

# Pragmatic Approach to Optimizing Antimicrobials: A Patient Case Discussion

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## Objectives:

1. Identify common medication errors associated with highly active antiretroviral therapy (HAART)
2. Recommend an appropriate treatment regimen for patients with urinary tract infections, pneumonia, and upper respiratory tract infections
3. Explain the importance of pharmacist practicing antimicrobial stewardship in the inpatient and outpatient setting

## 1) Urinary Tract Infections

- a) Clinical Manifestation<sup>1,2</sup>
- b) Definitions
  - i) Uncomplicated cystitis
  - ii) Complicated cystitis
  - iii) Pyelonephritis
  - iv) Asymptomatic bacteriuria
- c) Treatment of uncomplicated cystitis<sup>1,3</sup>
  - i) Nitrofurantoin monohydrate 100mg BID x 5 days
  - ii) Beta-lactams x 3-7 days
    - (1) e.g. cephalexin 500mg PO BID x 7 days
  - iii) Trimethoprim-sulfamethoxazole (TMP-SMX) 160/800mg BID x 3 days
  - iv) Fosfomycin 3g x 1 dose
  - v) Fluoroquinolones x 3 days
    - (1) Collateral damage
    - (2) FDA Warning
      - (a) Reserve for systemic, serious infection
- d) Treatment of complicated cystitis
  - i) TMP-SMX 160/800mg BID x 7 days
  - ii) Beta-lactams
    - (1) e.g. cephalexin 500mg PO QID x 7 days
  - iii) Fluoroquinolones x 5-7 days
- e) Treatment of pyelonephritis
  - i) TMP-SMX 160/800mg BID x 14 days
  - ii) Ciprofloxacin 500mg PO BID x 7 days
  - iii) Levofloxacin 750mg PO QD x 5 days
  - iv) Oral beta-lactam x 14 days
    - (1) e.g. cephalexin 500mg PO QID x 14 days

- 2) Upper Respiratory Tract Infections
  - a) Group A *Streptococcus* (GAS) Pharyngitis
    - i) Definition
      - (1) Acute infection of the oropharynx or nasopharynx
      - (2) AKA: 'Strep throat'
    - ii) Can be difficult to determine etiology of pharyngitis
      - (1) Signs and symptoms often associated with GAS pharyngitis<sup>4</sup>
        - (a) Sudden onset of sore throat, age 5-15, fever, headache, nausea, vomiting, abdominal pain, tonsillopharyngeal inflammation, patchy tonsillopharyngeal exudates, palatal petechiae, anterior cervical adenitis (tender nodes), winter and early spring presentation, history of exposure to Strep pharyngitis, scarlatiniform rash
        - (b) Signs and symptoms often associated with viral pharyngitis
          - (i) Conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema
    - iii) Diagnosis
      - (1) If rhinorrhea, cough, oral ulcers, and/or hoarseness are not present:
        - (a) Rapid Antigen Detection Test (RADT)
        - (b) Follow up culture
    - iv) Treatment
      - (1) Goal: to prevent complications, improve clinical signs and symptoms, to provide a rapid decrease in contagiousness
        - (a) Rheumatic fever, peritonsillar abscess, cervical lymphadenitis, mastoiditis, other invasive infections
      - (2) Is appropriate for GAS pharyngitis and other rare pathogens (e.g. *Corynebacterium diphtheria* and *Neisseria gonorrhoea*)
        - (a) No other organisms provide treatment benefit
      - (3) Medications
        - (a) Without Penicillin Allergy
          - (i) Penicillin V
            1. Children: 250 mg PO BID –TID
            2. Adolescents & Adults: 250 mg QID or 500 mg BID
          - (ii) Amoxicillin
            1. 50 mg/kg (max 1000 mg) daily
            2. 25/kg (max 500mg) BID
          - (iii) Benzathine penicillin G, IM
            1. <27 kg: 600,000 U
            2. ≥27 kg: 1,200,000 U
        - (b) Penicillin Allergy
          - (i) Cephalexin
            1. 20 mg/kg/dose BID (max 500mg/dose)

- (ii) Cefadroxil
  1. 30 mg/kg QD (max 1g)
- (iii) Clindamycin
  1. 7 mg/kg/dose TID (max 300mg/dose)
- (iv) Azithromycin
  1. 12 g/kg QD (max 500mg)
- (c) Duration of therapy
  - (i) Infectious Diseases Society of America guidelines suggest a treatment duration of 10 days except for:
    1. Azithromycin – 5 days
    2. Benzathine penicillin G – 1 dose
  - (ii) Cochrane Review found that in children treated with oral penicillin outcomes were similar with a 3-6 day duration as compared to a 10 day duration<sup>5</sup>
    1. Must interpret in caution in areas where prevalence of rheumatic heart disease is high

