The Antiretroviral Order/Prescription: Components to Check

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Learning Objectives

- Recognize common components of an antiretroviral (ARV) regimen
- Identify potential errors associated with an ARV order/prescription

Conflict of Interest Declaration

- I have no actual or potential conflict of interest in relation to this activity.

Ugh!

Orders for HIV meds!!! ???? HELP!

Classes of antiretrovirals (ARVs)

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Integrase inhibitors (IIs)
- Fusion inhibitors
- Chemokine receptor antagonists

> 20 FDA approved agents
ARV Agents Approved by the FDA

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</td>
<td>Abacavir</td>
<td>Zidovudine, ddC</td>
</tr>
<tr>
<td>Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</td>
<td>Efavirenz, Delavirdine, Nevirapine</td>
<td>Sustiva, Rescriptor, Viramune</td>
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<tr>
<td>Protease Inhibitors (PIs)</td>
<td>Indinavir, Saquinavir, Nelfinavir</td>
<td>Crixivan, Invirase, Viracept</td>
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<tr>
<td>Entry Inhibitors</td>
<td>Maraviroc, Enfuvirtide</td>
<td>Selzentry, Fuzeon</td>
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<tr>
<td>Integrase Inhibitors</td>
<td>Raltegravir, Emtricitabine, Tenofovir</td>
<td>Isentress, Emtriva, Viread</td>
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</tbody>
</table>

FDA Approved ARV Co-formulations

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Abacavir/Lamivudine</td>
<td>Epzicom®</td>
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<tr>
<td>Abacavir/Lamivudine/Zidovudine</td>
<td>Trizivir®</td>
</tr>
<tr>
<td>Emtricitabine/Tenofovir</td>
<td>Truvada®</td>
</tr>
<tr>
<td>Efavirenz/Emtricitabine/Tenofovir</td>
<td>Atripla®</td>
</tr>
<tr>
<td>Rilpivirine/Emtricitabine/Tenofovir</td>
<td>Complera®</td>
</tr>
<tr>
<td>Lamivudine/Zidovudine</td>
<td>Combivir®</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Kaletra®</td>
</tr>
</tbody>
</table>

Antiretroviral Therapy (ART)-Related Errors

- Carcelero et al: 189 patients with 247 admissions
  - 21.7% (41/189) patients with 60 errors identified
- Merchen et al: 248 patients with 381 admissions
  - 551 errors identified
- Pastakia et al: 72% (49/68) had at least one error
  - 56% with potential to cause harm
- Snyder et al: 77% (20/26) with 69 errors

Types Of Errors

- Dosing Errors
- Administration Errors (timing, food requirements)
- Drug Interactions
- Incorrect Regimens (omission, substitution)

Significant percentage of errors occur within 24 hours after admission

Potential results: HIV drug resistance, treatment failure or medication-related toxicity

Case Study 1

CJ is a 35 y/o HIV-infected female admitted for treatment of community-acquired pneumonia. In addition to verifying orders for the appropriate antibiotics, you receive the following order. CJ has NKDA and no other maintenance medications.

- Tenofovir/emtricitabine (Truvada®) 300/200mg, 1 tablet po daily
- Darunavir (Prezista®) 400mg, 2 tablets po daily

Should we verify these orders or do we need to obtain some more information?

RX Check List

- Does the combination seem appropriate?
- Is the dosage correct?
- Are there administration requirements to address?
- Any potential drug interactions?
RX Check List

Does the combination seem appropriate?

HAART: Treatment Naïve Patients*

1 Non-nucleoside Reverse Transcripase Inhibitor
   - Efavirenz

2 Nucleoside Reverse Transcripase Inhibitors
   - Tenofovir/Emtricitabine

OR

1 Boosted Protease Inhibitor
   - Atazanavir + ritonavir
   - Darunavir + ritonavir

OR

1 Integrase Inhibitor
   - Raltegravir

*Preferred Agents: efficacy, side effect profile, ease of administration


Ritonavir: Pharmacokinetic (PK) “Boosting”

• Rationale: improve PK of concurrent PI
  - Potent inhibitor of CYP-450 isoenzymes
  - CYP3A4 – primary enzyme involved in metabolism of most PIs
  - Present in the intestinal tract & liver role in PI first-pass metabolism
  - Inhibitor of efflux channel P-glycoprotein

• Result:
  - Bioavailability of concurrent PI increases
  - Decreases metabolism of concurrent PI → increase in AUC, C_{max}, C_{min} and t_{1/2}

Ritonavir: Pharmacokinetic (PK) “Boosting”

• Clinical advantages
  - Less frequent dosing of concurrent PI → improve adherence
  - Achieve higher sustained levels → high levels of viral suppression in both ARV naïve and PI-experienced population

• Ritonavir must be administered at the same time as other PIs in the regimen
  - Typical “boosting” dose ranges from 100mg daily to a maximum of 200mg twice daily

• Full dose (600mg BID) ritonavir is not commonly given and should be a RED FLAG


Ritonavir: Pharmacokinetic (PK) “Boosting”

• PIs REQUIRING boosting:
  - Darunavir
  - Lopinavir/ritonavir (combined product)
  - Saquinavir
  - Tipranavir

• All others: boosting recommended except Nelfinavir (no PK benefit shown)


- Monographs available for all the classes of antiretrovirals

RX Check List

Is the dosage correct?

