HIV AIDS Clinical Care: Adverse Events

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Introduction

HIV/AIDS clinical care has improved dramatically over the decades, given the availability of new medications and a better understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social issues. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease, confronting clinicians with complex and immediate care challenges.

Since the early days of the epidemic, clinicians have received training in HIV/AIDS clinical care through the AIDS Education and Training Centers (AETCs) Program – the clinical training arm of the Ryan White HIV/AIDS Program that is administered by the Health Resources and Services Administration (HRSA) and its HIV/AIDS Bureau (HAB). The AETC network conducts more than 14,000 training events each year with approximately 143,000 health care providers in attendance.

The *Guide for HIV/AIDS Clinical Care* is a pillar of the Ryan White HIV/AIDS Program's mission to continuously improve HIV/AIDS clinical care. The *Guide* was first published in 1993 as a collaborative effort of several regional AETCs. It was subsequently updated and expanded in 2006 and 2011. The version before you incorporates many new insights, but the time-tested format has been retained – easy access to crucial facts for a busy clinician.

The developers of the *Guide* strive to be responsive to how HIV/AIDS clinical care is provided today.

- With more routine HIV testing in medical settings, a large number of individuals are entering care via primary care sites that have relatively limited experience managing HIV/AIDS disease.
- A notable proportion of HIV/AIDS primary care in the United States is provided by advanced practice nurses and physician assistants.
- Shortages in the health care work force are worsening. Experienced staff members are aging and retiring, a limited number of new clinicians are entering primary care and specializing in HIV/AIDS care, and fewer clinicians are available in geographic areas with limited resources.

As a result, front line primary care providers may be less familiar with management of HIV/AIDS disease, as outlined in U.S. Department of Health and Human Services treatment guidelines (available at aidsinfo.nih.gov) and clinical practices presented in this *Guide*.

By presenting best practices in the clinical management of HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our Nation and for the world.

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Abbreviations for Dosing Terminology

BID = twice daily

BIW = twice weekly

IM = intramuscular (injection), intramuscularly

IV = intravenous (injection), intravenously

PO = oral, orally

Q2H, Q4H, etc. = every 2 hours, every 4 hours, etc.

QAM = every morning

QH = every hour

QHS = every night at bedtime

QID = four times daily

QOD = every other day

QPM = every evening

TID = three times daily

TIW = three times weekly

Important Notice

The U.S. Department of Health and Human Services (HHS) HIV/AIDS Bureau is committed to providing accurate information on the care of HIV-infected persons. It is important to be aware that management options and protocols change over time. Forthcoming HHS guidance on certain topics may differ from recommendations contained in this *Guide*. Readers are encouraged to check for updates to treatment guidelines at AIDS Info (aidsinfo.nih.gov) and for updates to drug information at Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda).

Adverse Reactions to HIV Medications

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Background

Clinicians and patients face many challenges associated with antiretroviral therapy (ART). These include making decisions about when to start therapy, what regimen to start, when to change medications, and how to switch if a regimen is failing. Although clinical research guides the selection of antiretroviral (ARV) regimens, it is important to remember that the best regimen for any patient is the regimen that individual is willing and able to take. No regimen, no matter how potent, will be effective if the patient does not take it properly. Adherence to ART is one of the most important predictors of treatment efficacy. Although many factors may interfere with proper adherence to ART, adverse reactions to the medications are among the most important. In one trial, patients experiencing adverse events were 13 times less likely than those not experiencing adverse events to have the highest levels (95-100%) of adherence. Monitoring and managing adverse reactions to ARVs are crucial to establishing a successful HIV regimen.

Although adverse reactions are common and often predictable, their management must be individualized. Several factors will affect the management of adverse reactions, including comorbid conditions, the patient's other current medications, the availability of alternative medications, and the patient's history of medication intolerance. In some cases, the patient's report of the severity of adverse effects can be inconsistent with the clinical interpretation (i.e., some patients may overemphasize symptoms, whereas others underemphasize them), and this must be considered when determining the management of adverse reactions.

Using a case-based approach, this chapter suggests strategies for the evaluation and management of adverse effects, and it reviews several of the most commonly noted adverse effects in patients starting an ARV regimen. It is not intended as a comprehensive guide to adverse effects. For detailed information regarding assessment of symptoms, see the complaint-specific chapters found in section *Common Complaints* of this manual. For information on common adverse reactions to ARV agents and to medications used to prevent and treat opportunistic infections, see chapter *Antiretroviral Therapy* and the Antiretroviral Reference Tables in this manual. In each case of suspected medication adverse effects, the patient should be evaluated for other possible causes of the symptoms. Consultation with an HIV expert can help in determining the best management strategy when symptoms may have multiple and overlapping causes.

S: Subjective

A pregnant woman presents 3 weeks after starting a new ARV regimen. She complains of fatigue, nausea, and rash. Her current ARV medications are nevirapine (NVP) plus a fixed-dose combination of zidovudine (ZDV) and lamivudine (3TC) (i.e., Combivir). This was selected on the basis of her pregnancy, her preferences, and her past treatment history. She also is taking trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis against PCP. Although she reports that she had not missed any doses of her medications and she likes the low pill burden of this regimen, she does not want to continue because she has been feeling so sick that she cannot adequately care for her children. She is asking to stop her ARV therapy because of "too many side effects."

