PharmGenEd™: Bridging the Gap Between Science & Practice

Train-the-Trainer Session
for HIV/AIDS

Monday, March 12, 2012

UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY
and PHARMACEUTICAL SCIENCES

Disclaimer

This presentation was supported by Grant Number IU38GD000070 from Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

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.

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

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.

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)

 5

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

 6

Author

Jennifer Cocohoba, Pharm.D., BCPS, AAHIVE
Health Sciences Associate Clinical Professor
University of California, San Francisco
School of Pharmacy

 7

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

 8

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)

Abacavir

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/mm^3 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

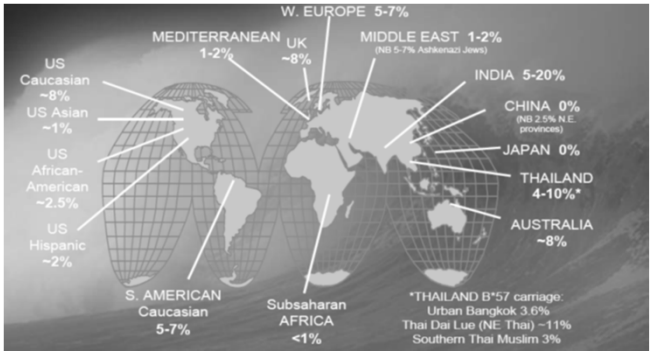
- *Description*: nucleoside reverse transcriptase inhibitor (NRTI), administered daily
- *Place in therapy*: second-line NRTI component
- *Adverse effects*: rash, hypersensitivity reaction

Abacavir

- Allele of interest
  - *HLA-B*5701* (Cutrell et al 2004, Mallal et al 2002, Hetherington et al 2002)
- 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

***HLA-B*5701* in Different Populations**



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

 17

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

 18

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

 19

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.

 20

*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

 21

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.

 22

Nevirapine

 23

Patient Case 2

- After 2 weeks, KK's symptoms have resolved.
- His most recent lab tests include
  - CD4 count: 410 cells/mm^3 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

 24

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

*HLA-B*35*	*HLA-Cw*04*	*HLA-DRB1*01*
• Asian: 10%	• Asian: 22%	• Asian: <1%
• Black: 13%	• Black: 29%	• Black: 11%
• White: 19%	• White: 24%	• White: 25%
• Thai: 8%	• Thai: 22%	

(Adapted from Yuan 2011)

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

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

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)

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

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.

 33

Efavirenz

 34

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?

 35

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

 36

Efavirenz: Allele of interest

Cytochrome P450 2B6 *(CYP2B6)*

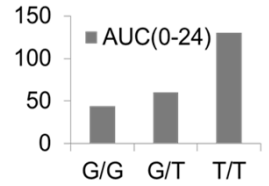
- *CYP2B6*6* allele contains two non-synonymous single nucleotide polymorphisms (SNPs) (Thorn et al 2010)
  - *CYP2B6 516 G>T*
  - *CYP2B6 785 A>G*

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 $AUC_{0\text{-}24}$ (g hr/ML) by genotype at position 516
(adapted from Haas et al 2004)



Efavirenz Population prevalence

G516T polymorphism	G516T SNP present in ~30% of Caucasians in Germany (Lang et al 2001)
	G516T SNP found in 42% of Caucasian, 48% of African American, 71% of Hispanic and 0% of Asian liver samples (Lamba et al 2003)
	TT genotype more prevalent in African Americans (20%) than in European Americans (3%) (Haas et al 2004)
CYP2B6*6 allele	More common in Blacks (38%) than Whites (25%) (Rotger et al 2007)
	Prevalence in a study of Japanese subjects was 16% (Hiratsuka et al 2002)
	Present in 18% of Han Chinese subjects and in 21% of Uygur Chinese subjects (Guan et al 2006)

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)

 41

Efavirenz: Clinical Relevance

- 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)

 42

Pharmacogenomic Test and Recommendations

- Genomic Testing: Genotype testing for *CYP2B6* is not commercially available.
- Recommendations: Routine testing for *CYP2B6* polymorphisms is not recommended.

