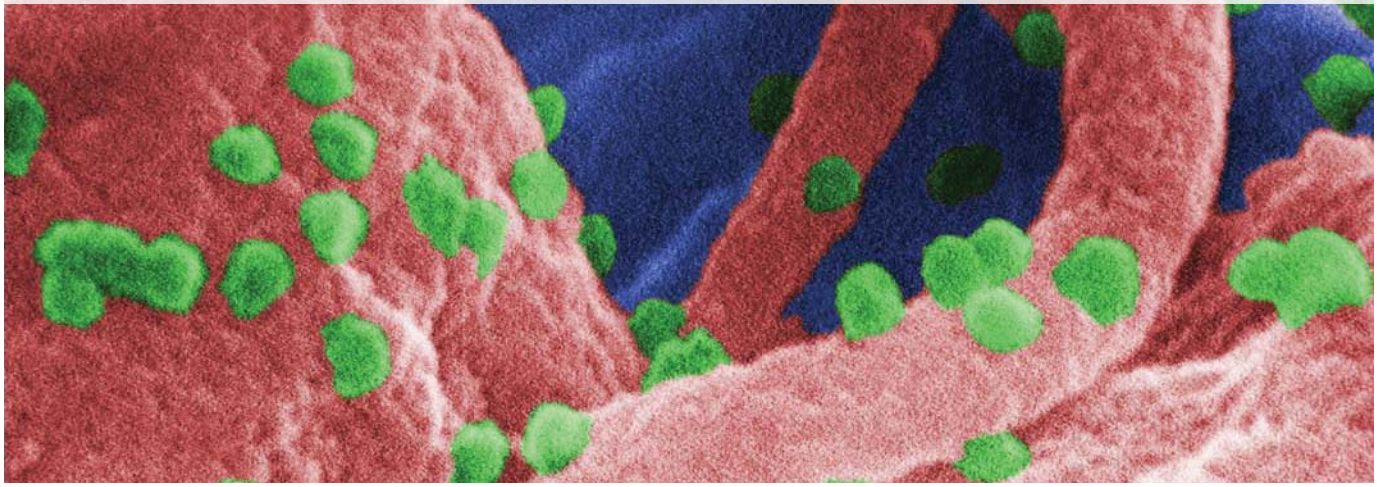
FEATURE

Drug Interactions Among HIV Patients Receiving Concurrent Antiretroviral and Pain Therapy

Antiretroviral therapy has been implicated in significant interactions among agents that are used to treat comorbid pain conditions, such as symmetrical polyneuropathy.



Sarah E. Crana, PharmD
Graduate Pharmacist
Albany College of Pharmacy and Health Sciences
Albany, NY

Jeffrey Fudin, BS, PharmD, FCCP
Adjunct Associate Professor of Pharmacy Practice
Albany College of Pharmacy and Health Sciences
Clinical Pharmacy Specialist in Pain Management
Samuel Stratton VA Medical Center
Albany, NY

The advent of highly active antiretroviral therapy (HAART) in 1996 represented a huge breakthrough in the treatment of HIV. The approach has changed a previously fatal disease into one that is chronic but manageable. However, antiretroviral therapy (ART) has been implicated in significant interactions with a variety of drug classes used to treat comorbid conditions in patients with HIV.

A recent survey conducted by Evans-Jones et al indicated that only 36% of clinically significant drug–drug interactions were identified by physicians in an HIV clinic.[1] Thus, more emphasis should be placed on identifying and managing pharmacokinetic interactions in this patient population. This article will assess the interactions between antiretroviral agents (Table 1) and neuropathic pain medications (both approved and off-label; Table 2), with the aim of assisting clinicians involved in pain management for patients with HIV.[1,2]

Distal Symmetrical Polyneuropathy

One of the most common neuropathies associated with HIV is distal symmetrical polyneuropathy (DSPN), which occurs in 35% to 67% of patients with HIV. The prevalence of DSPN may be increasing, however, because of the introduction of newer ARTs, and the incidence rate among different cohorts are variable.[3]

The pathogenesis of DSPN is unknown but is assumed to be multifactorial. The common clinical presentation includes bilateral numbness, tingling, stiffness, burning, and/or loss of sensation in the feet. Hyperpathia and contact sensitivity also may be present. A neurologic exam uncovers reduced or absent deep tendon reflexes of the ankles. Symptoms occurring in the distal upper extremities or knees are rare and generally indicate severe progression.[3,4]

In the pre-HAART era, risk factors for developing DSPN included lower CD4 lymphocyte counts, higher viral load, increased age, advanced HIV disease (ie, AIDS diagnosis), and use of dideoxynucleoside analog antiretrovirals. However, HAART has reduced disease progression, increased patient immunity and therapy options,

Table 1. Antiretroviral Agents	
Generic	**Brand**
Non-Nucleoside Reverse Transcriptase Inhibitors	
Delavirdine	Rescriptor
Efavirenz	Sustiva
Etravirine	Intelence
Nevirapine	Viramune, Viramune XR
Rilpivlrine[a]	Edurant
Nucleoside Reverse Transcriptase Inhibitors	
Abacavir	Ziagen, Epzicom (combination of abacavir and lamivudine)
Didanosine	Videx, Videx EC, generic
Emtricitabine	Emtriva
Lamivudine	Epivir
Stavudine	Zerit, generic
Tenofovir	Viread
Zidovudine	Retrovir, generic
Protease Inhibitors	
Atazanavir	Reyataz
Darunavir	Prezista
Fosamprenavir	Lexiva
Indinavir	Crixivan
Lopinavir-ritonavir	Kaletra
Nelfinavir	Viracept
Ritonavir	Norvir
Saquinavir	Invirase
Tipranavir	Aptivus
Fusion Inhibitors	
Enfuvirtide	Fuzeon
Maraviroc	Selzentry
Integrase Strand Transfer Inhibitor	
Raltegravir	Isentress