The patient should be evaluated in the clinic for her complaints about adverse effects.

O: Objective

The following are suggestions for this evaluation; they are not intended to be a complete review of the workup and management of each symptom or objective finding. For more-detailed information, refer to the complaint-specific chapters of this manual, as noted above.

Vital signs: Fever may indicate a hypersensitivity reaction (HSR) or acute hepatitis attributable to medications, or an immune reconstitution inflammatory syndrome in relation to an opportunistic infection in the setting of early ART therapy. See chapter *Fever* for a more complete discussion about fever workup and considerations. Tachycardia or hypotension may suggest anemia, HSR, dehydration, infection, or another illness.

Physical examination: Pay special attention to the skin (rash, pallor), mucous membranes, and liver (enlargement or tenderness). Positive physical examination findings should be evaluated for severity and extent of involvement.

Laboratory tests: Check the complete blood count when monitoring drugs that may cause bone marrow toxicity (e.g., anemia, neutropenia). Perform a complete metabolic panel including electrolytes and liver function tests (LFTs). If the history suggests pancreatitis, evaluate amylase and lipase.

Other studies: Perform as indicated by symptoms and examination (e.g., chest X-ray if respiratory symptoms are present).

A: Assessment

Step 1: Clarify the patient's reports of adverse reactions by requesting the following information for each symptom the patient describes:

- Characterize the symptoms by asking about severity, onset, timing, and frequency. It is helpful to have the patient describe whether the symptoms have been improving or worsening over time.
- Ask whether the patient has tried any remedies to alleviate the symptoms and whether they were helpful.
- Explore how the patient is currently taking the regimen. Closed-end questions (e.g., "What are your current medications?" "How often do you take them?" "How many pills of each medicine do you take?" and "Do you take your medicines with or without food?") can be helpful in determining whether the patient has been taking medications correctly. Incorrect administration of medications (e.g., taking higher dosages than recommended) can lead to adverse effects and often is overlooked by providers.

Step 2: Assess the severity of the reaction against the need to continue the current regimen. For this assessment, it is important to have an understanding of the relative availability of alternative ARV regimens. Also try to determine the patient's risks of adverse reactions to specific medications. A review of the patient's clinical status, treatment history, resistance tests, and other testing is important.

- Most adverse effects are self-limited and mild-to-moderate in severity. With supportive care, patients often are able to continue their current medications. This is particularly true with regard to gastrointestinal symptoms (e.g., nausea, vomiting, bloating, diarrhea). Supportive care for gastrointestinal adverse effects includes reminding the patient to take medications with food (if appropriate), suggesting the use of symptomatic remedies (e.g., ginger-containing beverages or foods to relieve nausea [see "Nausea," below]), and prescribing medications such as antiemetics or antidiarrheals if needed. Other symptoms that can be monitored carefully with supportive care include fatigue, malaise, mild rashes, abdominal pain, and bloating.

- More severe reactions often require discontinuation of the offending medication. These include fever, liver function abnormalities, rash with mucous membrane involvement, or severe systemic symptoms.
- Determining which medication in a multidrug regimen is causing the reaction is often challenging because it is common for patients to concurrently take several medications with overlapping toxicities.
- Some patient factors affect the risk of particular adverse drug effects. For example, patients with higher CD4 cell counts at the time that nevirapine is initiated have a greater risk of hepatotoxicity (specifically, women with CD4 counts of >250 cells/μL or men with CD4 counts of >400 cells/μL), and patients with the HLA-B*5701 allele have higher rates of abacavir HSR. In patients with these risk factors, these drugs should be avoided.
- It is important to consider the possibility that non-ARV medications in the patient's regimen could be causing the adverse effects. This could include medications given as prophylaxis (or treatment) for opportunistic infections (e.g., TMP-SMX), or medications to treat other comorbidities. Even with patients who have been on other non-ARV medications for months or years, initiation of a new ARV regimen (e.g., one with potent hepatic CYP 450 inhibition or induction effects) may alter serum levels of these other medications (see chapter *Drug-Drug Interactions with HIV-Related Medications*). For example, an increase in anxiety symptoms after starting a new ARV regimen could be attributable to altered drug concentrations of a chronic antidepressant or antianxiety medicine caused by an ARV, not to the new ARV medications themselves.
- The threshold for stopping a medication depends in part on the availability of alternative agents for the individual patient. Some patients have limited alternatives because their virus is resistant to other ARVs or because they have not tolerated certain ARVs in the past. For patients who develop significant adverse effects when starting their first ARV regimen, consider substituting alternative ARV medications (chosen with efficacy considerations in mind) that are better tolerated as early as possible to prevent nonadherence arising from a desire to avoid the adverse effects. For these situations, single-drug substitutions often improve tolerance and make it more likely that long-term viral suppression will be achieved.
- Some patients may refuse to attempt symptomatic treatment or to make substitutions in the ARV regimen. Although treatment interruptions generally should be avoided, in certain situations it may be best to discontinue all ARVs and return to an adherence-readiness assessment (see chapter *Adherence*) to determine when to restart ART and what medications to restart (see chapter *Antiretroviral Therapy*).

