hepatic decompensation have been reported. **ATV**: Jaundice due to indirect hyperbilirubinemia	**DTG**: Persons with HBV or HCV coinfection may be at higher risk of DTG-associated hepatotoxicity.	**MVC**: Hepatotoxicity with or without rash or HSRs reported.

5/6/2021 Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy | NIH

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC**: **Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. **HSR Symptoms (in Order of Descending Frequency)**: Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	**NVP**: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	**RAL**: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. **DTG**: Reported in <1% of patients in clinical development program	**MVC**: HSR reported as part of a syndrome related to hepatotoxicity.
Lactic Acidosis	**Reported with Older NRTIs, d4T, ZDV, and ddI,** but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A
Lipodystrophy	**Lipoatrophy**: Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, TAF or TDF.	**Lipohypertrophy**: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A

https://clinicalinfo.hiv.gov/en/table/table-17-common-andor-severe-adverse-effects-associated-antiretroviral-therapy 4/6

5/6/2021 Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy | NIH

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Myopathy/Elevated Creatine Phosphokinase	**ZDV**: Myopathy	N/A	N/A	**RAL and DTG**: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A
Nervous System/Psychiatric Effects	**History of Exposure to ddI, ddC, or d4T**: Peripheral neuropathy (can be irreversible)	**Neuropsychiatric Events**: EFV > RPV, DOR, ETR **EFV**: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. **RPV**: Depression, suicidality, sleep disturbances **DOR**: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm	N/A	**All INSTIs**: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A

https://clinicalinfo.hiv.gov/en/table/table-17-common-andor-severe-adverse-effects-associated-antiretroviral-therapy 5/6

5/6/2021 Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy | NIH

Adverse Effect	Drug Class				
	NRTIs	**NNRTIs**	**PIs**	**INSTIs**	**EIs**
Rash	**FTC**: Hyperpigmentation	All NNRTIs	ATV, DRV, and LPV/r	All INSTIs	MVC, IBA
Renal Effects/Urolithiasis	**TDF**: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. **TAF**: Less impact on renal biomarkers and lower rates of proteinuria than TDF.	**RPV**: Inhibits Cr secretion without reducing renal glomerular function.	**ATV and LPV/r**: Associated with increased risk of chronic kidney disease in a large cohort study. **ATV**: Stone or crystal formation. Adequate hydration may reduce risk. **COBI (as a Boosting Agent for DRV or ATV)**: Inhibits Cr secretion without reducing renal glomerular function.	DTG, COBI (as a Boosting Agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function	**IBA**: SCr abnormalities ≥Grade 3 reported in 10% of trial participants.
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV	Some reported cases for DRV, LPV/r, and ATV	RAL	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF, and greater with DOR than EFV.			INSTI > other ARV drug classes	N/A

Key : 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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Discussion on Adverse Drug Reactions and its Overview