[a] FDA appproved in May 2011

and aultimately decreased the pre-HAART risk factors. However, DSPN remains a common feature of HIV infection that may result from the use of certain nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) alone or in combination. Adjunctive medications—such as vincristine, dapsone, isoniazid, thalidomide, and hydroxyurea, which are commonly used for comorbid conditions—also have been implicated in the development of peripheral neuropathy (PN).[3,4]

Diagnosis and Treatment

Because DSPN can be difficult to distinguish from other disease states, clinicians will need to perform a differential diagnosis. Laboratory screening and physical examination should be performed to determine any underlying causes. Blood evaluations should include measurements of vitamin B_{12} and folate, hepatitis C antibody, thyroid-stimulating hormone, blood glucose, blood urea nitrogen, and creatinine, as well as serum protein electrophoresis, immunoelectrophoresis, and rapid plasma reagin. Other considerations, such as nutritional status and the presence of addiction (ie, chronic alcoholism), also may play a role and should be assessed. If these evaluations yield significant findings, the underlying cause should be corrected first. If the differential diagnostic screens are negative, the patient's medication therapy should be assessed for iatrogenic neuropathy.[3,4]

The dideoxynucleoside analogs known to cause PN are didanosine, stavudine, and zalcitabine (discontinued by the manufacturer in the United States in 2006).[5] These have the highest incidence of iatrogenic neuropathy and were the main cause of drug-induced DSPN prior to HAART. DSPN occurs more frequently with stavudine (8%-52%) than with didanosine (17%-26%).[5,6] Certain PIs and NRTIs (eg, saquinavir, ritonavir, and lamivudine) also have been implicated in the development of PN; however, the incidence tends to be lower compared with that seen with didanosine and stavudine. The incidence of PN occurs in up to 6% of patients using ritonavir, a PI commonly used in HAART as a pharmaco-enhancer.[4-7]

The proposed mechanism of neurotoxicity of these agents is inhibition of DNA polymerase-γ, leading to mitochondrial dysfunction. Iatrogenic DSPN is dose-dependent and occurs within 7 to 9 weeks of treatment initiation.[4,8] Symptom improvement can continue for 8 weeks after discontinuation or dose reduction of the offending agent. High viral load also may be associated with the development of DSPN. Therefore, maintaining therapeutic control is important, and viral load must be assessed when DSPN is suspected. [4,8]

Table 2. Agents Used in Treatment of Neuropathic Pain		
Generic	**Brand**	**Interaction With ART**
Anticonvulsants		
Carbamazepine[a]	Carbatrol, Epitol Equetro,Tegretol, Tegretol XR, generic	Yes
Gabapentin	Gralise, Horizant, Neurontin, generic	No
Lamotrigine[a]	Lamictal, Lamictal ODT, Lamictal XR, generic	Yes
Levetiracetam[a]	Keppra, Keppra XR, generic	No
Oxcarbazepine[a]	Trileptal, generic	No
Phenytoin[a]	Dilantin, Phenytek, generic	Yes
Pregabalin	Lyrica	No
Topiramate[a]	Topamax, Topamax Sprinkle, Topiragen, generic	No
Valproic acid[a]	Depakene, Stavzor, generic	Yes
Zonisamide	Zonegran, generic	No
Antidepressants		
Dopamine Reuptake Inhibitor		
Bupropion[a]	Aplenzin, Budeprion SR, Budeprion XL, Buproban, Wellbutrin, Wellbutrin SR, Wellbutrin XL, generic	Yes
Serotonin Norepinephrine Reuptake Inhibitors		
Duloxetine	Cymbalta	No
Milnacipran[a]	Savella	No
Venlafaxine[a]	Effexor XR, generic	Yes
Tetracyclic		
Mirtazapine	Remeron, Remeron SolTab, generic	No
Tricyclics		
Amitriptyline[a]	Generic	Yes
Clomipramine[a]	Anafranil, generic	Yes
Desipramine[a]	Norpramin, generic	Yes
Doxepin[a]	Silenor, generic	Yes
Imipramine[a]	Tofranil, Tofranil-PM, generic	Yes
Nortriptyline[a]	Pamelor, generic	Yes
Trimipramine[a]	Surmontil	Yes
Opioid Analgesics[b]		
Fentanyl	Abstral, Actiq, Duragesic, Fentora, Onsolis, generic	Yes
Hydrocodone/APAP	Anexsia, Ceta-Plus, Co-Gesic, Hydrocet, Hydrogesic, Hy-Phen, Lortab, Lorcet, Maxidone, Norco, Stagesic, T-Gesic, Vicodin, Xodol, Zydone, generic	Yes

Table 2. Agents Used in Treatment of Neuropathic Pain (Continued)		
Generic	**Brand**	**Interaction With ART**
Hydromorphone	Dilaudid, Exalgo, generic	No
Levorphanol	Generic	No
Dronabinol	Marinol, generic	Yes
Methadone	Dolophine, Methadone Intensol, Methadose, generic	Yes
Morphine	Avinza, Kadian, MS Contin, Oramorph SR, generic	No
Oxycodone	OxyContin, Roxicodone, generic	Yes
Oxymorphone	Opana, Opana ER, generic	No
Tapentadol	Nucynta	No
Tramadol	Rybix ODT, Ryzolt, Ultracet, Ultram ER, generic	Yes
Other		
Baclofen[a]	Generic	No
Capsaicin (topical)	Qutenza, generic	No
Ketamine[a]	Ketalar, generic	No
Lidocaine (topical)[a]	Lidoderm, generic	No
Memantine[a]	Namenda, Namenda XR	No
Mexiletine[a]	Generic	Yes

APAP, acetaminophen; ART, antiretroviral therapy; DSPN, distal symmetrical polyneuropathy
[a] Off-label use.
[b] Although no opioids have the specific indication for DSPN, all those listed are indicated for either acute or chronic pain, depending on the formulation.