Gathering Additional Subjective and Objective Information

For the patient who reported nausea, fatigue, and rash 3 weeks after starting nevirapine and ZDV/3TC (Combivir) (see above), additional history, physical examination, and laboratory work yielded the following information:

- **Nausea:** This has been present since she started ART 3 weeks ago. She has had difficulty taking the ARVs with food, because of nausea. No actual vomiting or other abdominal pain has occurred. She has not tried any remedies. The nausea is not worsening and perhaps has improved slightly over the past few days.
- **Fatigue:** This has been present since she started ARVs 3 weeks ago. She is able to exercise and perform normal daily activities.
- **Vital signs:** Normal, with no fever or signs of hemodynamic changes.

- **Skin:** Skin and conjunctival pallor is noted, along with mild-to-moderate maculopapular rash on the trunk, back, and extremities. These are associated with slight itching, but no pain. No mucous membrane involvement is noted. The rash has been present for 6 days, with slight improvement over the past day.
- **Abdomen:** Nontender, with normal liver size.
- **Complete blood count:** Normal, except for a slight increase in mean corpuscular volume (MCV), probably from ZDV therapy and not indicating macrocytic anemia.
- **LFTs:** Normal.
- **Pretreatment laboratory results:** CD4 count of 190 cells/μL, HLA-B*5701 negative.

Assessing Availability of Alternative Regimens

A clarified ARV history yielded the following information. The patient took ZDV for 5 months during another pregnancy a few years ago, and she recalls similar feelings of nausea and fatigue that caused her distress at the time. She was able to continue ZDV through the end of her pregnancy. She has taken several ritonavir-boosted protease inhibitors briefly in the past; she did not tolerate these and subsequently has refused treatment with protease inhibitors. The resistance test done prior to initiation of ART shows no significant ARV resistance. She has no comorbidities. The patient has a number of treatment options, but these may be limited by tolerance issues (e.g., protease inhibitor intolerance).

Summary Assessment

The patient's symptoms are mild and are most likely related to starting ARV therapy, although pregnance also can have associated nausea and fatigue. The laboratory evaluation does not reveal significant abnormalities (e.g., anemia, transaminitis). In particular, the symptoms, signs, and laboratory work are not consistent with HSR, hepatotoxicity, or other serious adverse effects. Thus, no additional workup is needed at this time. Careful monitoring is important because, if symptoms do not improve over the next few days, the patient should have a more extensive workup for other possible causes of the symptoms. If other causes of her symptoms are ruled out and she is unable to tolerate supportive care, alternative ARV medications (e.g., tenofovir, abacavir, an integrase inhibitor, or perhaps an unboosted protease inhibitor) could be substituted for medications in her current regimen, keeping in mind the need to maintain efficacy of the overall regimen and the recommendations for ART in pregnancy (see chapter *Reducing Perinatal HIV Transmission*).

P: Plan

A suggested treatment plan for the mild adverse effects exhibited by the patient described above is as follows:

Fatigue

Fatigue is a common adverse effect among patients who are starting ART. It is usually self-limited, and, with reassurance that symptoms should improve over a few weeks, most patients are able to continue their regimens without any changes. If fatigue does not resolve within the first weeks of treatment, it is important to rule out other causes of fatigue, including depression. For ZDV-containing regimens, clinicians should rule out ZDV-induced anemia, especially when patients are taking other medications that can cause bone marrow toxicity (e.g., TMP-SMX). Some patients experience fatigue from ZDV even without anemia. If fatigue persists for several weeks or becomes debilitating, and other causes are ruled out, consider replacing ZDV in this regimen. Patients taking regimens containing efavirenz also may complain of fatigue. With efavirenz, the fatigue often is related to sleep disturbances and other

central nervous system (CNS) effects of this medication. Efavirenz-related CNS adverse effects, including fatigue, are likely to resolve over a period of days to weeks. Toxicities can be minimized by ensuring that patients take efavirenz on an empty stomach (1 hour before or 2 hours after eating). (See chapter *Fatigue*.)

Nausea

Nausea is another common adverse effect described by patients starting a new ARV regimen. As with fatigue, it usually is self-limited, and patients without other systemic symptoms, acute hepatitis, HSR, or pancreatitis usually can continue their regimens. Supportive care often helps patients to continue their regimens. For example, patients should take their medications with food, unless contraindicated for the ARV. Small, frequent snacks may be helpful for patients with significant nausea. Clinical trials have suggested that ginger extract may relieve nausea symptoms. Patients can take ginger (available in a variety of forms, including ginger ale, tea, cookies, and candies) or antiemetics.