 43

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/mm^3
  - HIV RNA: <40 c/mL
- He is to return to clinic in 4 months.

 44

Atazanavir

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/mm^3 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/mm^3 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

 49

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)

 50

Atazanavir Population Prevalence

Frequencies of *UGT1A1* genotypes by race:

Genotype N=219	Caucasian (n=71)	Asian (n=47)	African American (n=101)
(wild type) 6/6	34%	70%	26%
6/7	55%	28%	37%
7/7	11%	2%	19%
Other	0	0	18%

(adapted from Beutler et al 1998)

 51

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

 52

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

 53

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

 54

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/mm^3

 55

Acknowledgements

- **Author**

  Jennifer Cocohoba, Pharm.D., BCPS, AAHIVE
  Health Sciences Associate Clinical Professor
  University of California, San Francisco, School of Pharmacy
- **Reviewers**
  - Brookie M. Best, Pharm.D., M.A.S., University of California, San Diego
  - Scott Johns, Pharm.D., BCPS(ID), VASDHS
  - Katrin Sangkuhl, Ph.D., Stanford University
- **Editors**
  - Cindy Gustafson-Brown, Ph.D., University of California, San Diego
  - Grace M. Kuo, Pharm.D., M.P.H., Ph.D. FCCP, University of California, San Diego
- **Editorial Staff**
  - Tiffany Sie, Eunice Hong, Heather Hutchinson

 56

References

Adam J, Pichler WJ, Yerly D. Delayed drug hypersensitivity: models of T-cell stimulation. Br J Clin Pharmacol, 2011; 71(5):701–707.

Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism. Proc Natl Acad Sci USA 1998 Jul 7; 95(14):8170-4.

Burchell B and Hume R. Molecular genetic basis of Gilbert's syndrome. J Gastroenterol Hepatol 1999 Oct; 14(10):960-6.

Busti AJ, Hali RG, Margolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. Pharmacotherapy 2004; 24:1732–1747.

Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, Manosuthi W, Tantisiriwat W, Charoenyingwattana A, Sura T, Chantratita W, Nakamura Y. HLA-BM3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenet Genomics 2009; 19:139–146.

Chessman D, Kostenko L, Lethborg T, Purcell AW, Williamson NA, Chen Z, Kjer-Nielsen L, Mifsud NA, Tait BD, Holdsworth R, Almeida CA, Nolan D, Macdonald WA, Archbold JK, Kellerher AD, Marriott D, Mallal S, Bharadwaj M, Rossjohn J, McCluskey J. Human Leukocyte Antigen Class I-Restricted Activation of CD8+ T Cells Provides the Immunogenetic Basis of a Systemic Drug Hypersensitivity. Immunity 2008 Jun; 28(6):822-32.

Ciccacci C, Borgiani P, Ceffa S, Sirianni E, Marazzi MC, Altan AM, Paturzo G, Bramanti P, Novelli G, Palombi L. Nevirapine-induced hepatotoxicity and pharmacogenetics: a retrospective study in a population from Mozambique. Pharmacogenomics 2010; 11:23–31.

Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi EM, Antinori A, Gatti F, Cassola G, Sighinolfi L, Castelli P, d'Arminio Monforte A; ICoNA Foundation Study Group. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. HIV Med 2010 Feb; 11(2):104-13. Epub 2009 Sep 1.

References

Cutrell AG, Hernandez JE, Fleming JW, Edwards MT, Moore MA, Brothers CH, Scott TR. Updated clinical risk factor analysis of suspected hypersensitivity reactions to abacavir. Ann Pharmacother 2004; 38:2171-2. Epub 2004 Nov 9.

Davis CM, Shearer W. Diagnosis and management of HIV drug hypersensitivity. J Allergy Clin Immunol 2008; 121:826-832.

Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. October 14, 2011; 1–167. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed December 20, 2011.

Desta Z, Saussele T, Ward B, Blievernicht J, Li L, Klein K, Flockhart DA, Zanger UM. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. Pharmacogenomics 2007; 8(6):547-58.

Figueroa SC, de Gatta MF, García LH, Hurlé AD, Bernal CB, Correa RS, Sánchez MJ. The convergence of therapeutic drug monitoring and pharmacogenetic testing to optimize efavirenz therapy. Ther Drug Monit 2010 Oct; 32(5):579-85.

