PharmGenEd™: Bridging the Gap Between Science & Practice
Train-the-Trainer Session for HIV/AIDS
Monday, March 12, 2012

Train-the-Trainer Agenda

1. Introduction
   • Objective of PharmGenEd™ program
   • Shared curriculum and format
   • Introduction of author

2. Review of educational content for selected therapeutic area

3. Contact information

4. Survey to assess program materials

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Overall Objective of PharmGenEd™ Program

• The “Pharmacogenomics Education Program: Bridging the Gap between Science and Practice” (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.

• The overall objective of the PharmGenEd™ program is to increase awareness about the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests.

Disclaimer
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The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.
Shared Curriculum

Educational Materials (each 1 hour)
- Asthma
- Cardiology I (warfarin & statins)
- Cardiology II (clopidogrel & beta blockers)
- Concepts and clinical applications
- Economic issues
- Oncology I (solid tumors)
- Oncology II (hematologic malignancies)
- Psychiatry I (depression)
- Psychiatry II (antipsychotics)

Therapeutic Area Discussion

Format for each drug:
- Patient case
- Gene/Allele of interest
- Functional effect
- Population prevalence
- Clinical relevance (dosing/selection, efficacy, and toxicity)
- Genomic test and testing recommendation
- Patient case summary

Learning Objectives

Upon completion of this program, participants will be able to:
- Identify specific drug therapies in which pharmacogenomic testing can be applied in the clinical setting
- Summarize evidence-based recommendations for pharmacogenomic testing
- Using patient case scenarios, formulate a plan for pharmacogenomic testing based upon available scientific evidence

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Presentation Outline
Pharmacogenomic effects of HIV/AIDS medications
• Abacavir
  – Major histocompatibility complex, Class I (HLA-B*5701)
• Nevirapine
  – Major histocompatibility complex, Class I (HLA-B & C)
  – Major histocompatibility complex, Class II (HLA-DRB1)
  – ABC transporter gene (ABCB1)
• Efavirenz
  – Cytochrome P450 (CYP) 2B6
• Atazanavir
  – Uridine diphosphate-glucuronosyltransferase (UGT1A1)

Challenges in HIV therapy
• Many different combinations of antiretroviral drugs may be prescribed
• The goal is durable virologic suppression with minimal toxicity and resistance
• Adverse drug effects may lead to poor adherence or treatment discontinuation (Yuan et al 2006, Vo et al 2008, Hart et al 2007, Cicconi et al 2010)
• These may lead to disease progression and drug resistance
• Pharmacogenomic testing to predict adverse effects may prevent treatment discontinuation (Lubomirov et al 2011)

Patient Case 1
• KK is a 28 year old HIV+ Caucasian male who presents to clinic to initiate antiretrovirals.
  – HIV acquired via unprotected sex with other men
  – CD4 count: 420 cells/mm³ HIV RNA: 53000 c/mL
• Physician instructs the patient to get blood drawn for labs, prescribes the following medications, and asks him to return to clinic prior to starting the medicines.
  – Abacavir/lamivudine 600/300 mg orally daily
  – Darunavir 400 mg two tablets orally daily
  – Ritonavir 100 mg orally daily
Patient Case 1

- 14 days later KK returns to clinic complaining of fever, rash, increasing nausea, and malaise.
- These symptoms started shortly after beginning antiretroviral therapy. He admits to starting his regimen prior to the scheduled visit and never got his laboratory tests, which included a test for HLA-B*5701.
- Question: Would KK have avoided experiencing a hypersensitivity reaction if he obtained the recommended pharmacogenomic testing?

Abacavir

- **Description**: nucleoside reverse transcriptase inhibitor (NRTI), administered daily
- **Place in therapy**: second-line NRTI component
- **Adverse effects**: rash, hypersensitivity reaction

Abacavir

- **Allele of interest**
- **Functional effect** (Nolan 2009, Adam et al 2011)
  - *HLA-B*5701 confers high risk of abacavir-induced hypersensitivity reaction (HSR)
  - Possible mechanisms:
    - Hapten model
      - Abacavir or its metabolite binds to endogenous proteins/peptides, which are processed and presented by MHC Class I → eliciting a CD8 T-cell response. (Adam et al 2011, Nolan 2009)
    - Direct interaction with MHC Class I
      - Abacavir or its metabolite binds directly to the peptide-binding groove of MHC Class I, resulting in activation of CD8 T-cells. (Adam et al 2011, Yang et al 2009, Chessman et al 2008)