Among the medications that the patient described above is taking, ZDV is the most likely culprit to cause persistent nausea. If nausea symptoms continue for several weeks despite taking the ARVs with food, using ginger, or taking other antiemetics, and if other underlying causes are ruled out, consider replacing ZDV in this regimen. (See chapter *Nausea and Vomiting*.)

Rash

Rash is a common adverse effect of certain ARVs and many other medications. It may present with a wide range of severity, as follows:

- Mild rash with no other related symptoms, resolving over the course of days or weeks
- Moderate rash, may be accompanied by systemic symptoms (e.g., fever, liver function abnormalities, myalgias)
- Life-threatening rashes (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) associated with pain, mucous membrane involvement, fever, liver function changes, and myalgias

If a patient is taking two or more medications that have rash as a possible adverse effect, it may be difficult to determine which medicine is the most likely cause of the rash. In the case of the patient described above, the rash most likely is related to one of two medications. Her rash currently is mild, but drug rash can range from mild to severe and life-threatening (including Stevens-Johnson syndrome).

- Nevirapine
  - Mild nevirapine rash: usually a self-limited reaction that can be treated symptomatically
  - Moderate to severe nevirapine rash, with or without hepatitis: requires discontinuation of nevirapine
- TMP-SMX reaction: may be mild or severe, and onset may be delayed
- Other reactions: can be caused by other medications, by immune reconstitution inflammatory effects, contact dermatitis, folliculitis, and other causes

If the clinician discontinues all of the suspect medications and the rash resolves, the patient will be relieved, but the clinician will not be able to determine which medication caused the rash. In cases of mild rash, it is reasonable to try to identify the offending agent by discontinuing one medication at a time (a substitution should be made for a discontinued ARV, to maintain regimen potency). This situation would require careful clinical judgment or consultation with an expert regarding the advantages or disadvantages of discontinuing each of the suspect medications.

Other Adverse Reactions

Patients may describe any number of adverse effects after starting new medications. Although some adverse effects are caused directly by the medications themselves, some symptoms may occur simply in the process of starting ART. The start of ART may precipitate a significant psychological shift in a patient's perception of self, in living with HIV infection, and in daily routine. In particular, patients who have kept their HIV infection distant from their "everyday" lives may notice significant psychological changes as they take medications every day, go to the pharmacy to pick up medications, and make frequent visits to the clinic for evaluation and laboratory work. Some patients become depressed upon realizing that the severity of their illness now requires them to be on treatment. These psychological adjustments can cause significant symptoms that should be assessed and managed in a manner similar to the way in which pharmacologic adverse reactions are managed.

These psychological effects can be considered "process" effects from starting ART rather than adverse effects of the ARV medications themselves. As with the self-limited adverse effects of early-stage ARV therapy, process effects should become more tolerable over time as the medication regimen becomes routine for the patient. One of the most common process effects is fatigue. Many patients hope that their ARV regimen will give them increased energy and health, and they become frustrated when they notice increasing fatigue after starting the regimen. These patients must be evaluated to rule out common adverse effects that contribute to fatigue (e.g., anemia, hepatitis, lactic acidosis). Equally important, especially for patients beginning a new regimen, symptoms of fatigue could indicate depression or signal that the "process" of taking medications is emotionally difficult. Counseling, peer support, and antidepressant medications can be used to treat this type of fatigue. Often, once patients realize that some of the goals of treatment are being achieved (e.g., the CD4 cell count increases, the HIV viral load becomes undetectable, or symptoms of HIV infection resolve), they recognize the benefits of ARV medications, and their fatigue or other adverse symptoms associated with the process of starting the regimen may lessen.

This discussion has focused on the adverse reactions to ARV medications that patients are most likely to describe as they start a new regimen. Patients and providers also need to consider counseling about and management of long-term toxicities such as lipodystrophy, renal dysfunction, peripheral neuropathy, cardiac disease, diabetes, and dyslipidemia. As these long-term toxicities continue to challenge providers and patients alike, clinical trials and expert guidelines will provide support and information.

Clinicians are encouraged to report adverse reactions to medications to the U.S. Food and Drug Administration (FDA) MedWatch program by telephone at 800-FDA-1088, via fax at 800-FDA-0178, via the Internet at www.fda.gov/Safety/MedWatch/HowToReport/, or by mail at MedWatch HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Patient Education

- All medications have potential to cause adverse reactions, which are defined as negative, unintended effects of medication use.
- Advise patients to report any adverse reaction to their medical care provider as soon as possible.
- Before starting a new medication, medical care providers or pharmacists should counsel patients about the most common adverse effects and about any remedies that are available to minimize the severity of those effects.
- Advise patients to talk to their provider or pharmacist before starting any new medications (including over-the-counter medications and herbs) because some drugs may interact with ARVs or other medications and can increase side effects or cause unwanted reactions.
- Nausea is one of the most common adverse effects. Counsel patients that nausea can be minimized by taking medications with food (if indicated, as some medications should be taken on an empty stomach) or by using ginger-based food or beverages (e.g., ginger ale, tea, cookies). If these measures do not work, patients should talk with their medical care provider; they may need medications to treat the symptoms.
- Counsel patients that they should not stop taking any medications unless instructed to do so by their medical care provider.