Gandhi M, Benet LZ, Bacchetti P, Kalinowski A, Anastos K, Wolfe AR, Young M, Cohen M, Minkoff H, Gange SJ, Greenblatt RM. Nonnucleoside reverse transcriptase inhibitor pharmacokinetics in a large unselected cohort of HIV-infected women. J Acquir Immune Defic Syndr 2009 Apr 15; 50(5):482-91.

Gatanaga H, Yazaki H, Tanuma J, Honda M, Genka I, Teruya K, Tachikawa N, Kikuchi Y, Oka S. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. AIDS 2007; 21:264–265.

Goldsmith DR and Perry CM. Atazanavir. Drugs 2003; 63:1679–1693.

References

Guan S, Huang M, Chan E, Chen X, Duan W, Zhou SF. Genetic polymorphisms of cytochrome P450 2B6 gene in Han Chinese. Eur J Pharm Sci 2006 Sep; 29(1):14-21.

Haas DW, Bartlett JA, Andersen JW, Sanne I, Wilkinson GR, Hinkle J, Rousseau F, Ingram CD, Shaw A, Lederman MM, Kim RB. Pharmacogenetics of nevirapine-associated hepatotoxicity: an adult AIDS Clinical Trials Group collaboration. Clin Infect Dis 2006; 43:783–786.

Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, Clifford DB, Hulgan T, Marzolini C, Acosta EP. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004; 18:2391–2400.

Hart E, Curtis H, Wilkins E, Johnson M. National review of first treatment change after starting highly active antiretroviral therapy in antiretroviral-naive patients. HIV Med 2007; 8:186–191.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002; 359:1121-2.

Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, Lafon S, Pearce G, Steel H. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Therap 2001; 23(10):1603-1644.

Hiratsuka M, Takekuma Y, Endo N, Narahara K, Hamdy SI, Kishikawa Y, Matsuura M, Agatsuma Y, Inoue T, Mizugaki M. Allele and genotype frequencies of CYP2B6 and CYP3A5 in the Japanese population. Eur J Clin Pharmacol 2002 Sep; 58(6):417-21.

Hofmann MH, Blievernicht JK, Klein K, Saussele T, Schaeffeler E, Schwab M, Zanger UM. Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver. J Pharmacol Exp Ther 2008 Apr; 325(1):284-92. Epub 2008 Jan 2.

References

Hughes CA, Foisy MM, Dewhurst N, Higgins N, Robinson L, Kelly DV, Lechelt KE. Abacavir Hypersensitivity Reaction: an Update. Ann Pharmacother 2008; 42:387-96.

Kauf TL, Farkouh RA, Earnshaw SR, Watson ME, Maroudas P, Chambers MG. Economic Efficiency of Genetic Screening to Inform the Use of Abacavir Sulfate in the Treatment of HIV. Pharmacoeconomics 2010; 28(11):1025-1039.

Kwara A, Tashima KT, Dumond JB, Poethke P, Kurpewski J, Kashuba AD, Court MH, Greenblatt DJ. Modest but variable effect of rifampin on steady-state plasma pharmacokinetics of efavirenz in healthy African-American and Caucasian volunteers. Antimicrob Agents Chemother 2011 Jul; 55(7):3527-33.

Lai-Goldman M and Faruki H. Abacavir hypersensitivity: a model system for pharmacogenetic test adoption. Genet Med 2008; 10(12):874-8.

Lamba V, Lamba J, Yasuda K, Strom S, Davila JC, Hancock M. Hepatic CYP2B6 expression: gender and ethnic differences and relationship to CYP2B6 genotype and CAR expression. J Pharmacol Exp Ther 2003; 307:906–922.

Lang T, Klein K, Fischer J, Nussler AK, Neuhaus P, Hofmann U. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics 2001; 11:399–415.

Likanonsakul S, Rattanatham T, Feangvad S, Uttayamakul S, Prasithsirikul W, Tunthanathip P, Nakayama EE, Shioda T. HLA-CwM04 allele associated with nevirapine-induced rash in HIV-infected Thai patients. AIDS Res Ther 2009; 6:22.

