

## Caring for Hospitalized HIV-Positive Patients from Admission to Discharge: Factors to Consider

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## Objectives

- Describe the most frequently encountered antiretroviral-related errors in hospitalized, HIV-positive patients.
- List strategies to avoid antiretroviral-related medication errors.

## Introduction

- Antiretroviral therapy (ART) has drastically decreased HIV-related morbidity and mortality
- As of March 27, 2012, DHHS HIV Guidelines recommend ART for all HIV-infected patients
- > 20 FDA-approved agents comprising six different classes
  - Combination ART consists of:
    - At least 3 antiretroviral agents with 2 different mechanisms of action

DHHS Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.  
Available at: <http://www.aidsinfo.nih.gov/guidelines>. Accessed on April 15, 2012.



## HIV-Related Errors

- Studies have demonstrated error rates of 5-84% in hospitalized HIV-infected patients
- Oftentimes despite availability of CPOE and targeted electronic decision support programs
- Majority of errors occur within the first 24 hours of hospital admission

Snyder AM, et al. Ann Pharmacother 2011; 45:459-68.  
Rastegar DA, et al. Clin Infect Dis 2006;43:933-8.  
Carcelero E, et al. HIV Med 2011; 12:494-499.



## Types of HIV-Related Errors

- Incorrect antiretroviral (ART) or opportunistic infection (OI) prophylactic regimens
  - Omission
  - Substitution
- Dosing errors
- Administration errors
  - Timing
  - Food requirements
- Drug interactions
- Therapeutic duplication



## Initial Rx

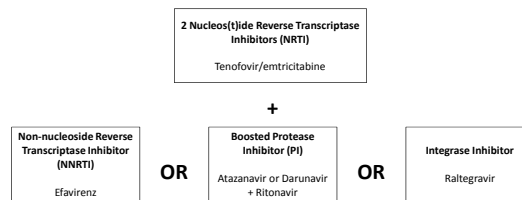
- IM is a 34 y/o M who presents to the ED with a non-productive cough, fever, and dyspnea for the last three weeks. His past medical history is consistent with HIV/AIDS (dx 2 years ago) and *Pneumocystis jirovecii* (PJP) pneumonia. He is being admitted for suspected pneumonia.
  - NKDA
  - T 38.5° C, WBC 6.5, Est CrCl 82 ml/min
  - Last CD4 count 24 (4%); VL > 100,000 c/ml (4 months ago)
  - CXR: ground glass appearance
  - Blood and sputum cultures pending
- Physician orders:
  - Tenofovir/emtricitabine 300/200mg 1 tablet PO Q12h
  - Sulfamethoxazole/trimethoprim 800/160mg 1 tablet PO daily
  - Ceftriaxone 1g IVPB Q24h, azithromycin 500mg IVPB daily



## Admission: First Steps

- Assess the appropriateness of all medications ordered including ART
  - Perform a medication history
    - Call patient's pharmacy to verify medication history and adherence
  - Refer to the most recent DHHS HIV Guidelines

## ART: Treatment Naïve Patients



Preferred agent selected based on efficacy, adverse effect profile, drug interactions, comorbidities, ease of administration/pill burden, and resistance profile

## Medication Reconciliation/Order Verification

- The patient and the pharmacy confirm the following:
  - Truvada/emtricitabine 300/200mg – 1 tablet PO daily
  - Atazanavir 300mg – 1 capsule PO daily
  - Ritonavir 100mg – 1 capsule PO daily
  - Sulfamethoxazole/trimethoprim 800/160mg – 1 tablet PO daily
  - Azithromycin 600mg – 2 tablets PO once weekly
- All prescriptions were last filled 4 months ago

## Back to IM...

- Physician ordered:
  - Tenofovir/emtricitabine 300/200mg 1 tablet PO Q12h
  - Sulfamethoxazole/trimethoprim 800/160mg 1 tablet PO daily
  - Ceftriaxone 1g IVPB Q24h
  - Azithromycin 500mg IVPB Q24h

What prescribing errors occurred?