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Drug-Drug Interactions with HIV-Related Medications

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Background

Drug-drug interactions are common concerns of patients with HIV and their health care providers. The issues involved in evaluating drug interactions are complex. Although many questions can be articulated simply (e.g., "What antidepressant is least likely to have drug interactions with antiretroviral medications?"), the responses to these questions involve more complex concerns (e.g., "In choosing an antidepressant for my patient with HIV, I must consider efficacy, adverse effects, and tolerability as well as drug interactions.").

This complexity is increased because antiretroviral (ARV) agents, particularly protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), the pharmacokinetic booster cobicistat, and the CCR5 antagonist maraviroc, can cause or be affected by alterations in the activity of the cytochrome (CYP) P450 enzyme system in the liver, as well as by other mechanisms of drug metabolism. Interactions between an ARV and another drug (whether another ARV or a different type of medication) may result in an increase or a decrease in the serum levels of either the ARV or the interacting drug, potentially changing the effectiveness or the toxicity risk of substrate drugs. Understanding drug-drug interactions is challenging because of several factors, including the following:

- Different drugs affect different P450 enzymes.
- Some medications have dosage-related responses that influence their effects on P450 enzymes.
- Formal pharmacokinetic studies on drug combinations are limited.
- Even when pharmacokinetic data exist for specific drug combinations, the clinical significance of any changes in pharmacokinetic parameters may not be clear.
- Patients taking ARVs often have complex drug regimens. Patients typically are taking three or more medications that could influence interactions. Pharmacokinetic studies that evaluate the clinical significance of drug interactions involving more than two medications are less likely to be available.
- Other metabolic pathways of medications such as P-glycoprotein (P-gp) and UDP-glucuronosyltransferase (UGT)-1A1, can be altered by drug interactions. The integrase inhibitors dolutegravir and raltegravir, for example, are metabolized by UGT-1A1.
- Some drug interactions involve effects on absorption or drug availability rather than metabolism. For example, the PI atazanavir and the NNRTI rilpivirine require gastric acidity for absorption; integrase inhibitor activity is impaired by polyvalent cations (e.g., iron, aluminum, calcium, and magnesium, and antacids, laxatives, supplements, and other preparations that contain them).
- Other influences on medication activity include food-drug interactions, protein binding, and altered intercellular activation of medications.

Information on various drug-drug interactions is available in guidelines and via the Internet (see "Resources," below). Such resources can provide data regarding two-drug combinations, but rarely consider all the complexities outlined above. What follows, therefore, is a suggested approach to considering drug-drug interactions in managing HIV-infected patients and making patient-specific decisions, illustrated by a case study.

S: Subjective

A new patient arrives for a clinic intake appointment. The patient receives medical care from a local infectious disease physician who treats only a handful of HIV-infected patients. The patient was recently released from hospital with a discharge diagnosis of pneumonia and *Mycobacterium avium* complex (MAC). The patient is not yet taking ARVs, but needs to start ART promptly, along with an adherence support program. The patient has other medical problems, including hyperlipidemia, erectile dysfunction, diabetes, depression, gastroesophageal reflux disease (GERD), and herpes. The clinician wants to review the patient's medication list to check for any potential drug-drug interactions.

O: Objective

Review the patient's pharmacy records for current medications, and ask about use of over-the-counter (OTC), herbal or natural products, and dietary supplements. As requested, the patient has brought in all medications from home for review. The current medication list includes the following:

- Clarithromycin 500 mg BID
- Ethambutol 1,000 mg QD
- Rifabutin 300 mg QD
- Trimethoprim-sulfamethoxazole (TMP-SMX) (Septra, Bactrim) double-strength, 1 tablet QD
- Lovastatin 20 mg QD
- Metformin 500 mg BID
- Bupropion 150 mg QD
- Acyclovir 400 mg BID
- Omeprazole 20 mg QD (patient buys OTC for heartburn)
- Milk thistle (silymarin) (patient takes as needed for energy and liver health)

A: Assessment

Step 1: Identify interactions and classify them as follows:

- Definite interactions
- Probable interactions
- Possible interactions

Definite Drug Interactions

A drug interaction is definite if a high level of evidence is available regarding the drug combination, the clinical significance of the interaction is well understood, and consensus exists regarding the management strategy (e.g., whether dosage adjustments are required, or concurrent use is contraindicated). Common definite interactions for HIV patients include the following:

- Certain combinations of HIV agents (e.g., certain PIs or integrase inhibitors with NNRTIs, maraviroc with PIs or NNRTIs, tenofovir with atazanavir)
- Rifamycins and PIs, NNRTIs, cobicistat, or maraviroc
- Statins with PIs or cobicistat
- Erectile dysfunction agents and PIs or cobicistat
- Methadone and certain PIs or NNRTIs
- Fluticasone and PIs or cobicistat

