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eHIV Review

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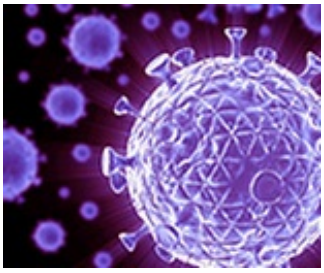

VOLUME 3 - ISSUE 2

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HIV: Management of Concomitant Conditions

After participating in this activity, the participant will demonstrate the ability to:

- Identify important drug-drug interactions that may impact the treatment of ischemic heart disease in people living with HIV.
- Summarize HIV medication interactions that could influence the treatment of common comorbid diseases.
- Describe potential drug-drug interactions between antiretroviral agents and common over-the-counter medications.

Guest Faculty Disclosure
Dr. Wurcel has disclosed that she is a site principal investigator for a ViiV Healthcare study.

Unlabeled/Unapproved Uses
Dr. Wurcel has indicated there will be no references to the unlabeled or unapproved use of any drugs or products in today's discussion.

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Podcast Transcript

BOB BUSKER: Welcome to this *e*HIV Review podcast.

I'm Bob Busker, managing editor of *e*HIV Review. Our guest today is Dr. Alysse Wurcel, assistant professor of medicine in the Division of Geographic Medicine and Infectious Disease at Tufts Medical Center. We're here today to follow up on her recent newsletter issue on HIV and Lung Disease.

***e*HIV Review is presented by the Johns Hopkins University School of Medicine. This program is supported by educational grants from Gilead Sciences, Inc. and ViiV Healthcare.**

Learning objectives for this audio program include:

- **Identify important drug-drug interactions that may impact the treatment of ischemic heart disease in people living with HIV.**
- **Summarize HIV medication interactions that could influence the treatment of common comorbid diseases.**
- **Describe potential drug-drug interactions between antiretroviral agents and common over-the-counter medications.**

Dr. Wurcel has disclosed that she is a site principal investigator for a ViiV Healthcare study, and she has indicated there will be no references to the unlabeled or unapproved use of any drugs or products in today's discussion.

Dr. Wurcel, thank you for joining us today.

DR. ALYSSE WURCEL: Thanks for having me.

MR. BUSKER: In your newsletter issue, you focused on some of the challenges in managing lung diseases in people living with HIV. Today I'd like to expand that focus to discuss some of the other common comorbid conditions affecting people on antiretroviral regimens, in particular potentially dangerous drug-drug interactions that clinicians may not be aware of. So please start with a patient scenario.

DR. WURCEL: A common patient scenario is a 55-year-old middle aged woman with a history of hypertension and HIV. She is on emtricitabine, tenofovir alafenamide, and ritonavir-boosted darunavir. She presents to the emergency room with chest pain. She's taken to the cath lab and found to have complete blockage of one of her coronary arteries that requires stenting, and then she goes to the cardiac care unit following the procedure.

MR. BUSKER: Is heart disease common among individuals with HIV, and do we know why?

DR. WURCEL: We've found it quite common. There is increasing data that people with HIV have something called premature aging, which means that things like heart disease show up earlier in their life span. People have postulated multiple mechanisms that might be related for increased risk of heart disease, including a higher prevalence of common risk factors such as smoking, diabetes, hypertension and hyperlipidemia, increased inflammation and immune activation, and also the side effects of antiretroviral medications, especially with some of the older antiretroviral medications.

There's been an increasing focus for HIV providers to look at the primary preventive measures in people living with HIV, such as cholesterol-lowering agents, smoking cessation, and dietary modifications. I recently had a patient come in with acute coronary artery syndrome, and interesting questions came up about managing acute care and postcatheterization care with the HIV medications she was on. Of course, the acute response to the cardiac event should take place first, and you can discuss medications afterward. But since HIV is a chronic disease, it's possible that when patients come in for acute coronary issues, the med list will not be reviewed intensely and interactions won't be recognized. And because HIV medications are evolving rapidly, it's often difficult for specialists who don't manage HIV medications daily to be familiar with the their names, doses, and interactions.

I found in my practice that the outpatient and inpatient pharmacist can be really helpful in pointing out potential interactions and preventing any adverse interactions between medications.