Littera R, Carcassi C, Masala A, Piano P, Serra P, Ortu F, Corso N, Casula B, La Nasa G, Contu L, Manconi PE. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. AIDS 2006; 20:1621–1626.

References

Lubomirov R, Colombo S, di Iulio J, Ledergerber B, Martinez R, Cavassini M. Association of Pharmacogenetic Markers with Premature Discontinuation of First-line Anti-HIV Therapy: An Observational Cohort Study. Journal of Infectious Diseases 2011; 203:246–257.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castely A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLAB*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002; 359:727-32.

Mallal S, Phillips E, Carosi G. PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008 Feb 7; 358(6):568-79.

Martin A, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, Carvalho F, Phillips E, Christiansen FT, Purcell AW, McCluskey J, Mallal S. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. PNAS 2005; 101(12):4180-4185.

Martin AM, Nolan D, James I, Cameron P, Keller J, Moore C, Phillips E, Christiansen FT, Mallal S. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts. AIDS 2005 Jan 3; 19(1):97-9.

Mello AF, Buclin T, Decosterd LA, Delhumeau C, di Iulio J, Fleurent A, Schneider MP, Cavassini M, Telenti A, Hirschel B, Calmy A. Successful efavirenz dose reduction guided by therapeutic drug monitoring. Antivir Ther 2011; 16(2):189-97.

Nolan D, Gaudieri S, Mallal S. Pharmacogenetics: a practical role in predicting antiretroviral drug toxicity? J HIV Ther 2003 May; 8(2):36-41.

Nolan, D. HLA-B*5701 screening prior to abacavir prescription: Clinical and laboratory aspects. Critical Reviews in Clinical Laboratory Science 2009; 46(3):153–165.

Popovic M, Shenton JM, Chen J, Baban A, Tharmanathan T, Mannargudi B, Abdulla D, Uetrecht JP. Nevirapine hypersensitivity. Handb Exp Pharmacol 2010; 196:437-51.

References

Rauch A, Nolan D, Thurnheer C, Fux CA, Cavassini M, Chave JP, Opravil M, Phillips E, Mallal S, Furrer H. Refining abacavir hypersensitivity diagnoses using a structured clinical assessment and genetic testing in the Swiss HIV Cohort Study. Antivir Ther 2008; 13(8):1019-28.

Rekić D, Röshammar D, Mukonzo J, Ashton M. In silico prediction of efavirenz and rifampicin drug-drug interaction considering weight and CYP2B6 phenotype. Br J Clin Pharmacol 2011 Apr; 71(4):536-43.

Ribaudo HJ, Haas DW, Tierney C, Kim RB, Wilkinson GR, Gulick RM, Clifford DB, Marzolini C, Fletcher CV, Tashima KT, Kuritzkes DR, Acosta EP; Adult AIDS Clinical Trials Group Study. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. Clin Infect Dis 2006 Feb 1; 42(3):401-7.

Ribaudo HJ, Liu H, Schwab M, Schaeffeler E, Eichelbaum M, Motsinger-Reif AA, Ritchie MD, Zanger UM, Acosta EP, Morse GD, Gulick RM, Robbins GK, Clifford D, Haas DW. Effect of CYP2B6, ABCB1, and CYP3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. J Infect Dis 2010 Sep 1; 202(5):717-22.

Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, González-Pardo G, Jiménez-Nácher I, González-Lahoz J, Soriano V. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. AIDS 2007; 21:41–46.

Rotger M, Colombo S, Furrer H, Bleiber G, Buclin T, Lee BL, Keiser O, Biollaz J, Décosterd L, Telenti A. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005 Jan; 15(1):1-5.

Rotger M, Taffe P, Bleiber G, Gunthard HF, Furrer H, Vernazza P, Drechsler H, Bernasconi E, Rickenbach M, Telenti A. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. J Infect Dis 2005 Oct 15; 192(8):1381-1386.

References

Rotger M, Tegude H, Colombo S, Cavassini M, Furrer H, Décosterd L, Blievernicht J, Saussele T, Günthard HF, Schwab M, Eichelbaum M, Telenti A, Zanger UM. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther 2007 Apr; 81(4):557-66.

Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W. High Sensitivity of Human Leukocyte Antigen–B*5701 as a Marker for Immunologically Confirmed Abacavir Hypersensitivity in White and Black Patients. Clinical Infectious Diseases 2008; 46:1111–8.

Saitoh A, Sarles E, Capparelli E, Aweeka F, Kovacs A, Burchett SK, Wiznia A, Nachman S, Fenton T, Spector SA. CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. AIDS 2007 Oct 18; 21(16):2191-9.

Schackman B, Scott CA, Walensky RP, Losina E, Freedberg KA, Sax PE. The cost effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS 2008; 22:2025–2033.

Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. J Acquir Immune Defic Syndr 2003; 34(Suppl. 1):S21–S33.

Taiwo BO. Nevirapine toxicity. Int J STD AIDS 2006; 17:364–370.

Thorn CF, Lamba JK, Lamba V, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP2B6. Pharmacogenet Genomics 2010 Aug; 20(8):520-3.

Tsuchiya K, Gatanaga H, Tachikawa N, Teruya K, Kikuchi Y, Yoshino M, Kuwahara T, Shirasaka T, Kimura S, Oka S. Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. Biochem Biophys Res Commun 2004 Jul 9; 319(4):1322-6.

References

U.S. Food and Drug Administration. Important safety-related label update for Ziagen (abacavir sulfate). Updated 06/18/2009. Available at: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121646.htm. Accessed November 21, 2011.

US Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of Antiretroviral Agents In HIV-1-Infected Adults and Adolescents. October 14, 2011. Available at: http://www.aidsinfo.nih.gov. Accessed November 21, 2011.

Vo TT, Ledergerber B, Keiser O. for the Swiss HIV Cohort Study. Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. J Infect Dis 2008; 197:1685–1694.

Watson ME, Patel LG, Ha B, Wannamaker P, Cuffe R, Shaefer M. A Study of HIV Provider Attitudes Toward HLA-B*5701 Testing in the United States. AIDS Patient Care and STDs 2009; 23(11):957.

Yang L, Chen J, He L. Harvesting candidate genes responsible for serious adverse drug reactions from a chemical-protein interactome. PLoS Comput Biol 2009; 5(7):e1000441. Epub 2009 Jul 24.

Yuan J, Guo S, Hall D, Cammett AM, Jayadev S, Distel M, Storfer S, Huang Z, Mootsikapun P, Ruxrungtham K, Podzamczer D, Haas DW. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. AIDS 2011 Jun 19; 25(10):1271-1280.

Yuan Y, L'italien G, Mukherjee J, Iloeje UH. Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort. HIV Med 2006 Apr; 7(3):156-62.

References

Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP glucuronosyl transferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. Drug metabolism and disposition 2005; 33(11):1729-39.

Ziagen® [abacavir sulfate] Prescribing Information. GlaxoSmithKline. September 2010. Available at: http://us.gsk.com/products/assets/us_ziagen.pdf. Accessed November 21, 2011.

Zucker S, Qin X, Rouster S, Yu F, Green R, Keshavan P, Feinberg J, and Sherman KE. Mechanism of indinavir-induced hyperbilirubinemia. Proc Natl Acad Sci USA 2001; 98:12671–12676.

END OF CONTENT SECTION

Contact for TTT for Faculty

PharmGenEd™ Training for Health Professional Schools
Kelly C. Lee, PharmD, BCPP
Phone: 858-822-3462
Email: kellylee@ucsd.edu

General Questions about PharmGenEd™
pharmacogenomics@ucsd.edu

Principal Investigator and Program Director
Grace M. Kuo, PharmD, MPH
Phone: 858-822-7754
Email: kuooffice@ucsd.edu

PharmGenEd™ Team

- **UCSD Faculty**
  - Grace M. Kuo, PharmD, MPH, PhD, FCCP (PI)
  - Kelly C. Lee, PharmD, BCPP, FCCP
  - Sarah McBane, PharmD, CDE, BCPS
  - Nathan A. Painter, PharmD, CDE
  - Cindy Gustafson-Brown, PhD
  - 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

 69