Optimal viral suppression is defined as a viral load that remains steadily below 20 to 75 copies/mL, which is considered the "detection level." Virologic failure is defined as a persistent viral load of greater than 200 copies/mL.

Many factors can contribute to virologic failure, including the medication regimen. Suboptimal pharmacokinetics, drug–drug interactions with concomitant medications, and prescription errors also have been cited.[1,4] Certain drug interactions can either decrease the effectiveness of an ART regimen or increase drug-related adverse effects. The latter can contribute to poor adherence, which in turn can lead to virologic failure. In particular, pain management often presents a therapeutic challenge due to cytochrome P450 (CYP) drug interactions. It is essential for clinicians to facilitate ART adherence whenever possible. Adherence is necessary to maintain viral suppression and prevent resistance, which can lead to a loss of potential drug classes for treatment and increases the risk for transmitting drug-resistant HIV.[9] Table 3 provides known CYP drug interactions and clinical management for all antiretroviral agents and neuropathic pain treatments.

Overview of Cytochrome P450

The CYP system is comprised of heme-containing enzymes that are differentiated by molecular weight, CO_2-binding spectra, electrophoretic and immunologic properties, and catalytic activities toward different drugs. They are named by their ability to absorb light at or near 450 nm. Individual purified CYPs are distinguished on the basis of spectral properties, molecular masses, substrate selectivities, and immunoreactivities by monoclonal antibodies that are specific for single epitopes (ie, antigen sequences in a molecule). An individual cytochrome in the P450 family may have several different epitopes. In general, CYP with greater than 40% sequence identity are included in the same family, and those with greater than 55% homology are included in the same subfamily.[10]

Medications that undergo metabolism within the CYP system are

Text Continued on Page 120

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Agent[a]	Interacting Agents	Interaction	Mechanism of Interaction[b]	Clinical Management
Antidepressants				
Tricylic Antidepressants Agents				
Amitriptyline	Atazanavir	↑ amitriptyline serum concentrations and potential toxicity	3A4 inhibition by atazanavir	Monitor plasma concentrations of amitriptyline and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Fosamprenavir		3A4 inhibition by fosamprenavir	
	Ritonavir		3A4 inhibition by ritonavir	
Clomipramine	Atazanazir	↑ clomipramine serum concentrations and potential toxicity	3A4 inhibition by atazanavir	Monitor plasma concentrations of clomipramine and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Fosamprenavir		3A4 inhibition by fosamprenavir	
Desipramine	Darunavir (ritonavir-boosted)	↑ desipramine serum concentrations and potential toxicity	3A4 inhibition by ritonavir	Concurrent use of ritonavir-boosted darunavir with desipramine can increase serum concentrations of desipramine; monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Fosamprenavir		3A4 inhibition by fosamprenavir	Monitor plasma concentrations of desipramine and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Ritonavir		3A4 inhibition by ritonavir	
	Tipranavir (ritonavir-boosted)		3A4 inhibition by tipranavir	
Doxepin	Fosamprenavir	↑ doxepin serum concentrations and potential toxicity	3A4 inhibition by fosamprenavir	Monitor plasma concentrations of doxepin and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
Imipramine	Atazanazir	↑ imipramine serum concentrations and potential toxicity	3A4 inhibition by atazanavir	Monitor plasma concentrations of imipramine and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Fosamprenavir		3A4 inhibition by fosamprenavir	
	Ritonavir		2D6 and 3A4 inhibition by ritonavir	

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Nortriptyline	Fosamprenavir	↑ nortriptyline serum concentrations and potential toxicity	3A4 inhibition by fosamprenavir	Monitor plasma concentrations of nortriptyline and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
Trimipramine	Atazanazir	↑ trimipramine serum concentrations and potential toxicity	3A4 inhibition by atazanavir	Monitor plasma concentrations of trimipramine and monitor for signs of toxicity (anticholinergic effects, confusion, sedation, cardiac arrhythmias)
	Fosamprenavir		3A4 inhibition by fosamprenavir	
Other Antidepressant Agents				
Bupropion	Nelfinavir	↑ bupropion serum levels	Inhibition of the hydroxylation of bupropion by nelfinavir	Monitor for increased bupropion side effects (insomnia, hallucinations, agitation, anxiety)
	Efavirenz	↓ bupropion serum levels	2B6 induction by efavirenz	Increase dose if necessary and do not exceed the maximum daily dose of 450 mg
	Lopinavir-ritonavir		2B6 induction by ritonavir	
	Ritonavir			
	Tipranavir (ritonavir-boosted)		2B6 induction by tipranavir	
Venlafaxine	Atazanavir	↑ venlafaxine serum levels	3A4 inhibition by atazanavir	Monitor for signs of venlafaxine toxicity (nausea, dizziness, drowsiness); decrease dose if necessary
	Indinavir	↓ indinavir serum levels	One study of 9 healthy volunteers found 150 mg/d of venlafaxine led to a 28% decrease in AUC and 36% decrease in C_{max} for a single 800-mg dose of indinavir; the clinical significance is unknown.[26]	Use caution; monitor for indinavir response
	Nelfinavir	↑ venlafaxine serum levels	3A4 inhibition by nelfinavir	Monitor for signs of venlafaxine toxicity (nausea, dizziness, drowsiness); decrease dose if necessary
	Ritonavir		2D6 and 3A4 inhibition by ritonavir	
	Saquinavir		3A4 inhibition by saquinavir	