For clinicians who are interested, there's a really great review about HIV and ischemic heart disease in the January 2017 edition of the *JAC* journal, *Journal of American Cardiology,* and there will be a link to this journal article available in the transcript version of the podcast.[1]

MR. BUSKER: In someone living with HIV who has an acute vascular event like a heart attack, what should the clinician know to minimize drug-drug interactions?

DR. WURCEL: The first question in this situation is usually related to the acute postlipid management. In the setting of an acute coronary event, cardiovascular guidelines usually recommend high-dose statins. Several large multicenter trials

compare a statin to placebo, a high potency statin to a lower potency statin, or a higher dose of a statin to a lower dose of a statin. These studies have found that giving a higher dose of a potent statin in or during the acute coronary syndrome leads to decreases in morbidity and mortality. The most commonly used statin is 80 mg of atorvastatin, but it is important to recognize that statins can interact with HIV medications. Some statins like simvastatin are metabolized by the CYP3A4 enzyme, and protease inhibitors are a potent inhibitor of the CYP3A enzyme. Simvastatin levels are significantly increased when someone is taking a protease inhibitor, so coadministration of simvastatin and a protease inhibitor has led to fatal rhabdomyolysis and should be avoided.

Coadministration of atorvastatin is not contraindicated ,but the dose should be reduced because atorvastatin is also metabolized by CYP3A4, but less completely than simvastatin. So again, discussions with pharmacists are helpful to decide what the dose should be. Each protease inhibitor will have a different level of interaction with a statin, so some people would use 20 mg of atorvastatin and others might even start at a lower dose.

The timing of the high-dose statin after a vascular insult is usually based on the LDL. It's an evolving practice, so I often consult with a cardiologist or neurologist who's seeing the patient to assist me in timing of when I could come down off that high-dose statin. If a patient needs a high-dose statin and is on ritonavir, one possibility is giving the statin, for example, atorvastatin, but dosing lower at 20 mg instead of 80 mg.

The safest statins by far are pitavastatin and fluvastatin, but those aren't usually used in the acute postcerebrovascular or coronary artery event.

Some things to worry about once the patient is out of the acute stage and on a high-dose statin or any statin is that diabetes, muscle toxicity, hair loss, and some other long-term complications have been linked to statins, so reducing unnecessary exposure is important. A good reference that I've used is by Wiggins et al, Recommendations for Managing Drug/Drug Interactions with Statins and HIV Medications. That was published this year in the *American Journal of Cardiovascular Drugs,* and the link to this article will be available in the transcript version of this podcast.[2]

MR. BUSKER: What about other vascular events, like strokes? What do clinicians need to be aware in those circumstances?

DR. WURCEL: Neurologists recommend 80 mg of atorvastatin largely because of the SPARCL trial, which was done in 2008. Dosing after the acute stroke needs similar adjustment. It's important to reduce the dose of the statin when possible. People presenting with strokes usually have fasting lipids drawn in the setting of stroke. Higher-dose atorvastatin is recommended right after the stroke, then the focus could be on lipid management by guidelines. And often high-dose atorvastatin is not needed to bring lipids to goal.

MR. BUSKER: So most patients with cardiovascular or cerebrovascular disease are going to be prescribed a statin after an event. How should patients with HIV be counseled when they begin statin therapy?

DR. WURCEL: I think, as with other patients without HIV who get a statin, you should have a conversation about potential side effects. The most common side effects seen with statins are muscle aches and pains, so everyone who's starting a statin medication should be counseled to watch for these types of side effects.

MR. BUSKER: Besides statins, what other medications commonly used for vascular events have interactions with HIV medications?

DR. WURCEL: Other than the statins, quite a few other medications are used for cardiovascular events that also have interactions with HIV meds. Warfarin, which is used to thin the blood, can interact with etravirine and efavirenz, so close monitoring is often necessary to make sure the INR is in the target range.

Clopidogrel, known by the trade name Plavix, is activated by one of the enzymes that etravirine inhibits. So if you're giving a patient clopidogrel and etravirine, there might be a risk that the clopidogrel is not at high enough levels to prevent restenosis of the artery.

People who have HIV also have other diseases in the setting of cerebrovascular events and cardiovascular events that make drug interactions more complicated. There are some reports of darunavir and ritonavir being given to a patient who also has latent TB and then gets clopidogrel on top of it, resulting in complex interactions that led to the clopidogrel not working.