## IM Prescribing Errors

- Tenofovir/emtricitabine 300/200mg should be once daily *versus* Q12h (dosing error)
- Atazanavir 300mg and ritonavir 100mg once daily (omission error)
- Sulfamethoxazole/trimethoprim 800/160mg should be dosed for PJP treatment *versus* prophylaxis
- May consider changing azithromycin to MAC prophylactic dose (1200mg once weekly)
- Reassess need for antimicrobial therapy for CAP *versus* PJP

## Formulary Substitution

- The pharmacy has tenofovir, lamivudine, and lamivudine/zidovudine on formulary but not, tenofovir/emtricitabine. Atazanavir and ritonavir are on formulary and available in the pharmacy.

Which one of the following options is the best ART regimen for IM while hospitalized?

- A. Substitute tenofovir/emtricitabine with lamivudine/zidovudine; continue atazanavir/ritonavir
- B. Continue tenofovir and substitute emtricitabine with lamivudine; continue atazanavir/ritonavir
- C. Order tenofovir/emtricitabine ; continue atazanavir and ritonavir in the meantime
- D. Order tenofovir/emtricitabine and hold atazanavir and ritonavir until regimen can be restarted together

## NO Formulary Substitutions Please

- Higher rates of errors observed
- Not recommended to split combination products
- Conversions to formulary agents frequently lead to errors of omission or dosing errors and potential for errors at discharge
- Formulary should be assess based on
  - Patient population and incidence of HIV
  - Commonly used ART
- Other benefits to adding ART to formulary improved drug interaction monitoring

Daniels LM, et al. Am J Health-Syst Pharm 2012;69:422-30.  
 Pastakia SD, et al. Ann Pharmacother 2008;42:491-7.



## Patients Own Medications

- Depends on hospital policy
- Should be verified by pharmacist
- Pros
  - Correct therapy
  - Minimal delays in therapy
  - Improved patient satisfaction
  - Improved discharge medication reconciliation
  - Reduced risk of administering part of a regimen
- Cons
  - “Non-formulary” listing with limited drug interaction evaluation



## Administration Errors

- IM is receiving tenofovir/emtricitabine, atazanavir, and ritonavir. The medications are scheduled daily at 2100.

Which one of the following is a potential error?

- A. tenofovir/emtricitabine needs to be administered with food
- B. atazanavir/ritonavir needs to be administered with food
- C. tenofovir/emtricitabine, atazanavir, and ritonavir all need to be administered with food
- D. No potential errors identified



## Administration Errors Continued

- IM now requires emergent intubation due to respiratory failure. He has subsequently been diagnosed with PJP and is receiving adequate treatment.

How should his ART be administered?

- A. Hold ART
- B. Switch ART to oral solutions
- C. Crush tenofovir/emtricitabine and open atazanavir and ritonavir capsules
- D. Crush tenofovir/emtricitabine, open atazanavir capsules, and give ritonavir as an oral solution



## Crush or Not to Crush

Drug	Okay to Crush or Sprinkle	Solution or Suspension Available	Food Considerations	Comments
Tenofovir/emtricitabine	No information	No	Without regard to meal	No PK studies, no enteric coating or sustained release, degrades in water, grape or orange juice, moisture sensitive and must be consumed immediately after mix.
Atazanavir	No	No	Absorption increases with food	---
Ritonavir	No	80mg/ml solution (peppermint or caramel flavored)	Should be taken with food	---

Adapted from: Nyberg CR, et al., Top Antivir Med 2011;19:126-131.

## Drug Interactions

- IM has been on pantoprazole 40mg daily for stress ulcer prophylaxis since intubation. He has now been extubated and his ART (tenofovir/emtricitabine, atazanavir, and ritonavir) is being restarted. The team wants to continue stress ulcer prophylaxis.