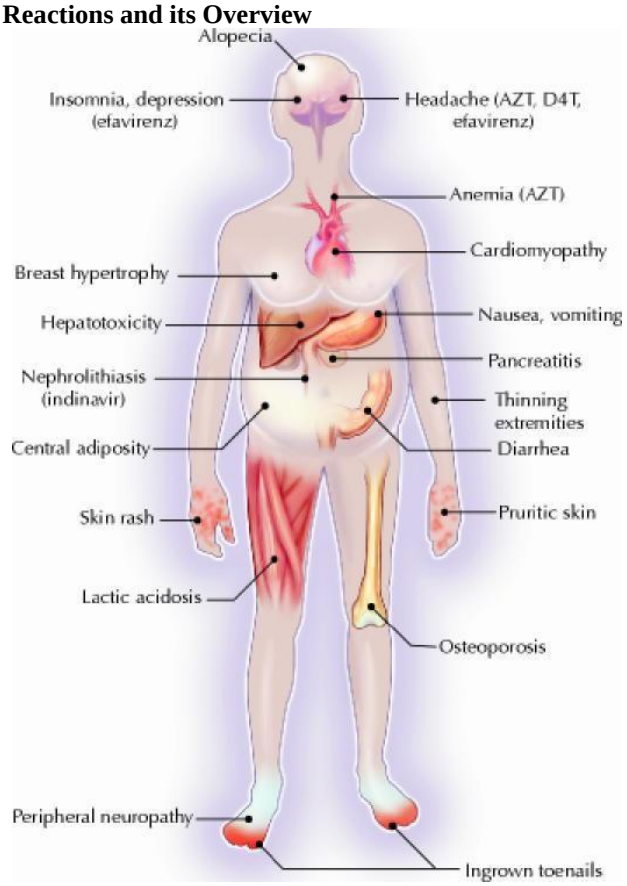

Figure 1: Common Adverse Drug Reaction on HIV Patients.

Lactic acidosis, hepatic steatosis and hyperlactatemia

NRTIs are nucleoside analogues that prevent DNA elongation and viral reproduction. These drugs are triphosphorylated intracellularly to become nucleotides and are then incorporated into the viral DNA chain by the viral reverse transcription enzyme; their presence in the DNA halts transcription. Unfortunately, these drugs can theoretically also function as substrates for other enzymes capable of DNA formation, including human DNA polymerase γ,7 the only enzyme involved in the replication of mitochondrial DNA. Recent work has described disruption of mitochondrial function through NRTI-mediated inhibition of human DNA polymerase γ, with subsequent adverse events ranging from nucleoside-associated lactic acidosis to hepatic steatosis. Lactic acidosis has been associated with AZT, ddI and d4T therapy. Given its potential lethality, awareness of the signs and symptoms of NRTI-associated lactic acidosis (Box 1) is important in the management of HIV- infected patients. The clinical course is characterized by often vague complaints of malaise, nausea and vomiting, fatigue and tachypnea, followed by liver failure, cardiac dysrhythmias and death.

Hepatotoxicity

Transaminitis and hepatotoxicity are associated with most of the antiretroviral agents, although initially most concern focused on the PIs. The hepatotoxicity of this drug class varies with the specific drug: in a prospective cohort study, 30% of patients who initiated treatment with ritonavir (RTV) but only 6% to 7% of those who initiated therapy with saquinavir, nelfinavir (NFV) or indinavir (IDV) experienced severe hepatotoxicity (defined as a grade 3 or 4 change in the serum levels of alanine aminotransferase and aspartate aminotransferase). The rate of severe hepatotoxicity associated with any PI among patients with hepatitis C infection was 12%, twice as high as among patients without hepatitis C infection.The risk of liver enzyme elevation among patients with chronic hepatitis B or C was, respectively, 2.77- or 2.47-fold greater after initiationof a PI-containing regimen than among patients without evidence of viral hepatitis. In this context, it has been suggested that successful treatment of hepatitis C in dually infected patients may facilitate the introduction of PI-containing antiretroviral therapy. Coadministration of low- dose RTV with other PIs is now common; in fact, the newest member of the class represents a coformulation of lopinavir and low-dose RTV The extent to which such combinations will affectthe safety profiles of the individual agents remains to be fully characterized. In addition, there have been recent attempts to understand the hepatic histologic changes, other than elevation of transaminases, that occur with PI-containing antiretroviral regimens. It was reviewed liver biopsy samples from 182 patients with both HIV and hepatitis C. The liver fibrosis stage was lower among patients receiving PIs than among those who had never received