### 3) HIV

#### a) Resources

- i) [www.aids.info.nih.gov](http://www.aids.info.nih.gov)
- ii) Lexicomp®
- iii) [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

#### b) Antiretroviral (ART) Classes

##### i) Entry/Fusion Inhibitors<sup>6,7</sup>

###### (1) Maraviroc (Selzentry®)

- (a) Targets CCR5
- (b) Viral tropism assay required prior to use
- (c) Side effect
  - (i) Dizziness

###### (2) Enfuvirtide (Fuzeon®)

- (a) Subcutaneous injection
- (b) Side effects
  - (i) Moderate – severe injection site reaction

##### ii) Nucleoside Reverse Transcriptase Inhibitors (NRTIs or ‘nukes’)<sup>6,7</sup>

###### (1) Class Side Effects: lactic acidosis, hepatic steatosis, pancreatitis

- (a) Emtricitabine
  - (i) Well tolerated, HBV activity
- (b) Lamivudine
  - (i) Well tolerated, HBV activity
- (c) Tenofovir Disoproxil Fumarate (TDF)
  - (i) Bloating, renal insufficiency, decreased bone mineral density
- (d) Tenofovir Alafenamide (TAF)
  - (i) Less renal insufficiency and less bone mineral density loss as compared to TDF

- (e) Abacavir
  - (i) Severe hypersensitivity reaction
    - 1. Must test for HLA-b \*5701 prior to use
- (f) Zidovudine
  - (i) Nausea, anemia, myopathy, headache
- (g) Stavudine
  - (i) Peripheral neuropathy, lipoatrophy
- (h) Didanosine
  - (i) Peripheral neuropathy, lipoatrophy, pancreatitis
- iii) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs or 'non-nukes')<sup>6,7</sup>
  - (1) Class side effects: rash, hepatotoxicity
    - (a) Efavirenz
      - (i) Dizzy, drowsy, vivid dreams
    - (b) Rilpivirine
      - (i) Depression, insomnia, headache
    - (c) Etravirine
      - (i) Nausea, rash
    - (d) Nevirapine
      - (i) BBW: contraindicated with higher CD4 count, rash, hepatotoxicity
- iv) Integrase Inhibitors (INSTI)<sup>6,7</sup>
  - (1) Class side effects: myopathy, rhabdomyolysis
    - (a) Dolutegravir
    - (b) Elvitegravir
    - (c) Raltegravir
- v) Protease Inhibitors (PI)<sup>6,7</sup>
  - (1) Class side effects: GI disturbances, hyperlipidemia, insulin resistance, lipoatrophy, hepatotoxicity
    - (a) Darunavir
    - (b) Lopinavir
    - (c) Atazanavir
      - (i) Asymptomatic bilirubinemia
    - (d) Ritonavir
      - (i) Diarrhea, PR interval prolongation
- vi) Pharmacokinetic Booster (PK Enhancer)<sup>6,7</sup>
  - (1) Enhances antiretroviral pharmacokinetic profile of PIs and EVG
    - (a) Allows for reduced dosing of antiretrovirals
    - (b) Many drug interactions
      - (i) Cobicistat ≠ ritonavir
  - (2) Ritonavir
    - (a) CYP P450 inhibitor
  - (3) Cobicistat
    - (a) CYP P450 inhibitor