Which one of the following options is the best strategy to manage the potential drug interaction between pantoprazole and atazanavir? Continue:

- A. ART and pantoprazole
- B. Pantoprazole and change atazanavir to darunavir
- C. ART and pantoprazole; separate the doses by 12 hours
- D. ART and change pantoprazole to famotidine 40mg Q12h



Gastric Acid Suppressants	ART and Effect	Recommendations (DHHS Guidelines)
Antacids	Atazanavir +/- ritonavir Simultaneous admin. ↓ atazanavir	• ART 2 hours before or 1 hour after; FPV may be administered simultaneously
	Fosamprenavir 38% ↓ amprenavir AUC	
	Tipranavir + ritonavir 27% ↓ tipranavir AUC	
	Rilpivirine Simultaneous admin. ↓ rilpivirine	
H2 Receptor Antagonists	Atazanavir +/- ritonavir ↓ atazanavir	• H2RA dose ≤ famotidine 40mg Q12h ART-naïve or 20mg Q12 ART-experienced; If unboosted, then famotidine 20mg Q12h in ART-naïve or famotidine 20mg daily in ART-experienced • ATV/r simultaneously and/or ≥10 hours after; if unboosted, then ATV 2 hours before and >10 hours after H2RA • If tenofovir and H2RA in ART-experienced use ATV 400mg + RTV 100mg
	Unboosted fosamprenavir 30% ↓ amprenavir AUC	• FPV 2 hours before H2RA if concomitant use necessary. Consider boosting with ritonavir
	Rilpivirine ↓ rilpivirine	• H2RA at least 12 hours before or 4 hours after
Proton Pump Inhibitors	Atazanavir +/- ritonavir ↓ atazanavir	• PPIs are not recommended in patients on unboosted atazanavir or in PI-experienced patients • If unboosted, then alternative acid reducers, ritonavir boosting, or alternative PI • If boosted, then PPIs ≤ omeprazole 20mg daily PI-naïve and separate by 12 hours
	Darunavir/r, tipranavir/r ↓ omeprazole	• May need to increase omeprazole dose when using TPV/r
	Saquinavir/r 82% ↑ saquinavir AUC	• Monitor for SQV toxicity
	Rilpivirine ↓ rilpivirine	• Contraindicated. Do not coadminister.

# Drug Interaction Review



## NRTI Drug Interactions

NRTI	Drug Interactions
<b>Tenofovir (TDF) Viread®</b>	<ul style="list-style-type: none"> <li>• Boceprevir</li> <li>• Ganciclovir, valganciclovir</li> <li>• Telaprevir</li> <li>• Raltegravir</li> <li>• Buprenorphine</li> </ul>
<b>Zidovudine (ZDV) Retrovir®</b>	<ul style="list-style-type: none"> <li>• Ganciclovir, valganciclovir</li> <li>• Ribavirin (avoid)</li> <li>• Buprenorphine, methadone</li> </ul>
<b>Didanosine (ddi) Videx®</b>	<ul style="list-style-type: none"> <li>• Ribavirin</li> <li>• Buprenorphine</li> <li>• Allopurinol</li> </ul>
<b>Lamivudine (3TC) Epivir®</b>	• Buprenorphine
<b>Abacavir (ABC) Ziagen®</b>	<ul style="list-style-type: none"> <li>• Methadone</li> <li>• Tipranavir/r</li> </ul>
<b>Stavudine (d4T) Zerit®</b>	<ul style="list-style-type: none"> <li>• Methadone</li> <li>• Didanosine</li> </ul>
<b>Emtricitabine (FTC) Emtriva®</b>	---

## NNRTI Drug Interactions

NNRTI	Drug Interactions
<b>Efavirenz (EFV) Sustiva®</b>	<ul style="list-style-type: none"> <li>• Warfarin</li> <li>• Carbamazepine, phenobarbital, phenytoin</li> <li>• Bupropion, paroxetine, sertraline</li> <li>• Azole antifungals (voriconazole)</li> <li>• Clarithromycin</li> <li>• Dexamethasone</li> <li>• Boceprevir, telaprevir</li> <li>• Hormonal contraception</li> <li>• All statins (esp. sim/lov)</li> </ul>
<b>Nevirapine (NVP) Viramune®</b>	<ul style="list-style-type: none"> <li>• Warfarin</li> <li>• Carbamazepine, phenobarbital, phenytoin</li> <li>• Azoles</li> <li>• Clarithromycin</li> <li>• Rifabutin, rifampin</li> </ul>
<b>Etravirine (ETV) Intelect®</b>	<ul style="list-style-type: none"> <li>• Warfarin, clopidogrel</li> <li>• Carbamazepine, phenobarbital, phenytoin</li> <li>• Azole antifungals</li> <li>• Clarithromycin</li> <li>• Rifabutin, rifampin</li> <li>• Alprazolam, diazepam</li> </ul>
<b>Rilpivirine (RPV) Edurant®</b>	<ul style="list-style-type: none"> <li>• Antacids, H2RA, PPIs</li> <li>• Carbamazepine, phenobarbital, phenytoin</li> <li>• Azole antifungals</li> <li>• Clarithromycin</li> <li>• Hormonal contraception</li> </ul>