PI therapy. The authors concluded that long-term use of PIs may have a beneficial impact on the progression of liver fibrosis in patients infected with HIV and hepatitis C. The NNRTIs are also associated withtransaminitis and hepatotoxicity. It was found that the rate of hepatotoxicity was 8.9% (95% confidence interval [CI] 6.6% to 11.2%) and 10.8% (95% CI 3.3% to 18.3%), respectively, among patients receiving NVP and EFV. These 2 drugs were significantly more likely to be associated with grade 3 or 4 elevation of transaminases than DLV (DLV v. NVP: OR 2.7 [95% CI 1.6 to 4.7], p = 0.003; DLV v. EFV: OR 2.5 [95% CI 1.2 to 5.5], p = 0.01). It have been observed similar rates of hepatotoxicity for NVP and EFV but found that elevation of CD4 cell count of more than 50/μL was most strongly linked to hepatotoxicity, perhaps due to adherence or immune reconstitution. The hypersensitivity reaction observed with NVP (characterized by rash and fever) can also include severe transaminitis. In one study in which NVP was used for postexposure prophylaxis, 2 patients experienced liver failure, and 1 of them required liver transplantation. Therefore, NVP is no longer used for postexposure prophylaxis and is used with caution in the setting of liver disease. Finally, as discussed in the previous section, the NRTIs are associated with risk of mitochondrial toxicity and hepatic steatosis. While these may be particular problems with d4T and ddI, the overall rate of severe hepatotoxicity with NRTI therapy reported by Reisler and colleagues was 12%, which highlights the complexity and difficulty of evaluating and managing hepatotoxicity associated with antiretroviral therapy.

Hyperglycemia

New-onset diabetes mellitus, clinically similar to type 2 diabetes, affects a small proportion (1% to 6%) of HIV-infected patients treated with PI-based antiretroviral regimens. Many more patients receiving PI therapy have evidence of insulin resistance without frank diabetes. However, insulin resistance may also be associated with HIV infection itself in patients not receiving PI therapy, perhaps resulting from the direct effects of the HIV virus on pancreaticβ cell function and insulin secretion.

Fat misdistribution

Lipodystrophy is part of a metabolic syndrome that includes dyslipidemias, insulin resistance and accelerated bone loss. Lipodystrophy affecting HIV-positive patients was first described in 1998. The main clinical features are peripheral fat loss (lipoatrophy) in the face, limbs and buttocks, accompanied by central fat accumulation in the abdomen and breasts and over the dorsocervical spine (the “buffalo hump”) and lipomas. PI therapy has been most strongly linked to the lipodystrophy syndrome, although NRTIs, especially d4T, have also been associated with lipodystrophy. The overall prevalence of at least one physical abnormality related to lipodystrophy has been estimated at about 50% after more than a year of antiretroviral therapy.

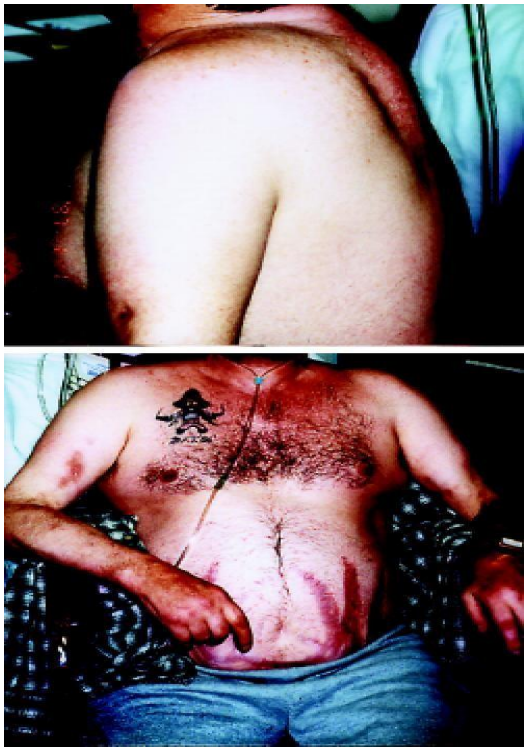

Figure 2: Fat Misdistribution on HIV Patients as ADR of medicines.

Increased bleeding episodes among patients with hemophilia

Soon after the introduction of PIs, several case reports suggested an association between these drugs and increased frequency and severity of bleeding in patients with hemophilia. In most patients, bleeding increased within the first few weeks of PI therapy, but the onset ranged from afew days to many months after initiation of therapy. Not only did bleeding occur more frequently, but it occurred at unusual sites such as the small joints of the hands and the soft tissues of the palms. Although most PIs have been implicated, RTV in particular is associated with this adverse effect. The mechanism is unknown. However, the patients' coagulation parameters are typically normal, and factor VIII replacement is not efficacious in resolving the bleeding.