Abacavir Population Prevalence

Nolan et al 2003
Abacavir: Clinical Relevance

- **Dosing/selection**
  - Dosing is not affected by pharmacogenomic testing
  - Drug selection is affected
    - Patients testing positive for HLA-B*5701 should *not* be prescribed abacavir if other effective options are available. (US FDA 2009, US DHHS 2011)

- **Efficacy**
  - No literature addresses how abacavir pharmacogenomics affects efficacy

Clinical Relevance: Toxicity

**HLA-B*5701** confers high risk of abacavir HSR

- Early onset
  - Usually appears first 6-8 weeks of treatment
  - Symptoms worsen with continued dosing

- Symptoms: fever, rash, gastrointestinal, flu-like, respiratory symptoms

- Fatal in cases of rechallenge
  - Hypotension, organ failure

Pharmacogenomic Test and Recommendations

- Testing: Genotype testing for HLA-B*5701 is widely available.
  - Patients testing positive for HLA-B*5701 should *not* be prescribed abacavir if other effective options are available. (US FDA 2009, US DHHS 2011)

- Recommendations:
  - U.S. Department of Health and Human Services recommends HLA-B*5701 screening prior to initiation of abacavir therapy.
  - Screening is recommended in the prescription information black box warning.

Clinical Relevance: Toxicity

**PREDICT-1** (Mallal et al 2008)

- N=1956
- Double blind, randomized, controlled trial
- HLA-B*5701 screening vs. standard of care
- Immunologically confirmed HSR occurred in 0% screened vs. 2.7% standard of care (OR 0.03; 95% CI, 0.00-0.18)
- Negative predictive value = 100%

**SHAPE** (Saag et al 2008)

- N=199
- Retrospective, matched case-control study
- Cases: HSR by clinical diagnosis, with or without skin patch confirmation
- 100% of skin patch-confirmed HSR cases were HLA-B*5701 positive
**HLA-B*5701 Testing Implementation**

- Healthcare provider attitudes (Watson et al. 2009)
  - 202 HIV providers completed surveys before & after a pharmacogenomics educational program
    - Perceived value of testing increased 98% → 100%
    - Perceived barriers to testing decreased 78% → 70%
  - 134 providers tested patients for HLA-B*5701
    - 89% of those plan to continue testing

- Pharmacoeconomics (Kauf et al. 2010)
  - Estimated cost = $17/patient to avoid 537 hypersensitivity reactions per 10,000 patients

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**Patient Case 1 Summary**

- All of KK’s antiretroviral medications are discontinued.
- KK is instructed to go to the laboratory, return to clinic in 2 weeks for follow up, and go to the emergency department if symptoms worsen.
- Laboratory test for HLA-B*5701 comes back positive. If KK had obtained this test earlier, abacavir (and the resultant HSR) could have been avoided.
- “Abacavir allergy” now noted in the patient’s chart.

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**Patient Case 2**

- After 2 weeks, KK’s symptoms have resolved.
- His most recent lab tests include
  - CD4 count: 410 cells/mm³ HIV RNA: 55,000 c/mL
  - AST: 22 (normal 7-26 IU/L)
  - ALT: 18 (normal 3-23 IU/L)
- KK requests antiretroviral therapy and is prescribed:
  - Tenofovir/emtricitabine 300/200 mg daily
  - Nevirapine 200mg orally daily for 21 days followed by nevirapine extended release tablets 400 mg orally daily
Patient Case 2

- 21 days later KK presents with a rash, right upper quadrant pain, and dark urine. Stat labs are drawn.
  - AST: 150 (normal 7-26 IU/L)
  - ALT: 120 (normal 3-23 IU/L)
  - Total bilirubin: 3.6 (normal 0.1-1.2 mg/dL)

- Questions
  - What is the likely cause of this adverse reaction? What risk factors did KK have?
  - Is there a pharmacogenomic test which could have predicted this drug reaction in KK?