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Anticonvulsant Agents				
Carbamazepine	Darunavir (ritonavir-boosted)	↑ carbamazepine serum levels	3A4 inhibition by ritonavir	Ritonavir-boosted darunavir can increase plasma concentrations of carbamzepine; if concurrent use is necessary, monitor carbamazepine levels and adjust dose as needed. On initiation, no dose adjustment is required
	Delviradine	↓ delaviridine serum levels	3A4 induction by carbamazepine	Concurrent use is not recommended; potential loss of delaviridine therapeutic effect
	Efavirenz	↓ efavirenz serum levels		Concurrent use is not recommended; potential loss of efavirenz therapeutic effect
	Etravirine	↓ etravirine serum levels		Concurrent use is not recommended; potential loss of etravirine therapeutic effect
	Fosamprenavir	↓ fosamprenavir serum levels		Concurrent use is not recommended; potential loss of fosamprenavir therapeutic effect
	Indinavir	↓ indinavir serum levels		Concurrent use is not recommended; potential loss of indinavir therapeutic effect
	Lopinavir-ritonavir	↓ lopinavir serum levels		Due to induction of lopinavir metabolism, of lopinavir-ritonavir should not be given once daily with carbamazepine; lopinavir-ritonavir–containing HAART can increase serum carbamazepine levels, resulting in toxicity; reduce carbamzepine dose by 25%-50% and monitor serum carbamazepine levels 3-5 days after initiating PI therapy.

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Carbamazepine (continued)	Maraviroc	↓ maraviroc serum levels	3A4 induction by carbamazepine nevirapine	Concurrent use is not recommended; potential loss of maraviroc therapeutic effect; if concurrent use is necessary, dose of maraviroc should be increased to 600 mg twice daily[43]
	Nelfinavir	↓ nelfinavir serum levels		Concurrent use is not recommended; potential loss of nelfinavir therapeutic effect
	Nevirapine	↓ nevirapine serum levels		Concurrent use is not recommended; potential loss of nevirapine therapeutic effect
	Ritonavir	↓ ritonavir serum levels		Concurrent use is not recommended; potential loss of ritonavir therapeutic effect
	Saquinavir	↓ saquinavir serum levels		Concurrent use is not recommended; potential loss of saquinavir therapeutic effect
Lamotrigine	Lopinavir-ritonavir	↓ lamotrigine serum levels	Glucuronidation induction by ritonavir[17]	Monitor for lamotrigine effectiveness and adjust dose as needed
	Ritonavir			
Phenytoin	Darunavir (ritonavir-boosted)	↓ steady state phenytoin levels	3A4 induction by phenytoin	Monitor phenytoin levels and adjust dose as needed
	Delaviridine	↓ trough plasma delaviridine concentrations		Concurrent use is not recommended; potential loss of delavirine therapeutic effect
	Efavirenz	↓ efavirenz and/or phenytoin serum levels	3A4 induction by efavirenz and phenytoin	Monitor phenytoin levels and efavirenz efficacy
	Etravirine	↓ etravirine serum levels	3A4 induction by phenytoin	Concurrent use is not recommended; potential loss of etravirine therapeutic effect

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Phenytoin (continued)	Fosamprenavir	↓ fosamprenavir serum levels and ↓ phenytoin serum levels if administered with ritonavir	3A4 induction by phenytoin; possible 2C9 induction by ritonavir can decrease phenytoin levels	Adjustments to fosamprenavir-ritonavir are not recommended if patient is receiving phenytoin concomitantly; monitor phenytoin levels and increase dose as needed
	Indinavir	↓ indinavir serum levels	3A4 induction by phenytoin	Use caution; monitor indinavir efficacy
	Lopinavir-ritonavir	↓ lopinavir serum concentrations and may ↓ steady-state phenytoin levels		Use caution; monitor phenytoin levels; do not administer once-daily dosing of lopinavir-ritonavir with phenytoin
	Maraviroc	↓ maraviroc levels		Concurrent use is not recommended; potential loss of maraviroc therapeutic effect; if concurrent use is necessary, the dose of maraviroc should be increased to 600 mg twice daily[43]
	Nelfinavir	↓ phenytoin serum levels	3A induction by nelfinavir	Monitor phenytoin levels; increase dose as needed
	Ritonavir	↓ phenytoin serum levels	2C9 induction by ritonavir	
	Saquinavir	↓ saquinavir serum levels	3A4 induction by phenytoin	Use caution; monitor for saquinavir efficacy
	Tipranavir	↓ tipranavir serum levels	3A induction by phenytoin	Use caution; monitor for tipranavir efficacy
	Zidovudine	↑ zidovudine serum levels	Inhibition of zidovudine glucuronidation	Monitor for signs of zidovudine toxicity (fatigue, nausea, asthenia, anemia, neutropenia, hepatotoxicity); decrease zidovudine dose when it is administered with phenytoin

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Valproic acid	Lopinavir-ritonavir	↓ valproic acid serum levels and ↑ lopinavir serum levels	Possible ritonavir induction of valproic acid metabolism via glucuronidation[18]	Monitor valproic levels and efficacy; monitor for lopinavir-ritonavir toxicity or increased AEs such as hepatotoxicity, rash, hypercholesterolemia, nausea, vomiting, diarrhea
	Ritonavir	↓ valproic acid and ↑ ritonavir serum levels[7]		Monitor valproic levels and efficacy; monitor for ritonavir toxicity or increased AEs such as vomiting, headache, rash, pancreatitis, liver failure, myelosuppression, heart block, and lactic acidosis
	Tipranavir	↓ valproic serum acid levels	Unknown[44]	Use caution; monitor for valproic efficacy and increase dose as needed
	Zidovudine	↑ zidovudine serum levels	UGT 2B7 inhibition by valproic acid[21]	Monitor for signs of zidovudine toxicity (fatigue, nausea, asthenia, anemia, neutropenia, hepatotoxicity); decrease zidovudine dose when it is administered with valproic acid if needed
Opioids				
Fentanyl	Atazanavir	↑ fentanyl serum levels	3A inhibition by atazanavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression); dose reduction is needed if continuous infusion or transdermal administration is used
	Fosamprenavir		3A inhibition by fosamprenavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression)
	Indinavir		3A inhibition by indinavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression); dose reduction is needed if continuous infusion or transdermal administration is used
	Lopinavir-ritonavir		3A4 inhibition by ritonavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression[45])