## PI Drug Interactions

PI	Drug Interactions
<b>All PIs</b>	<ul style="list-style-type: none"> <li>• Phenobarbital</li> <li>• Tricyclic antidepressants (boosted PIs)</li> <li>• Rifampin</li> <li>• Benzodiazepines (midazolam, triazolam)</li> <li>• Bosentan</li> </ul>
<b>Atazanavir (ATV) Reyataz®</b>	<ul style="list-style-type: none"> <li>• Gastric acid suppressants</li> <li>• Warfarin</li> <li>• Carbamazepine, phenytoin</li> <li>• Trazodone</li> </ul>
<b>Fosamprenavir (FPV) Lexiva®</b>	<ul style="list-style-type: none"> <li>• Gastric acid suppressants</li> <li>• Warfarin</li> <li>• Carbamazepine, phenytoin</li> <li>• Paroxetine</li> </ul>
<b>Darunavir (DRV) Prezista®</b>	<ul style="list-style-type: none"> <li>• Gastric acid suppressants</li> <li>• Warfarin</li> <li>• Carbamazepine, phenytoin</li> <li>• Paroxetine, sertraline</li> </ul>

## PI Drug Interactions

PI	Drug Interactions
<b>Lopinavir/r (LPV/r) Kaletra®</b>	<ul style="list-style-type: none"> <li>• Gastric acid suppressants</li> <li>• Warfarin</li> <li>• Carbamazepine, lamotrigine, phenytoin, valproic acid</li> <li>• Bupropion, trazodone</li> </ul>
<b>Saquinavir (SQV) Invirase®</b>	<ul style="list-style-type: none"> <li>• Proton pump inhibitors</li> <li>• Warfarin</li> <li>• Carbamazepine, phenytoin</li> <li>• Trazodone</li> </ul>
<b>Tipranavir (TPV) Aptivus®</b>	<ul style="list-style-type: none"> <li>• Gastric acid suppressants</li> <li>• Warfarin</li> <li>• Carbamazepine, phenytoin</li> <li>• Bupropion, trazodone</li> </ul>
<b>Indinavir (IDV) Crixivan®</b>	---
<b>Nelfinavir (NFV) Viracept®</b>	---

## CCR5 Antagonist and Integrase Inhibitor Drug Interactions

CCR5	Drug Interactions
<b>Maraviroc (MVC) Selzentry®</b>	<ul style="list-style-type: none"> <li>• Carbamazepine, phenobarbital, phenytoin</li> <li>• Itraconazole, ketoconazole, voriconazole</li> <li>• Clarithromycin</li> <li>• Rifabutin, rifampin</li> <li>• St. John's wort</li> <li>• Hormonal contraceptives</li> <li>• Methadone</li> </ul>
<b>Raltegravir (RAL) Isentress®</b>	<ul style="list-style-type: none"> <li>• Omeprazole</li> <li>• Rifabutin, rifampin</li> <li>• Boceprevir, telaprevir</li> <li>• Hormonal contraceptives</li> <li>• Buprenorphine, methadone</li> </ul>

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## Opportunistic Infections

- IM completed 21 days of PJP treatment, restarted ART, and is now stable on the general medical floor.

Which of the following statements is accurate?