Nevirapine

- Description: non-nucleoside reverse transcriptase inhibitor (NNRTI), administered once or twice daily
- Place in therapy: widely used as 1st line therapy in developing countries; also used to prevent mother-to-child transmission
- Adverse effects: hepatotoxicity, rash, hypersensitivity reaction (HSR)
  - Nevirapine HSR more serious than the “typical” NNRTI rash, involving more systemic symptoms such as fever. May occur with or without hepatic involvement

Nevirapine: Genes of interest

- Several genes:
  - MHC Class I
    - HLA-B*3505 (Chantarangsu et al 2009, Yuan et al 2011)
    - HLA-Cw*0401 (Likanonsakul et al 2009, Yuan et al 2011)
    - HLA-Cw*08 (Littera et al 2006, Gatanaga et al 2007)
  - MHC Class II
    - HLA DRB1*0101 (Martin et al 2005, Yuan et al 2011)
    - ABCB1 (Haas et al 2006, Ciccacci et al 2010)

- Relevant alleles vary with ethnicity/race and are associated with different hypersensitivity reaction (hepatic vs. cutaneous) types (Yuan et al 2011)

Nevirapine: Functional effect

- MHC Class I & II alleles and mutations in ABCB1 may contribute to nevirapine hypersensitivity reaction
  - Mechanisms not well understood
  - HSR may result from immune recognition of nevirapine-associated antigens or generation of reactive nevirapine metabolites (Popovic, 2010, Yuan 2011).
  - Mutations in ABCB1 influence nevirapine transport, though association between increased concentrations and HSR is unclear.

- Occurrence of HSR is influenced by gender as well as CD4+ cell counts
  - Women with CD4 counts > 250 at higher risk
  - Men with CD4 counts > 400 at higher risk
**Nevirapine**

**Population Prevalence**

<table>
<thead>
<tr>
<th>HLA</th>
<th>Asian</th>
<th>Black</th>
<th>White</th>
<th>Thai</th>
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</thead>
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<td>13%</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>HLA-Cw*04</td>
<td>22%</td>
<td>29%</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>HLA-DRB1*01</td>
<td>&lt;1%</td>
<td>11%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from Yuan 2011)

- Note: Data regarding distribution of HLA-Cw*08 and ABCB1 polymorphisms not available

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**Nevirapine Clinical Relevance**

- **Dosing/selection**
  - Dosing not affected by pharmacogenomic testing
  - Pharmacogenomic testing may be useful for drug selection, if it predicts that a patient is at higher risk for nevirapine HSR

- **Efficacy**
  - No literature linking treatment efficacy to alleles associated with nevirapine hypersensitivity reaction

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**Pharmacogenomic Test and Recommendations**

- **Genomic Testing:** Genotype testing is not widely available
- **Recommendations:** Routine testing for the different HLA Class I and Class II polymorphisms is not recommended

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**Nevirapine Clinical Relevance**

- **Toxicity**
  - Presence of HLA types associated with increased odds of having hypersensitivity reaction (Yuan, 2011)
    - HLA-DRB*0101 OR= 3.02 in Whites
    - HLA-Cw*04 OR=18.90 in Blacks
    - HLA-B*35 OR= 3.47 in Asians
  - Hypersensitivity reaction (Taiwo 2006)
    - Combination of fever, rash, hepatitis
    - Occurs early during therapy
    - Life-threatening reactions in case reports, estimated 0.5-1% for cutaneous events. (Davis, 2008)
Patient Case 2 Summary

• KK denies having a rash in any of his mucous membranes. His temperature is mildly elevated.

• All of KK’s antiretroviral medications are discontinued. He is sent home with strict instructions to return to the emergency department if symptoms worsen.

• The likely cause for his adverse reaction is nevirapine. KK’s CD4 cell count >400 may have been a predisposing factor. At the time there was no commercially available pharmacogenomic test which may have predicted his reaction.

• Over the next 4 weeks, his liver function tests return to normal and his rash dissipates.

Patient Case 3

• 4 months later, KK returns to clinic. An HIV+ friend recommended her regimen because she did not experience side effects.
  – Efavirenz/emtricitabine/tenofovir 600/200/300 mg orally daily

• KK returns to clinic one month after starting this regimen. While he likes the simplicity of the regimen, he has had some difficulty concentrating at work which is unrelated to any stress or depression. He asks whether this is a side effect of the medicines.