Some of the newer direct Xa inhibitors, like clopidogrel, are often processed through the cytochrome 3A4, so protease inhibitors may increase their concentrations of these meds and lead to increased risk of bleeding. Additionally, drugs like efavirenz may decrease the concentrations. So there are many complex interactions with all these meds. What's easiest is to consult some of the online resources. One of the ones I use is the Guidelines For The Use Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, which is offered through the US Department of Health and Human Services. The link will be provided as part of the transcript for this podcast.[3]

MR. BUSKER: Thank you for that case and discussion. We'll return with Dr. Alysse Wurcel from Tufts Medical Center in just a moment.

MR. BOB BUSKER: You've been listening to *e*HIV Review, a combination newsletter and podcast program delivered via email to subscribers.

Newsletters are published every other month. In each issue, an expert author reviews the current literature in an area of specific importance to clinicians treating patients with HIV, including infectious disease specialists, primary care physicians, nurse practitioners, physician assistants, and others.

In the month following each newsletter, the expert author provides a case-based podcast discussion like the one you're listening to now to help translate that new information into clinical practice. These podcasts are also available as downloadable transcripts.

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Thank you.

MR. BUSKER: Welcome back to this *e*HIV Review podcast. I'm Bob Busker, managing editor of the program. We've been talking with Dr. Alysse Wurcel from Tufts Medical Center about managing concomitant diseases in people living with HIV and the potential dangers of drug-drug interactions. So, to continue in that vein, please bring us another patient scenario.

DR. WURCEL: A 25-year-old woman with a history of asthma, depression, and opioid dependence comes to you because she has a new diagnosis of HIV. Her CD4 count is 500. She's interested in starting HIV medication. Her current medications include an albuterol inhaler, which she takes once a month for her asthma, methadone, and an oral contraceptive.

MR. BUSKER: New HIV-positive diagnosis with among other things preexisting asthma. From the perspective of asthma and HIV drug-drug interactions, what should clinicians be aware of?

DR. WURCEL: Asthma is pretty common, so understanding the interactions is important. Glucocorticoids like fluticasone and budesonide are metabolized through that CYP3A4 mechanism. Ritonavir and cobicistat, which are two medications used to boost or enhance HIV meds and allow for once daily dosing, can inhibit the CYP450/3A4 isozyme. Ritonavir is a much stronger inhibitor than cobicistat.

When patients take an inhaled corticosteroid, sometimes even an intranasal corticosteroid, the steroid levels can be increased in the body. Several case reports of iatrogenic adrenal insufficiency arising when people take ritonavir to help treat the HIV and then use intranasal or inhaled steroids to treat lung disease or sinus disease.

Some symptoms associated with adrenal insufficiency include facial swelling, central obesity, weight gain, striae, and easy bruising. A great case report by Saberi et al, which I review in the newsletter, found that about 5% of people who experienced adrenal insufficiency in the setting of concomitant inhaled steroids and intranasal steroids did not normalize their cortisol levels after discontinuation.[4] They had long-term effects, which is pretty scary for a clinician and for the patient.

So for someone with asthma or COPD or even seasonal allergies, avoiding ritonavir may prevent future med interactions and make treatment of their other diseases easier. Otherwise, some inhaled steroids like beclomethasone and flunisolide are catabolized by the non-CYP3A4 enzymes, so they can be safely used with HIV medications.

Another alternative I've been using with one patient is a noncorticosteroid called a leukotriene receptor antagonist, also known as montelukast. It may be helpful if drug interactions are complicating decisions for HIV medications.

Most important, communication between the clinician treating the HIV and the clinician treating the lung disease is important to make sure they're on the same page about potential interactions.

MR. BUSKER: What about the hormonal contraceptive she's on? Would you expect that to be a problem?

DR. WURCEL: The relationship between hormonal contraceptives and HIV medications is complicated. Hormonal contraceptives may contain estrogen, progestin, or both and are often metabolized through the same CYP mechanisms. The parent compound, their active metabolites, are also processed through this mechanism.

Certain HIV medications like efavirenz, cobicistat, and even the older-school nevirapine, can cause fluctuations in the concentration of hormones and breakthrough pregnancies have been reported. So if patients are on those meds, barrier protection is important to recommend.