Probable Drug Interactions

A drug interaction is probable if the limited available evidence suggests that an interaction may occur, even if the clinical outcome or significance may not be clearly established. Effective management of a probable interaction

is based on assessment and clinical judgment about the risks and benefits of a particular combination for each patient. Examples of probable interactions with HIV-related medications include the following:

- Antidepressants and PIs or NNRTIs
- Oral contraceptives and PIs or cobicistat
- Warfarin and PIs, NNRTIs, or cobicistat
- Proton pump inhibitors (PPIs) or H-2 blockers and atazanavir or rilpivirine
- Polyvalent cations (e.g., calcium, iron, cation-containing antacids) and integrase inhibitors
- Certain antifungal agents and PIs, NNRTIs, or cobicistat (except in the case of voriconazole, for which definite information on interactions is available)
- Certain antiepileptic medications and PIs, NNRTIs, or cobicistat

Possible Drug Interactions

Possible drug interactions may be difficult to distinguish from probable drug interactions, but in these cases, only theoretical evidence is available. The proper management of such interactions requires weighing the risks and benefits of the combination and making sound clinical judgments. Examples of possible drug interactions with HIV medications include the following:

- Herbal products and PIs, NNRTIs, or cobicistat (except in the case of St. John's wort, for which definite information on interactions is available)
- Antidiabetic medications and PIs or NNRTIs
- Antipsychotic agents and PIs, NNRTIs, or cobicistat

Memorizing all the potential drug interactions is impossible. It is possible, however, to remember a few commonly encountered drug combinations that have the potential for clinically significant interactions. It is also important to recognize that PIs (particularly ritonavir), NNRTIs, and cobicistat very commonly interact with other medications. The above examples of definite, probable, and possible interactions are reasonable "red flag" drug combinations that can be recalled easily. In addition, certain Internet resources allow providers to submit all of a patient's current medications and planned additions (e.g., atazanavir/ritonavir as part of a new ARV regimen) and receive information on potential interactions (see "Resources," below). Finally, consultation with clinical pharmacists can aid in identifying and classifying potential interactions.

P: Plan

Step 2: The patient described above will start an ARV regimen of atazanavir/ritonavir + tenofovir + emtricitabine. The PI may cause problematic drug-drug interactions with some of the patient's preexisting medications, and tenofovir interacts with atazanavir. Develop a plan for management when these ARVs are added. For this patient, the following definite interactions should be of concern:

- Rifabutin and atazanavir/ritonavir
- Lovastatin and atazanavir/ritonavir
- Tenofovir and atazanavir
- Clarithromycin and atazanavir/ritonavir

Refer to available references for management suggestions. Such references include the following:

- U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (aidsinfo.nih.gov/guidelines), relevant tables
- HIV InSite Database of Antiretroviral Drug Interactions (hivinsite.ucsf.edu/interactions)
- University of Liverpool HIV Drug Interaction Charts (www.hiv-druginteractions.org)

- Clinical Care Options (www.clinicaloptions.com/HIV.aspx)

Most of these resources include specific dosage adjustments or alternative agents to consider when managing these drug combinations. The suggestions for this patient are as follows:

- Rifabutin levels are increased by atazanavir/ritonavir. The rifabutin dosage should be decreased to 150 mg daily with standard atazanavir/ritonavir dosing. Alternatively, discuss with the patient's primary care provider whether rifabutin is important to the current MAC regimen or whether the patient could be treated adequately with just clarithromycin + ethambutol to avoid the above-cited interactions.
- Lovastatin levels are increased substantially by atazanavir/ritonavir; concurrent use with a PI can lead to potentially fatal rhabdomyolysis. Lovastatin should be discontinued when atazanavir/ritonavir is initiated. To manage hyperlipidemia, the patient should be switched to a statin whose metabolism is less affected by these PIs, such as pravastatin or low-dose atorvastatin (simvastatin, also is contraindicated for use by patients who take a PI).
- Tenofovir can decrease plasma concentrations of unboosted atazanavir, but can be administered safely with ritonavir-boosted atazanavir.
- Clarithromycin levels are increased by atazanavir/ritonavir; concurrent use can lead to QTc prolongation. If clarithromycin is co-administered with atazanavir/ritonavir, its dosage should be reduced by 50%.

Although this patient's current medication list does not contain an erectile dysfunction agent, the patient should be educated about the definite interactions and dosage adjustments recommended for patients using those agents with PIs. Some patients may obtain erectile dysfunction agents outside the care of their physician and, if unaware of the interactions and suggested dosage adjustments, may be at risk of life-threatening consequences.