Hemophiliac patients taking PIs should be monitored for increased bleeding, and PI therapy should be discontinued if it occurs. If undergoing surgery, these patients may benefit from temporary cessation of PI therapy during the perioperative period. When possible, a non-PIregimen should be considered for these patients.

Osteonecrosis, osteopenia and osteoporosis

Osteonecrosis results in cell death of various bone components, including fat marrow and mineralized tissue. It is not a specific entity but a final common pathway of several conditions that may impair blood supply to the bone. The first report of osteonecrosis in association with HIV infection described an HIV-infected woman who presented post partum with avascular necrosis of multiple bones, as well as a similar

case in a young HIV-positive man with no other risk factors who was not receiving antiretroviral therapy. After HAART became available, additional cases emerged, some linked to hyperlipidemia and others to alcoholism, pancreatitis, corticosteroid therapy and hypercoagulability, all previously described risk factors for osteonecrosis. There is no apparent difference in the overall use of PIs among HIV-infected patients with and without osteonecrosis.

Osteonecrosis occurs only rarely in HIV patients. For example, in one series 6 cases occurred among 508 HIV patients (of whom 280 were receiving triple therapy). Although unusual, osteonecrosis is a serious bone abnormality that can lead to the need for joint replacement. HIV- infected patients presenting with persistent hip, knee or shoulder pain, especially in the absence of trauma, should undergo MRI to evaluate for possible osteonecrosis.

The diagnosis of osteoporosis is based on measurement of bone mineral density, which can beaccomplished by a variety of techniques. However, the current standard of care and the most widely accepted method is dual-energy x-ray absorptiometry (DEXA) at the spine and hip.

Osteoporosis in HIV-infected patients was reported in the pre-HAART era, when it was thoughtto be secondary to poor nutrition or perhaps increased cytokine levels related to chronic infection. After the introduction of HAART, Tebas and collaborators reported a cross-sectional

DEXA analysis of whole body, lumbar spine and proximal femur bone mineral density in 112 male subjects: 50% of the HIV-positive patients receiving PIs, but only 23% of HIV-positive patients not receiving PIs and 29% of healthy seronegative controls, had osteoporosis or osteopenia ($p = 0.02$).

The pathophysiology of osteoporosis in the setting of HIV infection is unclear. In some studies osteoporosis occurred in conjunction with antiretroviral-associated lactic acidosis, a situation in which phosphate may act as a buffer. It was postulated that PIs may inhibit new bone formation by stimulating osteoclast activity or inhibiting osteoblast activity. The PIs are metabolized by cytochrome P450 enzymes, and inhibition of 2 cytochrome P450 mixed-function oxygenases that mediate vitamin D activation has been suggested as a possible mechanism for development of osteoporosis. It was found that the PIs IDV, RTV and NFV all inhibited conversion of 25- hydroxy vitamin D to 1,25-dihydroxy vitamin D in vitro.

The need for formal osteoporosis evaluation and therapy in HIV-infected patients remains to be clarified. However, patients with additional risk factors for osteoporosis (e.g., corticosteroid use, postmenopausal) should be considered for evaluation with DEXA scanning. Treatment of osteoporosis in the setting of antiretroviral therapy is evolving, and referral for specialist assessment, when possible, is warranted. Standard therapy, including vitamin D and calcium supplementation and exercise, as well as pharmacologic measures such as hormone replacement and bisphosphonate therapy, may be indicated. Review of the patient's current antiretroviral combination should also be considered, although the links between specific medications and risk of osteoporosis have yet to be defined.

Skin rash

Rash is a common adverse effect of the NNRTIs, particularly NVP. Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash, with or without pruritus, on the trunk, face and extremities, within the first 6 weeks on therapy. If the rash occursduring the initial 2-week dose lead-in period, the dose should be held at 200 mg daily until the rash resolves. Although most rashes are self-limited, NVP should be permanently discontinued if the rash is severe or accompanied by constitutional symptoms.Severe rashes occur in about 6.5% of NVP-treated patients, mainly during the first 4 weeks of treatment, including Stevens- Johnson syndrome and toxic epidermal necrolysis in less than 1% of all patients treated with NVP.