Metabolism/Elimination

- NRTIs:
  - Renally excreted, all require dose adjustment with changes in CrCl (usually starting at a CrCl ≤ 50ml/min)
  - Exception: abacavir, adjustment for hepatic dysfunction
- NNRTs, PIs, maraviroc:
  - Substrates of CYP450 enzymes
  - Dose adjustment based on concurrent medications
RX Check List

Are there administration requirements to address?

Administration Requirements (food)

- Empty stomach
  - Etavirenz: increased absorption with high fat meals, can lead to increased CNS adverse effects
  - Didanosine
- With food: enhance absorption
  - Atazanavir
  - Rilpivirine
  - Etravirine
  - Darunavir
  - Saquinavir
  - Tipranavir

Food administration recommended for all PI-based regimens to improve tolerability

Administration: solutions, food requirements

Case Study 1

tenofovir/emtricitabine (Truvada®) 300/200mg, 1 tablet po daily
darunavir (Prezista®) 400mg, 2 tablets po daily

Scr: 0.8mg/dl, CrCl: >60ml/min

Combination seem appropriate?

Need to add ritonavir 100mg po daily administered at the same time as darunavir

Dosage correct?

Administration requirements addressed?

Instructions should include with food

Drug interactions assessed?

Case Study 2

DM is a 38 y/o HIV-infected male, admitted with a diagnosis of PE, on IV heparin, now starting warfarin. His HAART includes:

Tenofovir/emtricitabine (Truvada®) 300/200mg po daily
Atazanavir (Reyataz®) 300mg po daily
Ritonavir (Norvir®) 100mg po daily

Your receive orders for the following:

Omeprazole 20mg po daily
Warfarin 5mg po daily

What are the drug interaction considerations?
**RX Check List**

Any potential drug interactions?

**Case Study 2**

- Warfarin metabolism
  - S-isomer: CYP2C9
  - R-isomer: CYP3A4, 1A2
- Ritonavir
  - Potent inhibitor of CYP3A4
  - Inducer of CYP2C9!
  - Clinically: higher warfarin dose requirement anticipated
- Efavirenz/Etravirine
  - Inducers of CYP3A4
  - Inhibitors of CYP2C9,2C19
  - Clinically: Unclear direction

**ARV: drug-drug interaction potential**

- NNRTIs, PIs
  - Substrates of CYP450 isoenzyme system
  - Effects on CYP450 enzymes: Inhibit, induce or mixed properties
- Maraviroc
  - Substrate of CYP3A4
  - Dosing based on concurrent medications
    - With CYP3A4 inhibitor: 150mg po bid (ritonavir)
    - With CYP3A4 inducer: 600mg po bid (rifampin, efavirenz)
- Raltegravir
  - UGT-1A1-mediated glucuronidation

**Case Study 2**

Requires acidic environment for absorption:

- Atazanavir:
  - Treatment experienced patients: PPI is not recommended, H2-blockers may be used with appropriate separation of administration times
  - Treatment naïve patients: PPIs or H2-blockers are OK with appropriate separation of administration times
- Rilpivirine:
  - PPI contraindicated for both treatment naïve and experienced patients
  - H2-blockers are ok for both treatment naïve and experienced patients with appropriate separation of administration times

Case Study 2

Tenofovir/emtricitabine (Truvada®) 300/200mg po daily
Atazanavir (Reyataz®) 300mg po daily
Ritonavir (Norvir®) 100mg po daily
Omeprazole 20mg po daily
Warfarin 5mg po daily

Drug interactions assessed? Does pt need acid suppression? If yes, consider H2-blocker.
Monitor INR closely and expect need for higher warfarin doses.

Resources: HIV Websites

- Guidelines, Educational:
  - www.aidsinfo.nih.gov
  - www.iasusa.org/guidelines/index.html
  - www.aids.ed.org
  - Hivinsite.ucsf.edu/
  - www.medscape.com/hiv
  - www.hiv-druginteractions.org/


Summary

- The approach to the ARV order should include careful consideration of the drug combination, dosing and administration requirements and assessment for drug-drug interactions.
- Multiple HIV resource websites are available for reference.
- Pharmacists familiar with HIV pharmacotherapy can play an important role in reducing order-related errors.
- TALK TO YOUR PATIENT!

Learning Assessment Question 1:

- Which of the following is an ARV combination recommended for treatment naïve patients based on the October, 2011 DHHS guidelines?
  A. Tenofovir/Emtricitabine (Truvada®)
  B. Tenofovir/Emtricitaine (Truvada®)+ Atazanavir (Reyataz®)
  C. Efavirenz/Emtricitabine/Tenofovir (Atripla®)
  D. Ritonavir (Norvir®) + Raltegravir (Isentress®)

Learning Assessment Question 2:

- Which of the following ARV(s) require dose adjustment with renal insufficiency?
  A. Efavirenz/Emtricitabine/Tenofovir (Atripla®)
  B. Darunavir (Prezista®)
  C. Raltegravir (Isentress®)
  D. Efavirenz (Sustiva®)
Learning Assessment Question 3:

- You receive an order for omeprazole on a patient who’s current medication list includes tenofovir/emtricitabine (Truvada®), and rilpivirine (Edurant®). You decide to?

A. Do nothing, order looks good to you, verify.
B. Recommend the physician change the order to an H2-blocker (with appropriate administration separation) due to an interaction between omeprazole and the rilpivirine.
C. Recommend the physician change the order to an H2-blocker (with appropriate administration separation) due to an interaction between omeprazole and the NRTIs.
D. Recommend the physician change the ARV regimen as this combination is not recommended.

References