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Fentanyl (continued)	Nelfinavir	↑ fentanyl serum levels	3A inhibition by nelfinavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression); dose reduction is needed if continuous infusion or transdermal administration is used
	Nevirapine	↓ fentanyl serum levels	3A4 induction by nevirapine	Adjust/increase fentanyl dose as needed
	Ritonavir	↑ fentanyl serum levels	3A4 inhibition by ritonavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression)
	Saquinavir		3A inhibition by saquinavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression); dose reduction is needed if continuous infusion or transdermal administration is used
	Tipranavir (ritonavir-boosted)		3A inhibition by ritonavir	Monitor for signs of fentanyl toxicity (CNS depression, respiratory depression); dose reduction is necessary if continuous infusion or transdermal administration is used
Hydrocodone/ APAP	Zidovudine	APAP toxicity, neutropenia and hepatotoxicity	Unknown/conflicting literature	Avoid chronic or multiple-dose APAP; if given concurrently, monitor white blood cell count and liver function tests (hepatotoxicity may occur); aspirin or ibuprofen are suitable alternatives
Dronabinol	Ritonavir	↑ dronabinol serum levels and potential toxicity[7]	Unknown/lack of literature	Monitor for signs of toxicity (constipation, headache, sedation, diarrhea); decrease dose as needed
Methadone	Abacavir	↑ methadone clearance, decreasing serum levels	Unknown/lack of literature[46,47]	Monitor for methadone withdrawal and adjust dose as needed
	Atazanavir	↑ risk for QT interval prolongation and subsequent ventricular tachycardia	Additive AE based on case reports[34]	Use caution and monitor cardiac function

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Methadone (continued)	Darunavir (ritonavir-boosted)	↓ methadone serum levels	3A induction by ritonavir	Concurrent use of methadone with darunavir-ritonavir therapy may result in decreased methadone levels due to CYP3A metabolism induction by ritonavir; monitor for clinical response to methadone and withdrawal symptoms during maintenance therapy and adjust dose as necessary
	Delaviridine	↑ methadone serum levels	3A inhibition by delaviridine	Monitor for increased methadone AEs and reduce methadone dose[48]
	Didanosine	↓ didanosine bioavailability	Unknown/lack of literature;. hypothesized ↑ didanosine degradation in the GI tract[33]	Use caution; if concurrent use is required, use enteric-coated beadlet formulation (Videx EC); do not use pediatric powder for solution formulation with methadone because it causes significant decreases in didanosine concentration[32]
	Efavirenz	May ↓ methadone serum levels and increase risk for opioid withdrawal symptoms	3A4 induction by efavirenz	Use caution; monitor for signs of opiate withdrawal (nausea, sweating, pain, anxiety, insomnia); increase methadone dose as needed
	Etravirine	May ↑ risk for opiate withdrawal symptoms in methadone-maintained patients	Unknown	Manufacturer states that if etravirine is administered with CYP3A, 2C9, and/or 2C19 substrates, the therapeutic effect or AE profile of the coadministered drug may be altered; methadone is a 3A substrate, but these drugs can be administered together without dose adjustments; clinical monitoring for opiate withdrawal symptoms in methadone-maintained patients is recommended[39]
	Fosamprenavir	↓ methadone serum levels	3A4 induction and protein-binding displacement by fosamprenavir	Literature suggests the interaction is not clinically relevant, but the manufacturer recommends the use of caution and monitoring for signs of opiate withdrawal (nausea, sweating, pain, anxiety, insomnia); increase methadone dose as necessary[49]

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Methadone (continued)	Lopinavir-ritonavir	↓ methadone serum levels	3A induction by ritonavir	Monitor for signs of opiate withdrawal and methadone efficacy; increase methadone dose as needed; use caution if lopinavir-ritonavir is discontinued in methadone-maintained patients because this may increase methadone AEs such as QT interval prolongation[45,50]
	Nelfinavir		3A induction by nelfinavir	Monitor for signs of methadone efficacy and opiate withdrawal; increase methadone dose as needed
	Nevirapine		3A4 induction by nevirapine	
	Ritonavir		3A induction by ritonavir	
	Saquinavir (ritonavir -boosted)	↓ methadone serum levels and additive QT interval prolongation	3A induction by ritonavir	Use caution and only use together if no alternatives are available; if used concurrently, monitor methadone efficacy and adjust dose
	Stavudine	↓ stavudine bioavailability	Unknown/lack of literature. Hypothesized ↑ stavudine degradation in the GI tract.[34]	Use caution and monitor for stavudine efficacy
	Tipranavir (ritonavir-boosted)	↓ methadone serum levels	3A induction by ritonavir	Use caution if patient is receiving ritonavir-boosted tipranavir; monitor for methadone efficacy and increase methadone dose as needed
	Zidovudine	↑ zidovudine serum levels	Unknown	Monitor for signs and symptoms of zidovudine toxicity (bone marrow toxicity—anemia, leukopenia, thrombocytopenia— nausea, vomiting, increased liver enzymes and neurologic symptoms—ataxia, lethargy, peripheral neuropathy); discontinue methadone if needed