• Question: What is the cause of this adverse effect? Can pharmacogenomic testing predict the severity to which KK might experience this adverse effect?

Efavirenz

• **Description**: non-nucleoside reverse transcriptase inhibitor (NNRTI), administered daily

• **Place in therapy**: U.S. Department of Health and Human Services HIV treatment guidelines recommend efavirenz for initial therapy, combined with 2 nucleoside reverse transcriptase inhibitors (NRTI)

• **Adverse effects**: hepatotoxicity, rash, dizziness, drowsiness, “foggy” or “hangover” feeling, abnormal dreams
Efavirenz: Allele of interest

Cytochrome P450 2B6 (CYP2B6)

- CYP2B6*6 allele contains two non-synonymous single nucleotide polymorphisms (SNPs) (Thorn et al 2010)
  - CYP2B6 516 G>T
  - CYP2B6 785 A>G

Efavirenz: Functional Effect

- The rate of efavirenz metabolism varies among patients
- CYP2B6 is one of the enzymes responsible for efavirenz metabolism prior to its ultimate excretion
- CYP2B6*6 is associated with ↓ protein expression and enzyme activity (Hofmann et al 2008, Desta et al 2007)
- This can lead to 3 fold increases in efavirenz area under the curve (Haas et al 2004, Rotger et al 2005a)

Efavirenz: Clinical Relevance

- Selection
  - No literature related to CYP2B6*6 impacting drug selection.
- Dosing
  - Standard dose 600 mg daily
  - Studies have used pharmacogenomic testing for CYP2B6*6 in combination with therapeutic drug monitoring to lower efavirenz dose to 400 or 200 mg for those at risk for toxicity (Mello et al 2011, Figueroa et al 2010)
Efavirenz: Clinical Relevance

- Dosing: managing drug interactions
  - In HIV/TB co-infection, rifampin can suppress efavirenz levels
    - efavirenz dose may be increased to 800 mg daily, based on weight. (DHHS, 2011)
  - CYP2B6 testing may be useful for individualizing dose adjustments with this drug interaction (Kwara et al 2011)
    - although it is unknown how predictive genotype is compared to other factors (Rekic et al 2011)

- Efficacy
  - CYP2B6*6-related increases in efavirenz exposure may improve HIV viral suppression (Ribaudo 2010)
  - May also increase risk of acquiring resistance mutations if all HIV medications are discontinued while efavirenz remains in plasma. (Ribaudo 2006)

- Toxicity
  - CYP2B6*6 leads to increased efavirenz exposure
    (Haas et al 2004, Rotger et al 2005a)
  - ↑ efavirenz leads to CNS adverse effects:
    - dizziness, abnormal dreams, feeling “foggy”
      (during the first week)
  - However, central nervous system side effects may wane despite continued higher exposure (Haas, et al 2004)

Pharmacogenomic Test and Recommendations

- Genomic Testing: Genotype testing for CYP2B6 is not commercially available.

- Recommendations: Routine testing for CYP2B6 polymorphisms is not recommended.

Patient Case 3 Summary

- Despite having neurocognitive side effects from efavirenz, KK decides to stay on this antiretroviral regimen because he likes the convenience of taking one pill.

- After 8 weeks of treatment he says he no longer notices the side effects. His labs also show a fully suppressed HIV viral load.
  - CD4 count: 440 cells/mm³
  - HIV RNA: <40 c/mL

- He is to return to clinic in 4 months.
Patient Case 4

• KK has been taking the combination efavirenz/emtricitabine/tenofovir for 8 months and has been stable on this regimen. He returns to the clinic for routine laboratory monitoring.
  – CD4: 300 cells/mm³ HIV RNA: 20,000 c/mL
  – HIV genotype: K103N mutation

• KK’s physician tells him that his viral load has increased and that he is now resistant to efavirenz. KK admits that he has been poorly adherent due to the side effects he has been experiencing. However, he knows it is important to take antiretrovirals and wants to start a new regimen.