The following probable or possible interactions should be considered if PIs are begun, including:

- Omeprazole with atazanavir/ritonavir
- Bupropion with atazanavir/ritonavir
- Milk thistle with atazanavir/ritonavir

The web-based resources and other references listed above include some information about these potential interactions. The following are suggestions:

- **Omeprazole:** PPIs and H2-blockers decrease serum levels of atazanavir, even when boosted with ritonavir, but the clinical significance of this interaction has not been demonstrated. In general, it may be best to avoid concomitant use of these acid-blocking medications with atazanavir by either discontinuing the GERD medication or switching to another ARV. Unboosted atazanavir should not be used with PPIs. For patients without evidence of ARV resistance in whom coadministration of these medications is judged unavoidable, atazanavir/ritonavir may be used, but doses of omeprazole should not exceed 20 mg and must be taken at least 12 hours prior to taking atazanavir/ritonavir. Note that tenofovir also can lower atazanavir levels, so increasing atazanavir to 400 mg/day with ritonavir 100 mg/day could be considered.
- **Bupropion and milk thistle:** Specific management or dosage adjustments based on data are not available. This patient should be monitored for increased or decreased effects of bupropion and educated about potential interactions with milk thistle. Clinical judgment and decision making with the primary care provider and other specialists (e.g., psychiatrists) may be required.

Consultation with clinical pharmacy services may assist in evaluating the potential significance of drug interactions and developing management strategies.

Patient Education

- Instruct patients that HIV medications, in particular PIs, NNRTIs, cobicistat, and maraviroc, have a high potential for significant drug interactions.
- Tell patients to bring all their medicines, including any herbal, nutritional, and dietary supplements and OTC remedies, with them to all medical appointments. If they cannot bring the actual containers with them, they should bring a list of current prescribed medications, supplements, and OTC medications.
- Patients should have their primary care provider or pharmacist review any newly prescribed medications along with their current list of medicines. This is especially important if another physician prescribes a new medication.
- Patients should not "borrow" medications from friends or family. Assure patients that if they have a problem that needs medical treatment, their primary care provider will discuss it and choose the safest treatments for them.
- Tell patients that, if they are considering buying a new nutritional or herbal supplement or an OTC product, they should consult their pharmacist or primary care provider about interactions with drugs on their current medication list.
- Not all drug interactions are cause for alarm. Some drug combinations are safe for certain people, but less safe for others. Warn patients not to stop taking any medicines without the advice of their primary care provider.

Resources

- HIV InSite Database of Antiretroviral Drug Interactions (hivinsite.ucsf.edu/interactions)
- University of Liverpool HIV Drug Interaction Charts (www.hiv-druginteractions.org/)
- Clinical Care Options (www.clinicaloptions.com/HIV.aspx)

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Antiretroviral Medications and Hormonal Contraceptive Agents

Background

Few pharmacokinetic or clinical studies have examined interactions between antiretroviral (ARV) medications and hormonal contraceptives, but it is known that certain protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), as well as the boosted integrase inhibitor combination elvitegravir/cobicistat, do interact with hormonal contraceptives. These interactions may increase the risk of medication failure or medication adverse effects of either the ARV or the contraceptive. There are no known interactions between hormonal contraceptives and nucleoside analogues or the CCR5 antagonist.

Oral Contraceptives

All oral contraceptives currently marketed in the United States, with the exception of progestin-only pills (which contain norethindrone), contain both ethinyl estradiol and a progestin (desogestrel, drospirenone, ethynodiol diacetate, levonorgestrel, norethindrone, norethindrone acetate, norgestimate, or norgestrel). The oral contraceptives ethinyl estradiol and norethindrone may interact in complex ways with PIs and NNRTIs. The mechanism of these interactions may be multifactorial and includes the activity of these agents on cytochrome P450 enzymes. Pharmacokinetic studies have shown changes (either increases or decreases) in levels of ethinyl estradiol and norethindrone in women who are taking certain PIs, NNRTIs, or elvitegravir/cobicistat. Other studies have shown decreases in levels of amprenavir (the active agent of fosamprenavir) in women taking oral contraceptives.

The clinical significance of these drug interactions has not been evaluated thoroughly, but may cause oral contraceptive failure, ARV failure, or medication toxicity, depending on whether drug levels are lowered or raised by the interacting drug. The consequences of decreased hormone levels may include an increased risk of pregnancy, so an alternative or additional method of contraception is commonly recommended. The consequences of decreased ARV levels may include virologic failure and development of resistance mutations. The consequences of a higher level of hormones may include risk of thromboembolism, breast tenderness, headache, nausea, and acne.

The available pharmacokinetic data are summarized in Table 1. For further discussion of oral and non-oral contraceptives for HIV-infected women, see chapter *Health Care of HIV-Infected Women Through the Life Cycle*.

Table 1. Interactions Between Antiretroviral Agents and Oral Contraceptives

Key to symbols:

☒ Use alternative/additional method or do not administer together ! Use with caution ✓ Safe to use in combination or no dosage adjustment necessary