Table 3. Drug Interactions Between Agents Used to Treat Neuropathic Pain and Antiretroviral Agents

Oxycodone	Atazanavir	↑ oxycodone serum levels and ↓ oxycodone clearance	3A4 inhibition of oxycodone	Monitor for increased oxycodone AEs because concurrent use may increase risk for fatal respiratory depression; use caution if used together, monitoring patient frequently and adjusting dose as needed
	Darunavir			
	Fosamprenavir			
	Indinavir			
	Lopinavir			
	Nelfinavir			
	Ritonavir			
	Saquinavir			
	Tipranavir			
Tramadol	Ritonavir	↑ tramadol serum levels and increased risk for tramadol toxicity	3A4 inhibition by ritonavir	Monitor for signs and symptoms of tramadol toxicity (respiratory depression, sedation) and decrease tramadol dose as needed
Miscellaneous				
Mexiletine	Delavirdine	↑ mexiletine levels	2D6 inhibition by delavirdine	Monitor for increased mexiletine AEs
	Etravirine	↓mexiletine levels	Unknown	Monitor for mexiletine therapeutic effectiveness
	Ritonovir	↑ mexiletine levels	2D6 inhibition by ritonovir	Monitor for increased mexiletine AEs
	Tipranavir	↑ mexiletine levels	2D6 inhibition by tipranavir	Monitor for increased mexiletine AEs

AE, adverse event ; APAP, acetaminophen; AUC, area under the curve; CNS, central nervous system; CYP, cytochrome P450; GI, gastrointestinal; HAART, highly active antiretroviral therapy; PI, protease inhibitor; UGT, uridine diphosphate glucuronsyltransferase

[a] The following agents used in the treatment of neuropathic pain have no known CYP450 interactions: antidepressants (duloxetine, milnacipran, and mirtazapine), anticonvulsants (gabapentin, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide), opioids (hydromorphone, levorphanol, morphine, oxymorphone, and tapentadol), and miscellaneous (baclofen, capsaicin, ketamine, lidocaine, and memantine).

[b] Cytochromes are listed according to enzyme family, subfamily, and individual enzyme. In all cases were individual enzyme number is not listed, data was unavailable.

Continued from Page 108 ››

said to be *substrates* to certain metabolic enzymes. Some medications may have a direct impact on the metabolic profiles of others. These can be characterized into two groups—inducers and inhibitors. An inducer is a medication, food, or other substance that stimulates the activity of one or more CYP enzymes. When an inducer is introduced, the medication (substrate) will undergo increased metabolism, which ultimately can decrease the serum level efficacy of an affected substrate.

An inhibitor is a medication, food, or other substance that reduces the activity of one or more CYP enzymes. When an inhibitor is introduced, the medication (substrate) will undergo decreased metabolism that ultimately can increase the serum level efficacy of an affected substrate. In short, enzyme inducers may cause subtherapeutic levels of substrate medications and enzyme inhibitors may result in toxic levels of the substrate medications.[11]

Autoinducers present yet another complex issue that further complicates the understanding of CYP interactions. Autoinducers are medications that share both properties, in that they are inducers of the very same enzyme that metabolizes

them. For example, carbamazepine is a substrate for CYP3A4 enzymes.[12] Carbamazepine also is an inducer of CYP3A4 enzymes.[12] Therefore, although a patient may have perfectly therapeutic levels 2 weeks after initiating therapy, the carbamazepine serum levels may drop to a subtherapeutic level within 6 weeks of therapy because the very same enzymes that are metabolizing carbamazepine are present in greater quantities 6 weeks after therapy was initiated.[12]

Drug Interactions and Management

Anticonvulsant–Antiretroviral Interactions

Anticonvulsants often are used in the treatment of neuropathic pain. Carbamazepine and phenytoin are associated with clinically significant CYP-mediated interactions with ART. Both anticonvulsants are potent CYP3A4 enzyme inducers, which can have a negative impact on patients receiving HAART.[12,13] Both can induce the metabolism on a broad spectrum of ART, including PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the C-C chemokine receptor type 5 inhibitor maraviroc, which results in subtherapeutic HAART levels. Ultimately, this interaction can cause virologic failure.

As a result, use of an anticonvulsant other than carbamazepine and phenytoin is recommended.[9] Acceptable alternatives are zonisamide, topiramate, gabapentin, pregabalin, and levetiracetam.[13,14] These agents are not implicated in any drug interactions with antiretrovirals.[9,12-14]

Additionally, a reduction in phenytoin levels has been demonstrated when it is coadministered with ritonavir-boosted PIs. Lim et al studied the coadministration of lopinavir-ritonavir and phenytoin.[15] The authors hypothesized that a two-way drug interaction existed. Phenytoin is primarily metabolized by CYP2C9 and partially by CYP2C19. They found that the phenytoin area under the curve (AUC) was decreased by 22% with fosamprenavir-ritonavir and by 31% with lopinavir-ritonavir. Their data is the first clinical in vivo evidence that lopinavir-ritonavir may be a CYP2C9 inducer. Although the study was not designed to test for this interaction, the authors recommended that if these agents are used together, the efficacy of both medications should be monitored, or an alternative anticonvulsant should be used.[15,16] Vand Der Lee et al also found that the combination of lopinavir-ritonavir reduces lamotrigine plasma concentrations in healthy adults.[17]