- c) Building a complete regimen
  - i) 2 NRTIs plus one of the following: PI, INSTI, NNRTI
- d) Single Tablet Regimens (STR) (See Appendix B)
  - i) Stribild® (EVG/COBI/FTC/TDF)<sup>6-9</sup>
    - (1) Administration: once daily with food
    - (2) Side effects:
      - (a) Nausea, diarrhea
      - (b) Abnormal dreams, headache
      - (c) Falsely elevates SCr 0.12 mg/dL<sup>10</sup>
        - (i) Monitor closely if SCr elevates 0.4 mg/dL
    - (3) Less favorable in patients with renal impairment and bone disorders compared to Genvoya® (EVG/COBI/FTC/TAF)
      - (a) Higher plasma tenofovir levels
    - (4) Not recommended when CrCl <50 mL/minute
  - ii) Genvoya® (EVG/COBI/FTC/TAF)<sup>6-9</sup>
    - (1) Administration: Once daily with food
    - (2) Side Effects: Nausea, diarrhea, headache, fatigue
    - (3) Place in therapy:
      - (a) Renal impairment
      - (b) Patients undergoing treatment with Harvoni® (ledipasvir/sofosbuvir)
    - (4) Not recommended when CrCl <30 mL/minute
  - iii) Triumeq® (DTG/ABC/3TC)<sup>6-9</sup>
    - (1) Administration: Once daily without regard to food
    - (2) Side effects:
      - (a) Insomnia, headache, fatigue
      - (b) Neuropsychiatric or central nervous system side effects
      - (c) Suicidal ideation (DTG)
    - (3) Best for patients with HIV RNA <100,000 copies/mL
    - (4) Check HLA-B\* 5701
    - (5) May have increased cardiac risk (ABC)
    - (6) Good option for pts. that cannot take tolerate TDF or TAF due kidney and bone profiles
    - (7) Not recommended when CrCl <50 mL/minute
  - iv) Atripla® (EFV/FTC/TDF)<sup>6-9</sup>
    - (1) Administration: Once daily on an empty stomach, preferably at bedtime
    - (2) Side effects:
      - (a) Caution in patients with depression & psychiatric conditions (EFV)
      - (b) Dizziness, abnormal/vivid dreams, difficulty concentrating (FTC)
      - (c) Nausea, diarrhea, headache
      - (d) Fatigue, insomnia
    - (3) Caution in first trimester of pregnancy (EFV)
      - (a) Monitor kidney function - Initially and as clinically indicated
    - (4) Not recommended when CrCl <50 mL/minute

- v) Complera<sup>®</sup> (RPV/FTC/TDF)<sup>6-9</sup>
  - (1) Administration: Once daily with a standard meal (540 kcal) (RPV)
  - (2) Side effects:
    - (a) Insomnia, headache
    - (b) Suicidal ideation (RPV)
    - (c) Rash, increase in liver enzymes (RPV)
  - (3) Best for patients with HIV RNA <100,000 copies/mL
  - (4) Not recommended when CrCl <50 mL/minute
- vi) Odefsey<sup>®</sup> (RPV/FTC/TAF)<sup>6-9</sup>
  - (1) Administration: Once daily with a standard meal (540 kcal) (RPV)
  - (2) Side effects:
    - (a) Insomnia, headache
    - (b) Depression/suicidal ideation (RPV)
    - (c) Rash, increase in liver enzymes (RPV)
  - (3) Best for patients with HIV RNA <100,000 copies/mL
  - (4) Safer bone and kidney profile vs. Complera<sup>®</sup> (RPV/FTC/TDF)
  - (5) Not recommended when CrCl <30 mL/minute
- e) Medication Errors in HIV<sup>7-8,11</sup>
  - i) Wrong medication
    - (1) e.g. single medication instead of combination
  - ii) Wrong dose/frequency
    - (1) Dosage adjustments in renal failure
    - (2) Reformulations
  - iii) Wrong administration time
    - (1) With food vs. on an empty stomach
    - (2) Medications should be given at the same time as their boosters (e.g. darunavir and atazanavir should be given at the same time)
  - iv) Most common drug interactions (See Appendix B)
    - (1) Resources
      - (a) [www.aids.info.nih.gov](http://www.aids.info.nih.gov)
      - (b) Lexicomp<sup>®</sup>
      - (c) [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
  - v) Case Discussion
- 4) Pneumonia
  - a) Etiology<sup>12</sup>
  - b) Definitions
    - i) Community acquired pneumonia (CAP)<sup>12</sup>
    - ii) Health-care associated pneumonia (HCAP)
    - iii) Hospital acquired pneumonia (HAP)<sup>13</sup>
    - iv) Ventilator associated pneumonia (VAP)<sup>13</sup>
  - c) Scoring tools<sup>12</sup>
    - i) CURB-65

- d) CAP Outpatient Drug Therapy<sup>12</sup>
  - i) Previously healthy no risk factors for drug-resistance *S. pneumoniae* (DRSP)
    - (1) Azithromycin **OR**
    - (2) Doxycycline
  - ii) Comorbidities, risk DRSP
    - (1) Levofloxacin **OR**
    - (2) Beta-lactam plus Macrolide
- e) CAP Inpatient Drug Therapy<sup>12</sup>
  - i) Beta-lactam plus macrolide **OR**
  - ii) Fluoroquinolone
- f) Duration of therapy<sup>12,14-15</sup>
  - i) 5 days
    - (1) Afebrile for 48-72 hours
      - (a) No more than 1 CAP-associated sign of clinical instability
        - (i) Heart Rate  $\geq 100$  beats/min
        - (ii) Respiratory Rate  $\geq 24$  breaths/min
        - (iii) Systolic Blood Pressure  $\leq 90$  mmHg
        - (iv) Arterial oxygen saturation  $\leq 90\%$  or  $pO_2 \leq 60$  mmHg on room air
  - ii) 6-7 days (or longer)
    - (1) Initial therapy was not active against pathogen
    - (2) Infection complicated by extra-pulmonary infection (e.g. meningitis, bacteremia, etc.)