Ritonavir-boosted regimens may reduce concentrations of the hormones, and even unboosted regimens like atazanavir can lead to increased hormone concentrations.

Certain medications like raltegravir and rilpivirine are pretty safe with oral contraceptives, so that might be your go-to if you know someone wants to be on oral contraceptives.

Alternatively, intrauterine devices, also known as IUDs, and the depot shots, seem safe with most antiretroviral medications, so patients can be counseled about the benefits of these forms of contraception.

There's no data to suggest that the implantable or the intravaginal hormone delivery devices interact with HIV medications. Most important, though, the conversation with patients about what they would like and what would make their life easiest for oral contraception or other types of contraception is always the best practice.

MR. BUSKER: Depression is another of this patient's comorbid conditions. What are the important drug-drug interactions to consider?

DR. WURCEL: Comorbid depression is common in people living with HIV, and treatment of depression is important to increase the adherence to HIV meds. Overall, SSRIs are preferred over the tricyclics. Some case reports and pharmacokinetic studies show that there are changes leading to increased levels of SSRIs with ritonavir-based treatments, and one article reports an SSRI and protease inhibitor leading to serotonin syndrome.

General recommendations are starting low and titrating to patient response. Counseling the patient to avoid any medications that are not given as a prescription is really important. Medications like alprazolam and diazepine are common drugs of misuse, and they can interact with ritonavir.

Also, conversations about illicit drugs like ecstasy, methamphetamines, and something called bath salts is also important because they can interact with HIV meds. We should try to focus on being open and nonjudgmental with our patients so they can let us know what meds that they are taking and what illicit meds they have been experimenting with so we can decide the best options for treating their HIV.

MR. BUSKER: And finally with this patient: what about methadone and her opioid use disorder?

DR. WURCEL: Like the other things I talked about, methadone has complex interactions with HIV meds. I experienced this recently with a patient on methadone who is interested in switching meds.

Medications to be avoided if someone is on methadone include efavirenz, nevirapine, and etravirine. If needed because of a resistant virus or limited other options, they can be used, but close collaboration with the methadone provider is necessary because methadone adjustments may be necessary.

Efavirenz and nevirapine both increase the metabolism of methadone, leading patients to feel withdrawal symptoms. If people are switching off efavirenz or nevirapine to another agent, the interaction is removed, resulting in less methadone metabolism, and patients may feel more sedated. There should be communication between the HIV provider and the methadone program about how the HIV med change could be increasing methadone levels in the person's body and the methadone dose needs to be titrated down.

Older boosted PI combinations like lopinavir/ritonavir have also been shown to reduce methadone concentrations, although we don't use lopinavir/ritonavir anymore.
Buprenorphine is often used to treat people with opioid use disorder. It's a partial mu antagonist and it will have decreased concentrations with efavirenz, but withdrawal symptoms have not been reported. Coadministration of buprenorphine and atazanavir have been associated with increased buprenorphine concentrations and drowsiness in some patients.

MR. BUSKER: Thank you, Dr. Wurcel. Let's move on now to another patient scenario.

DR. WURCEL: On a routine checkup in a 58-year-old man whose virus has been controlled on a boosted atazanavir and two NRTIs for several years, you notice his HIV viral load has increased from undetectable to about 1,000 copies. He reports he's taking a new medication that he bought at a local pharmacy for acid reflux.

MR. BUSKER: How common is it that over-the-counter products interact with HIV medications?

DR. WURCEL: The most common over-the-counter medications are acid lowering agents like proton pump inhibitors and H2 antagonists. These can inhibit the absorption of HIV medications. That's particularly true for medications such as rilpivirine and atazanavir, which rely on high gastric acidity for adequate absorption.

Changes in time of taking meds can help with the H2 blockers. If patients take the H2 blockers like ranitidine two hours before or two hours after taking their HIV medication, that might be okay. But coadministration with proton pump inhibitors is not recommended if the patient is taking rilpivirine or atazanavir.

Interestingly, things like calcium and magnesium, which are found in over-the-counter medications for gastric acidity, can also interact with HIV medications. For people with severe reflux, providers may consider switching to a medication like darunavir, which is not affected by gastric acid; or even switching to a non-PI like an integrase inhibitor.