Valproic acid is a weak CYP inhibitor of 3A4 and has the potential to affect the metabolism of some PIs. However, valproic acid is extensively metabolized by the liver via glucuron-conjugation (50%) and beta oxidation (40%).[17] Less than 10% of valproic acid is metabolized through the CYP system, so the pathway plays only a minor role in the drug's clearance.[18] Due to its primary metabolism by glucuronidation, valproic acid levels may decrease when it is coadministered with ritonavir-boosted PIs, such as tipranavir and lopinavir. Ritonavir affects CYP metabolism and also is a glucuronidation inducer. A case report submitted by Sheenan et al hypothesized that the valproic acid concentration in one of their patients was decreased as a result of induced clearance by the ritonavir-lopinavir combination.[18] The AUC of lopinavir has been shown to increase by 75% as well, but the mechanism is not well understood at this time. Therefore, until more clinical evidence is generated, it is necessary to monitor for efficacy and toxicity in patients treated with valproic acid combined with ritonavir-boosted PIs and lopinavir.[18]

One exception for valproic acid is its affect on the NRTI zidovudine. Zidovudine undergoes glucuronidation by the uridine diphosphate glucuronsyltransferase (UGT) 2B7 isoenzyme for its metabolism and valproic acid is a UGT 2B7 inhibitor; therefore, increased zidovudine concentrations may result.[6,19,20] In six patients, Letora et al found that the clearance of zidovudine (100 mg every 8 hours) was decreased by 38% after administration of valproate (250 or 500 mg every 8 hours).[19] Therefore, monitoring for zidovudine toxicity is recommended in patients who are concomitantly treated with valproic acid.[19,21]

Antidepressant–Antiretroviral Interactions

Tricyclic antidepressants (TCAs) often are used off-label to treat neuropathic pain.[14] Despite the rol of TCAs in pain management, their use in patients receiving HAART may present a challenge. All TCAs interact with ritonavir-boosted PIs, including atazanavir, fosamprenavir, and tipranavir. TCAs are metabolized primarily through CYP3A, making them vulnerable to 3A inducers and inhibitors. PIs are CYP3A4 inhibitors; therefore, when they are coadministered with a TCA, PIs may significantly increase the serum concentrations of a TCA. This may lead to an increase in TCA adverse events (AEs) and toxicity. Considering the narrow therapeutic index of TCAs and their significant toxicity profile, extreme caution should be exercised if TCAs must be used in patients receiving HAART. The lowest possible TCA dose should be used and the dose should be adjusted based on clinical assessment.[9] Monitoring for an increase in AEs and toxicity is necessary, as is measurement of TCA serum levels, if applicable. Signs of TCA toxicity include anticholinergic effects, confusion, sedation, seizure,

and cardiac arrhythmias.

Other antidepressants have emerged as treatment options for neuropathic pain. Duloxetine, milnacipran, and mirtazapine are three such medications that do not have any drug–drug interactions with current antiretrovirals.[22] Duloxetine is a moderate CYP2D6 inhibitor and undergoes metabolism by CYP1A2 and 2D6.[23] Milnacipran is a favorable option because it has demonstrated minimal drug–drug interactions. Milnacipran undergoes minimal metabolism, with most of it excreted in the urine unchanged or as the inactive glucurono-conjugate.[24,25] Mirtazapine also avoids CYP metabolism. It is primarily metabolized by demethylation and hydroxylation, followed by glucurono-conjugation.[26]

Bupropion, a dopamine and norepinephrine reuptake inhibitor, and venlafaxine, a serotonin norepinephrine inhibitor, also have interactions with certain antiretroviral agents. Venlafaxine is a CYP3A4 and 2D6 substrate, making its metabolism particularly susceptible to PIs, which are CYP3A4 inhibitors (ritonavir is also a 2D6 inhibitor).[27] The concomitant use of ART and venlafaxine can potentially increase venlafaxine serum concentrations, so caution is warranted. Monitoring for an increase in AEs such as nausea, dizziness, and drowsiness is recommended. If this occurs, it may be necessary to reduce the venlafaxine dose.

Another interaction occurs when indinavir is coadministered with venlafaxine. One study with nine healthy volunteers found that 150 mg per day of venlafaxine led to a 28% decrease in AUC and 36% decrease in C_{max} for a single 800-mg dose of indinavir.[27] The clinical significance of this interaction is unknown; however, the manufacturer recommends exercising caution with this combination and monitoring indinavir response closely.[27,28]

Decreased levels of bupropion can occur when it is coadministered with efavirenz, ritonavir, or the ritonavir-boosted PIs lopinavir and tipranavir because of CYP2B6 inhibition.[7,29,30] Buproprion AUC was decreased by 57% and 46%, respectively, by lopinavir-ritonavir and tipranavir-ritonavir.[9] Titrating the buproprion dose to achieve therapeutic effectiveness may be necessary if it is coadministered with the aforementioned PIs. One exception is the PI nelfinavir, which acts to increase buproprion levels due to the inhibition of bupropion hydroxylation in the liver.[9] Because this will inhibit bupropion metabolism, caution is warranted and monitoring for increased AEs such as hallucinations, agitation, anxiety, and insomnia is necessary.

Opioid–Antiretroviral Interactions

Fentanyl, methadone, tramadol, and to a lesser extent oxycodone, are implicated as the opioids most likely to interact with antiretrovirals because they all undergo metabolism through the CYP450 system.