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## Appendix A

Table 1: Single Tablet Regimens<sup>6-10</sup>

Single Tablet Regimen	With Food	Without Food	Without Regards to Food	Depression/suicidal ideation	Safer kidney profile	Safer bone profile	Renal Cutoff <50 mL/min	Renal Cutoff <30 mL/min
Stribild®	X						X	
Genvoya®	X				X	X		X
Triumeq®			X	X	X	X	X	
Atripla®		X		X			X	
Complera®	X			X			X	
Odefsey®	X			X	X	X		X

## Appendix B

Table 2: Common Antiretroviral Drug Interactions<sup>7-8,11</sup>

Medication	Antiretroviral(s)	Predicted effect	Clinical Management
Antacids	INSTIs, atazanavir ±r, tipranavir/r, rilpivirine	↓ ART	<ul style="list-style-type: none"> <li>Separate</li> </ul>
H <sub>2</sub> Receptor Antagonist	Atazanavir ±r, rilpivirine	↓ ART	<ul style="list-style-type: none"> <li>ATV/r can be administered simultaneously</li> <li>Separate</li> <li>Max doses of famotidine based on regimen</li> </ul>
Proton Pump Inhibitors	Atazanavir ±r, rilpivirine	↓ ART	<ul style="list-style-type: none"> <li>Concurrent use not recommended with unboosted ATV or in PI-experienced patients</li> <li>Max daily dose of omeprazole equivalents = 20 mg</li> <li>Separate</li> </ul>
Antiepileptics (AED): Carbamazepine (CBZ), phenytoin (PHT), and phenobarbital	PIs	↓ PI, ↑CBZ, ↓ PHT	<ul style="list-style-type: none"> <li>Do not co-administer</li> <li>Consider alternative AED</li> </ul>
	EFV, NVP	↓ AED, NNRTI	<ul style="list-style-type: none"> <li>Monitor AED concentrations or use alternative</li> </ul>
	ETR, RPV	↓ AED, ETR, RPV	<ul style="list-style-type: none"> <li>Do not co-administer</li> <li>Consider alternative AED</li> </ul>
	DTG	↓ DTG	<ul style="list-style-type: none"> <li>Consider alternative AED</li> </ul>
	TAF	↓ TAF	<ul style="list-style-type: none"> <li>Consider alternative AED</li> </ul>
Lamotrigine	PIs	↓ LTG AUC (30-50%)	<ul style="list-style-type: none"> <li>Dose increase for LTF may be warranted</li> <li>Monitor AED concentrations</li> <li>Use alternative</li> </ul>
Amiodarone	PIs	↑ Amiodarone, ↑ PIs	<ul style="list-style-type: none"> <li>Use with caution</li> <li>Additional amiodarone monitoring</li> </ul>
Fluticasone	3A4 Ritonavir and cobicistat boosted regimens, EVG	↑ fluticasone	<ul style="list-style-type: none"> <li>May result in adrenal insufficiency and Cushing's syndrome</li> <li>Consider beclomethasone for long-term use</li> <li></li> </ul>

Medication	Antiretroviral(s)	Predicted effect	Clinical Management
Benzodiazepines (BDZ)			<ul style="list-style-type: none"> <li>Minimal interaction with lorazepam, oxazepam, temazepam</li> </ul>
	PIs, EFV	↑ BDZ	<ul style="list-style-type: none"> <li>Avoid use of midazolam and triazolam</li> </ul>
	PIs, COBI	↑ BDZ	<ul style="list-style-type: none"> <li>Use alprazolam, diazepam, and flurazepam with caution</li> </ul>
Ticagrelor, Clopidogrel	Boosted PIs, EVG/c ETR	↑ Antiplatelet ↓ Clopidogrel bioactivation	<ul style="list-style-type: none"> <li>Avoid concurrent use</li> <li>Avoid concurrent use</li> </ul>
Apixiban, dabigatran, edoxaban, rivaroxaban	Boosted PIs, EVG/c	↑ Anticoagulant	<ul style="list-style-type: none"> <li>Adjustments for dabigatran based on renal function</li> <li>Separate dabigatran administration time by 2 hrs with boosted PIs</li> <li>Avoid dabigatran with EVG/c</li> </ul>
Warfarin	PI/r, NVP, EVG/c, EFV, ETR	↓ warfarin ↓ or ↑ warfarin	<ul style="list-style-type: none"> <li>Monitor INR and adjust warfarin accordingly</li> </ul>