MR. BUSKER: What about other alternative medications like herbal supplements or vitamins? Can those affect HIV medications?

DR. WURCEL: Several studies have shown that complementary or alternative medicines are frequently taken by people living with HIV. Patients may not recognize it, but these compounds contain pharmacologically active materials that are not regulated by the FDA. Some common complementary or alternative medications include echinacea, garlic, St. John's wort, gingko, ginseng, and even high dose vitamin C — these can all interact with HIV medications. Often they don't make it to the patient's med list, so specifically asking patients what over-the-counter or complementary medications they are taking is important.

I want to talk specifically about St. John's wort, which is tricky and can decrease the concentration of many HIV medications, including protease inhibitors, rilpivirine, dolutegravir, efavirenz, and TAF. I've even seen some patients with muscle cramps who have been prescribed magnesium, but magnesium supplements are contraindicated with raltegravir. Similarly to antacids, magnesium decreases the absorption of raltegravir and can lead to resistance. Other integrase inhibitors have this interaction, but it's not as severe as the interaction with raltegravir.

Another possibility is changing the dosing so magnesium is taken two to three hours after the raltegravir. Meds that are probably most commonly used for sleep such as melatonin, doxylamine, and diphenhydramine, don't have any known interactions with HIV meds.

MR. BUSKER:I think we've got time for one more patient scenario.

DR. WURCEL: You're seeing a patient who is on an efavirenz-containing regimen who experiences vivid dreams at night (a very common complaint of people who are on efavirenz) and would like to switch medications. This patient is also on methadone for opioid use disorder.

He reports that he has a seizure disorder — not on meds — and COPD, and he wants to take a once-a-day pill that can be taken without food. You decide to switch him to elvitegravir/cobicistat/emtricitabine/TAF.

MR. BUSKER: In a patient like this, Dr. Wurcel, what medication interactions does the clinician need to be aware of?

DR. WURCEL: Since efavirenz increases the metabolism of methadone, when you switch him off the efavirenz to the new medication,
the methadone dose in his body will increase. The patient should be told he may feel more sedated and should potentially avoid driving right after the med change.

There should also be some communication between the HIV doctor and the methadone program. All inhalers he's taking for COPD should be reviewed to minimize the potentiation of steroid effects. We think of TAF as a safe medication, especially since we're often switching people off of TDF to TAF to prevent bone and kidney issues, but I was surprised recently when I found out that TAF has interactions that are not present with TDF.

For example, some medications that treat seizures like carbamazepine interact with TAF, so in anyone with a history of a seizure disorder you need to be careful with TAF.
Another inducer of the P-glycoprotein mechanism, which TAF is processed through, is rifampin. Since people with HIV sometimes have tuberculosis, if they're on TAF you should watch out for use of rifampin.

MR. BUSKER: Doctor Wurcel, thank you for sharing your expertise in today's cases and discussion. Let's wrap things up now by reviewing what we've talked about in light of our learning objectives. So, to begin: drug-drug interactions that may affect treatment of ischemic heart disease in people living with HIV.

DR. WURCEL: The take-home message is to be aware in the setting of an acute coronary event or even acute cerebrovascular event that medications like statins, like clopidogrel or even like warfarin, can potentially interact with HIV meds and involving the ID pharmacist or looking up these interactions online is important to make sure that there are no negative sequelae to the HIV or to the treatment of the heart disease or stroke.

MR. BUSKER: And our second learning objective: HIV medication interactions that could influence the treatment of common comorbid conditions.

DR. WURCEL: It's important to be aware that common comorbid conditions that we see in people with HIV, like asthma, opioid use disorder, depression, or even oral contraceptives, all require medications that can interact with HIV and choosing meds that work well with what the patient wants and also will not affect their HIV treatment.

MR. BUSKER: Finally: drug-drug interactions between antiretroviral agents and commonly used over the counter medications.

DR. WURCEL: Medications like proton pump inhibitors and St. Johns wort can be bought over the counter and can interact with HIV meds. It's important for HIV clinicians to specifically ask patients about taking over-the-counter medications.

MR. BUSKER: Dr. Alysse Wurcel from Tufts Medical Center, thank you for participating in this *e*HIV Review Podcast.
DR. WURCEL: Thanks for having me, I hope this has been helpful to your listeners.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ehivreview.org/test.

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