Methadone is metabolized by CYP3A4, 2B6, 2C19 and, to a lesser extent, 2C9 and 2D6.[31] The ritonavir-boosted PIs act to decrease methadone levels through 3A4 induction by ritonavir. Ritonavir has a dose- and time-dependent inhibitory and induction effect on CYP3A. It can induce CYP3A4, 1A2, 2B6, 2C9, 2C19, and UDP-UGT enzymes.[6] Therefore, methadone induction by ritonavir may involve multiple CYP isoenzymes. Other antiretrovirals that demonstrate methadone metabolism induction by CYP3A include efavirenz and nevirapine.[6,29,32]

Methadone has been shown to decrease the bioavailability of both didanosine and stavudine. When a chronic maintenance dose of methadone was coadministered with a single 200-mg dose of didanosine, the AUC and C_{max} of didanosine were reduced by 57% and 66%, respectively.[31,33] Rainey et al found a decrease in the AUC and C_{max} for both didanosine and stavudine when they were administered with methadone.[34] They found that after 6 hours, stavudine C_{max} and AUC were reduced by 44% and 25%, respectively. The authors hypothesized that because methadone decreases gastric motility, the degradation of both antiretrovirals is increased in the gastrointestinal tract. Methadone pharmacokinetics remained unaltered.[34] Caution is warranted if concomitant use is necessary because the patient may be at risk for a decrease in HAART efficacy and virologic failure.[13]

In addition to metabolism issues, monitoring for QTc prolongation is necessary. Methadone has the potential to independently cause QT prolongation and torsades de pointes. Certain antiretrovirals can cause an additive effect when they are administered with methadone and can increase the risk for cardiac arrhythmias. These agents include atazanavir, ritonavir, saquinavir, efavirenz, and nelfinavir. Case reports were generally associated with methadone doses higher than 200 mg per day, but evidence suggests that methadone can cause cardiac AEs at lower maintenance doses as well.[31,35] Caution should be used in patients who are at risk for developing a prolonged QT interval due to cardiac abnormalities or concomitant medication use.[31] If concomitant use is necessary, electrocardiogram (ECG) monitoring must be initiated. Genentech, the manufacturer of saquinavir spells out specific guidelines for determining whether or not therapy should be discontinued:[36]

- If baseline QT interval is >450 milliseconds, do not initiate concurrent therapy.

- If baseline QT interval is <450 milliseconds, initiate therapy and perform ECG 3 to 4 days after the start of therapy.
- If during concurrent therapy QT interval is >480 milliseconds or increases >20 milliseconds from baseline, consider discontinuing one medication or both.

Another concern is the impact on methadone when a patient either starts or stops an antiretroviral agent. Certain NNRTIs, such as efavirenz and nevirapine, are significant CYP3A4 inducers. They have been shown to decrease methadone concentrations substantially and cause opioid withdrawal symptoms. Efavirenz and nevirapine decreased methadone AUC by 55% and 63%, respectively.[37] Opioid withdrawal was seen in 9 of 10 patients who also received nevirapine. Therefore, dose increases are necessary for such potent inducers. Abruptly stopping a potent CYP3A4 inducer can increase the plasma concentration of methadone significantly. This can cause an increase in AEs and toxicities (ie, respiratory depression and cardiac arrhythmias). If the methadone dose was increased to overcome an inducer interaction, it is important to counsel the patient on proper medication adherence. Patients should be advised not to discontinue ART without first consulting their physician about their methadone dose to avoid any potential AEs or toxicities.[37]

PI combination therapies such as darunavir-ritonavir and lopinavir-ritonavir have been shown to decrease methadone AUC as well. These combinations have resulted in opioid withdrawal in patients receiving these combinations.[37] Although PIs are CYP3A4 inhibitors, they can induce CYP2C19 and intestinal P-glycoprotein, which may contribute to the interaction. However, this interaction is not seen across the PI class because other PIs have not been shown to have a significant effect on methadone AUC.[37]

The interaction between fentanyl and PIs is mainly mediated by the PI inhibition of CYP3A4 because fentanyl is a CYP3A substrate. This may cause an increase in fentanyl levels. However, ritonavir also may result in an interaction. The results of a randomized controlled crossover study in 11 healthy volunteers receiving ritonavir and fentanyl demonstrated that ritonavir may decrease fentanyl clearance by 67%.[10] It is necessary to monitor for increased fentanyl AEs and toxicities in patients receiving this common combination.[6,38]

Miscellaneous Interactions With Antiretrovirals

Baclofen, ketamine, and memantidine and the topical analgesics lidocaine and capsaicin do not have any drug-–drug interactions with antiretrovirals.[39-41] Baclofen, ketamine, and memantidine are not metabolized by the CYP pathway. Memantidine and ketamine are metabolized by hydroxylation and glucuronidation. Approximately 85% of an administered baclofen dose is excreted unchanged in the urine and feces, whereas the rest is metabolized by deamination.[39] Memantidine also is known to undergo deamination, and 48% of its administered dose is excreted unchanged in the urine.[41] Although ritonavir is a glucuronidation inducer, it does not produce any clinically significant effect on these medications.

Mexiletine, an antiarrhythmic agent, is a CYP2D6 substrate. It interacts with potent CYP2D6 inhibitors such as delaviridine, ritonavir, and tipranavir. This inhibition results in a increased effect of mexiletine, which warrants the need for therapeutic monitoring. Caution also is indicated with the concomitant use of etravirine with mexiletine per the prescribing information for etravirine. Although the mechanism of the interaction is unknown, there is a possibility for mexiletine levels to decrease, resulting in loss of pharmacologic effect.[42]

Conclusion

The therapeutic management of a patient with HIV presenting with DSPN can be a challenge. It is imperative that clinicians are educated about the consequences of drug metabolism and how it can affect therapeutic outcomes. Understanding the pharmacokinetics of both DSPN treatment and antiretrovirals can help guide prescribing decisions and optimize pain management, while minimizing the risk for antiretroviral resistance due to drug interactions associated with analgesic therapy. ■

Authors' Bios: *Sarah E. Crana, PharmD, is staff pharmacist at Shop Rite Pharmacy. At the time of submission, she was a student pharmacist at the Albany College of Pharmacy & Health Sciences.*

Dr. Jeffrey Fudin is adjunct associate professor of pharmacy practice at Albany College of Pharmacy & Health Sciences and clinical pharmacy specialist in pain management at the Samuel Stratton VA Medical Center in Albany, NY.

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