- PJP prophylaxis should be changed to dapsone as patient failed sulfamethoxazole/trimethoprim prophylaxis
- Sulfamethoxazole/trimethoprim 800/160mg should be continued daily
- Patient no longer requires prophylaxis as he has already experienced PJP
- Sulfamethoxazole/trimethoprim should be changed to 400/80mg three times a week to improve adherence

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## Infection (Opportunistic) Prevention

Infection/OI	Indication Criteria	First Choice	Alternative
<i>Pneumocystis jirovecii</i> (carinii) pneumonia	CD4 < 200 cells/mm <sup>3</sup> or <14% or oropharyngeal candidiasis	Sulfamethoxazole/trimethoprim (1 DS tablet or 1 SS tablet po daily)	<ul style="list-style-type: none"> <li>• Sulfamethoxazole/trimethoprim (1 DS tablet po three times a week</li> <li>• Dapsone 100mg 1 tablet po daily</li> <li>• Pentamidine 300mg inhaled Qmonth</li> <li>• Atovaquone 1500mg po daily</li> </ul>
<i>Toxoplasma gondii</i>	Toxoplasma IgG antibody + CD4 < 100 cells/mm <sup>3</sup>	Sulfamethoxazole/trimethoprim (1 DS tablet po daily)	<ul style="list-style-type: none"> <li>• Sulfamethoxazole/trimethoprim (1 SS tablet po daily</li> <li>• Dapsone 50mg po daily + pyrimethamine 50mg po daily + leucovorin 25mg po Qweek</li> <li>• Dapsone 200mg po Qweek + pyrimethamine 75mg Qweek + leucovorin 25mg Qweek</li> <li>• Atovaquone 1500mg daily ± pyrimethamine 25mg daily + leucovorin 10mg po daily</li> </ul>
<i>Mycobacterium avium</i> complex (MAC)	CD4 < 50 cells/mm <sup>3</sup>	Azithromycin 1200mg po Qweek or clarithromycin 500mg po Q12h	• Rifabutin 300mg po daily
<i>Streptococcus pneumoniae</i> Hepatitis B Td/Tdap	CD4 > 200 cells/mm <sup>3</sup>	1 or 2 doses < 65 years old, then 1 dose ≥ 65 years old Three doses (high dose?) Substitute 1-time dose of Tdap for Td then repeat Td Q10 years	
Influenza virus	All patients annually	Inactivated trivalent influenza vaccine 0.5ml IM	

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## IM is Ready for Discharge

- IM is being discharged from the hospital after 26 days. He will be going home on the following:
  - Truvada/emtricitabine 300/200mg – 1 tablet PO daily
  - Atazanavir 300mg – 1 capsule PO daily
  - Ritonavir 100mg – 1 capsule PO daily
  - Sulfamethoxazole/trimethoprim 800/160mg – 1 tablet PO daily
  - Azithromycin 600mg – 2 tablets PO once weekly

What are the steps involved in the discharge process?

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## Discharge: First Steps

- Perform discharge medication reconciliation
- Discharge counseling is key
  - Stress patient adherence
  - Reduce readmission potential
- Ensure patient is able to access medications and follow-up
  - Insured/no insurance?
  - Utilize Care Managers/Coordinators
  - Many Patient Assistance Programs and rebates available through manufacturers

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## Strategies to Prevent Errors in HIV-Positive Hospitalized Patients

- Heelon and colleagues significantly reduced the time until an error was rectified in hospitalized HIV-positive patients
  - Pharmacist reviewed all patients who had ART ordered for HIV
- Create a checklist and reassess regularly
- Consider the most common types of errors and address for ART and/or OI treatment/prophylaxis

Heelon M, et al. Am J Health-Syst Pharm 2007;64:2064-8.

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## Strategies to Prevent Errors in HIV-Positive Hospitalized Patients

- **ART/OI:** Does the regimen seem appropriate? Does it contain all components? No formulary substitutions? Are there duplications? Does the patient require OI prophylaxis?
- **Dosing errors:** Are all doses appropriate? Do the medications need to be renally or hepatically dose adjusted?
- **Administration errors:** Are there specific timing or food requirements? Is the patient temporarily NPO?
- **Drug interactions:** ALWAYS double-check. Keep the most common in mind.

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## Strategies to Prevent Errors in HIV-Positive Hospitalized Patients

- ART should be considered a team
  - “Hold one, hold all”
- Perform medication reconciliation at admission and discharge
- If possible no formulary substitutions
- Ensure access to medications prior to discharge
- Know when to ask for help and consult an expert

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## Summary

- More patients will be receiving ART
- High potential for a variety of errors
- Errors in this patient population have devastating consequences
- Pharmacists play a large role in error prevention

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