The nucleoside analogue ABC causes a hypersensitivity syndrome in 3% to 5% of patients, who present with nonspecific symptoms (including malaise and fever, with or without rash) starting during the first 6 weeks of treatment. The symptoms worsen with continued therapy and resolve gradually after discontinuation of the drug. Rechallenge with ABC after a hypersensitivity reaction should not be attempted, as severe symptoms may occur rapidly, including life- threatening hypotension and death. Risk factors for ABC hypersensitivity have not been identified.

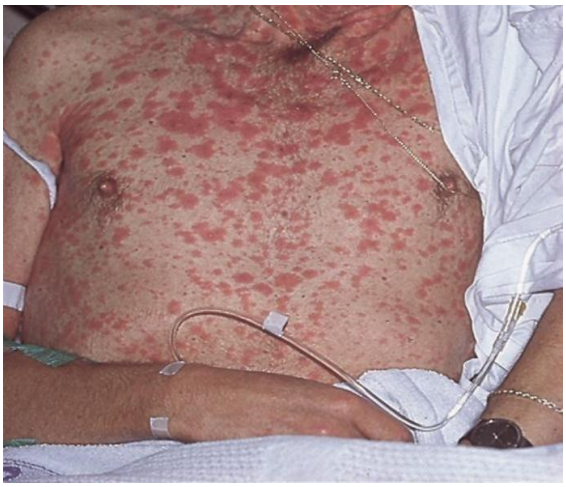

Figure 3: Skin Rashes as Adverse Drug Reaction.

Monitoring of patients who are receiving HAART

Routine laboratory monitoring should be done

approximately every 3 months to determine whether the patient has asymptomatic abnormalities. Monitoring laboratory tests include complete and differential blood counts and measurement of electrolyte, creatinine, liver transaminase, bilirubin and amylase levels. Patients should also be monitored at regular intervals (approximately every 3 months) for dyslipidemia, diabetes, and lipoaccumulation or lipoatrophy. This laboratory work should include determination of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and fasting blood glucose levels. Patients should be asked about and examined for changes in fat distribution. Imaging tests, such as abdominal CT to detect visceral fat, are not recommended for routine monitoring.

Patients switching from PI-based therapy to NNRTI or triple-nucleoside regimens have shown improvements in lipodystrophy, dyslipidemia and insulin resistance. However, not all switch studies have shown beneficial effects. As well, some patients have no alternatives to PI-based regimens because their infection is resistant to other classes of antiretrovirals. In this situation, treatment for dyslipidemia should be the same as for dyslipidemia in the general population, including lifestyle modifications and pharmacotherapy. Diabetes and insulin resistance should also be treated in accordance with national guidelines. Lipodystrophy has no easy and proven treatment. Intense exercise can decrease central fat accumulation but may increase peripheral fat wasting. Surgery, such as implants for facial atrophy and liposuction for buffalo humps, is another option but is not widely recommended.

NRTIs have few interactions with other medications. Clinically significant interactions usuallyinvolve additive toxicity (e.g., bone marrow suppression or neuropathy) or problems with drugabsorption (e.g., ddI buffered tablets when given with fluoroquinolones.)

PIs and NNRTIs are metabolized through the cytochrome P450 enzyme system and can also be inducers or inhibitors of this system. Levels of antiretrovirals and concomitant medications that are metabolized by this system can be dramatically altered if these agents are given together, which can result in toxic effects or ineffectiveness of therapy. RTV is the most potent inhibitor of the cytochrome P450 system and the most likely to interact with other medications. Caution is advised when interpreting drug interaction information. Most such information covers only 2- way interactions, whereas most HIV-infected patients take 3 or more medications.

CONCLUSIONS

Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient nonadherence. To optimize adherence, and hence efficacy, clinicians must focus on preventing adverse effects, when possible, and distinguishing those that are self-limited from those that are potentially serious. As efforts continue in the development of medications with more favourable adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with antiretroviral use.

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