Patient Case 4

• KK is prescribed:
  – Zidovudine/lamivudine 300/150 mg orally twice daily
  – Tenofovir 300 mg orally daily
  – Atazanavir 300 mg orally daily
  – Ritonavir 100 mg orally daily

• KK returns to clinic one month later. He is tolerating this regimen, with the exception of some mild diarrhea at the start. He has also noticed some yellowing in his eyes.
  – CD4: 350 cells/mm³ HIV RNA: <40 c/mL
  – Total bilirubin: 2.4 mg/dL (normal 0.1-1.2 mg/dL)

• Question: Is pharmacogenomic testing warranted prior to starting atazanavir to predict whether or not hyperbilirubinemia will occur?

Atazanavir

• Description: protease inhibitor administered once daily

• Place in therapy: Recommended by U.S. HIV treatment guidelines for initial therapy when combined with 2 NRTI and ritonavir (DHHS, 2011)

• Adverse effects: nausea, vomiting, diarrhea, hyperbilirubinemia with jaundice (Busti et al 2004, Goldsmith et al 2003)
Atazanavir: Allele of Interest

Uridine diphosphate-glucuronosyltransferase (UGT1A1)
• Wild type allele has 6 thiamine-adenine (TA) repeats in the promoter region
• UGT1A1*28 allele has 7 TA repeats in the promoter region

Atazanavir Functional effect

• UGT1A1 is the enzyme responsible for the glucuronidation and subsequent clearance of bilirubin (Burchell and Hume 1999)
• Promoter of the UGT1A1*28 allele is less active than wild type, leading to hyperbilirubinemia (Beutler et al 1998)
• Atazanavir inhibits activity of UGT1A1 (Zucker et al 2001, Zhang et al 2005)
• Patients taking atazanavir have a higher risk of hyperbilirubinemia if they carry the UGT1A1*28 allele (Rodriguez-Novoa et al 2007, Rotger et al 2005b)

Atazanavir Population Prevalence

Frequencies of UGT1A1 genotypes by race:

<table>
<thead>
<tr>
<th>Genotype</th>
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<th>Asian (n=47)</th>
<th>African American (n=101)</th>
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<td>34%</td>
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<td>19%</td>
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<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>18%</td>
</tr>
</tbody>
</table>

(adapted from Beutler et al 1998)

Atazanavir Clinical Relevance

• Dosing/selection
  – No current literature related to UGT1A1 impacting dosing/selection of atazanavir
  – In the future, pharmacogenomic testing in combination with therapeutic drug monitoring may guide clinicians to lower atazanavir doses in patients at risk of jaundice or scleral icterus.
  – Also, pharmacogenomic testing may help clinicians avoid prescribing atazanavir for patients at risk for jaundice or scleral icterus.

• Efficacy
  – No literature related to UGT1A1 impacting drug efficacy
Atazanavir
Clinical Relevance

• Toxicity
  – Patients taking atazanavir have a higher risk of grade 3-4 hyperbilirubinemia if they carry the UGT1A1*28 allele (Rodriguez-Novoa et al 2007)
  – Patients may have poor adherence to atazanavir when hyperbilirubinemia manifests as jaundice or scleral icterus

• Current clinical practice
  – Atazanavir started, then discontinued if jaundice and scleral icterus are bothersome to patients
  – Pharmacogenomic testing may help clinicians avoid initial selection of atazanavir in patients at risk for jaundice and scleral icterus

Pharmacogenomic Test and Recommendations

• Genomic Testing: Genotype testing for UGT1A1 is commercially available

• Recommendations: Routine testing for UGT1A1 polymorphisms is not recommended when prescribing atazanavir

Patient Case 4 Summary

• Pharmacogenomic testing to predict hyperbilirubinemia is not routinely recommended prior to starting atazanavir.

• KK opts to stay on this antiretroviral regimen, as he feels that the yellowing of his eyes is not too noticeable.

• 8 weeks later, KK remains adherent to his regimen, his viral load remains suppressed, and his CD4 cell count is rising.
  – HIV RNA: <40 c/mL
  – CD4: 350 cells/mm³

Acknowledgements

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• Reviewers
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  – Philip E. Bourne, PhD
  – Theodore Ganiats, MD
  – Palmer Taylor, PhD

The program is 100% funded by the CDC (Grant Number IU38GD000070)
Post-training Survey

• For participants
  https://kuooffice.wufoo.com/forms/pharmgeneda-hiv/

• For faculty trainers
  https://kuooffice.wufoo.com/forms/pharmgeneda-hiv-trainers/

• Evaluate knowledge, attitudes, and self-efficacy