Antiretroviral Agent	Pharmacokinetic Changes with Oral Contraceptives		Comments
Protease Inhibitors			
Atazanavir (ATV, Reyataz) (unboosted)	• EE AUC ↑ 48% • NE AUC ↑ 110%	!	• OC should contain ≤30 mcg EE. Monitor for side effects, or use alternative method.
ATV/r	• EE AUC ↓ 19% • 17-deacetyl norgestimate (active metabolite of NG) AUC ↑ 85%	!	• OC should contain ≥35 mcg EE. • OCs containing progestins other than norethindrone or norgestimate have not been studied.
Darunavir (DRV, Prezista) DRV/r	• EE AUC ↓ 44% • NE AUC ↓ 14%	☒	• Use alternative or additional method of contraception.
Fosamprenavir (FPV, Lexiva)	• EE C_{min} ↑ 32% • NE C_{min} ↑ 45%; AUC ↑ 18% • Amprenavir AUC ↓ 22% • Amprenavir C_{min} ↓ 20%	☒	• Data are derived from studies with amprenavir (the active metabolite of FPV). • Risk of ARV failure and of EE or NE adverse effects: do not coadminister fosamprenavir with OCs. • Use alternative method of contraception.
FPV/r	• EE AUC ↓ 37% • NE AUC ↓ 34%	☒	• Risk of contraceptive failure and of ritonavir adverse effects. • Use alternative method of contraception.
Indinavir (IDV, Crixivan)	• EE AUC ↑ 24% • NE AUC ↑ 26%	✓	• No dosage adjustment is recommended. • Monitor for EE or NE adverse effects.
IDV/r	• No data	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.
Lopinavir/r (LPV/r, Kaletra)	• EE AUC ↓ 42% • NE AUC ↓ 17%	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.
Nelfinavir (NFV, Viracept)	• EE AUC ↓ 47% • NE AUC ↓ 18%	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.
Ritonavir (RTV, Norvir)	• EE AUC ↓ 40%	☒	• Risk of contraceptive failure; use alternative method of contraception.
Saquinavir (SQV, Invirase)/r	• No data; theoretic EE ↓ • SQV kinetics not affected by OC	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.
Tipranavir (TPV, Aptivus)/r	• EE AUC ↓ 48% • NE no significant change	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.

Antiretroviral Agent	Pharmacokinetic Changes with Oral Contraceptives		Comments
Nonnucleoside Reverse Transcriptase Inhibitors			
Efavirenz (EFV, Sustiva)	• EE AUC no significant change • 17-deacetyl norgestimate (active metabolite of NG) AUC ↓ 64% • LN AUC ↓ 58-83% • NE: AUC ↓ predicted	☒	• Decrease in progestin levels: risk of contraceptive failure [including failure of emergency contraception (Plan B)]; use alternative or additional method of contraception.
Etravirine (ETR, Intelence)	• EE AUC ↑ 22% • NE AUC ↓ 5%	✓	• No dosage adjustment is necessary.
Nevirapine (NVP, Viramune)	• EE AUC ↓ 20% • NE AUC ↓ 19%	☒	• Risk of contraceptive failure; use alternative or additional method of contraception.
Rilpivirine (RPV, Edurant)	• EE AUC ↑ 14% • NE no significant change	✓	• No dosage adjustment is necessary.
CCR5 Antagonist			
Maraviroc (MVC, Selzentry)	• No significant effect on EE or LN	✓	• No dosage adjustment is necessary.
Integrase Inhibitor			
Dolutegravir (DTG, Tivicay)	• No significant change in EE AUC or NG AUC	✓	• No dosage adjustment is necessary
Elvitegravir (EVG, Stribild)	• NE AUC ↓ 25%, C_{min} ↓ 44% • NG AUC, C_{max}, C_{min} ↑ >2-fold	!	• Risk of NG adverse effects (not fully known; may include venous thrombosis); consider alternative method of contraception.
Raltegravir (RAL, Isentress)	• No significant change in EE AUC or NG AUC	✓	• No dosage adjustment is necessary.

Abbreviations: AUC = area under the time-concentration curve (drug exposure); C max = maximum concentration; C min = minimum concentration; EE = ethinyl estradiol; LN = levonorgestrel; NE = norethindrone; NG = norgestimate; OC = oral contraceptive; RTV = ritonavir; /r = low-dose ritonavir

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines.

Non-Oral Hormonal Contraceptives

Hormonal contraceptives using delivery methods other than oral include the following:

- Products containing both progestin and estrogen components: transdermal patch, vaginal ring
- Products containing a progestin alone (medroxyprogesterone acetate, levonorgestrel, norelgestromin, or etonogestrel): subcutaneous or IM injection, intrauterine system, implantable device

There has been little research on the interactions between ARVs and most of these agents. Theoretically, interactions with ARVs would be less likely with contraceptive methods that have primarily local action and minimal systemic absorption, and for injection or transdermal delivery systems, since first-pass metabolism is avoided. However, caution is still warranted, as this assumption has not been proven.

Because the transdermal patch and vaginal ring contain ethinyl estradiol, women who take ARVs that increase or decrease serum estradiol levels (see Table 1) are advised to use an alternative (or additional) contraceptive method. Small studies of depo-medroxyprogesterone acetate (DMPA, or Depo-Provera) have shown no significant interactions between DMPA and nelfinavir, efavirenz, or nevirapine. Interactions between DMPA and other ARVs have not been studied, but DMPA's interactions with PIs and NNRTIs would be expected to be similar to those of norethindrone (see Table 1). For other non-oral hormones, pending further study, an alternative (or additional) method of contraception should be considered.

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