

**Pharmacogenetic of Drug  
Hypersensitivity:  
Personalising Medicine & Predicting  
the Unpredictable**

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# Genetics & Adverse Drug Reactions

*“If it were not for the great variability among individuals, medicine might as well be a science and not an art”*

Sir William Osler, 1892



**Personalizing Medicine= *defining optimal diagnostic, management & treatment strategies for the individual patient***

**Pharmacogenetics**

- specific tests to prevent toxicity (eg. HLA-B\*5701 screening for abacavir hypersensitivity)
- guide dosing of drugs
- HLA and other immune markers to guide vaccine development and predict response

**Pharmacoeecology**

- individualizing the patient's environment to optimize therapeutic outcome
- PK/PD interactions with drugs, herbal medicines and nutritional supplements
- food effects on drugs (absorption/bioavailability)
- adherence (cultural & socioeconomic influences)
- intercurrent disease of host state (eg organ failure, pregnancy)
- diurnal variation in pharmacokinetics/dynamics
- individual drug taking behaviour

**Personalized Prescription**

# Characteristics of Drug Reactions

Classification	<b>TYPE A = Pharmacological</b>	<b>TYPE B = “Bizarre”</b>
Predictable	Yes	No
Dose Dependent	+++	+
Host Dependent (Genetic factors)	+	+++
Immunologic basis	-	+++
Examples	Gastrointestinal intolerance, seizures with penicillin etc	Allergic and idiosyncratic syndromes, <b>hypersensitivity syndromes</b>

# Classification of ADRs

## Drug Reaction

Predictable Reactions  
(dose dependent)

Unpredictable Reactions  
(less dose dependent)

### Idiosyncratic

- Reactive Metabolite Syndromes (eg, Drug *Hypersensitivity* Syndrome)
- Hepatitis
- SJS/TEN

### *Hypersensitivity/* Immunogenetic

- Type I
- Type II
- Type III
- Type IVa-d

### Pseudoallergic

- ASA
- Vancomycin
- Contrast

# TYPE B REACTIONS: Associated Drugs

## ● Anticonvulsants

- phenytoin, phenobarbital, carbamazepine
- lamotrigine

## ● Antimicrobials

- sulfonamides (sulfa antimicrobials), penicillins, dapsone
- nitrofurantoin, minocycline, metronidazole

## ● Allopurinol

## ● Antiinflammatories (eg oxicam-NSAIDS, Valdecoxib)

## ● Antiretrovirals

## ● Alternative medicines

- Chinese herbals etc.

## ● Antineoplastics

## ● mAbs

- “Ximab” (infliximab, rituximab) > “Zumab” (omalizumab) > “Mumab”(adalimumab)

# Pharmacogenetics

Drug → Disease → Gene

## TYPE A

### Dose Dependent Disease

- Drug Efficacy or toxicity
- Often multifactorial (eg age, gender, BMI, concurrent medications)
- Often related to polymorphism(s) in drug metabolizing enzymes (eg CYP) or pharmacodynamic factors
- eg Warfarin, efavirenz, clopidogrel

<sup>1</sup>Mallal S et al Lancet 2002;359:727-32

<sup>2</sup>Chung WH et al. Nature 2004;428:486

Locharenkul et al Epilepsia 2008;49:2087-91

<sup>3</sup>Shuen-lu Hung et al PNAS 2005;102:4134-9

<sup>4</sup>Kindmark et al. Pharmacogenomics J 2008;8:186-95

<sup>5</sup>Martin & al. AIDS 2005;19:97-99; Littera et al. AIDS 2006;16:21-6; Gatanga H et al AIDS 2007;21:264-5; Vitezica et al AIDS 2008;540-1; Chantarangsu et al Pharmacogenomics 2009;9:139-46.

## TYPE B

### Dose Independent Disease

#### -HLA & Drug Hypersensitivity

<sup>1</sup>abacavir hypersensitivity (HLA-B\*5701)

<sup>2</sup>carbamazepine SJS/TEN (HLA-B\*1502)

phenytoin SJS/TEN (HLA-B\*1502)

<sup>3</sup>allopurinol SJS/TEN/HSR (HLA-B\*5801)

<sup>4</sup>ximelagatran hepatotoxicity (HLA-DRB1\*07; DQA1\*02)

<sup>5</sup>nevirapine rash and rash associated hepatitis (class I (HLA-DRB1\*0101 + CD4+, HLA-B\*1402, HLA-Cw8, HLA-B\*3505)

# HLA & Drug Hypersensitivity

Articles

Lancet March 2, 2002

## Association between presence of *HLA-B\*5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

S Mallal, D Nolan, C Witt, G Masel, A M Martin, C Moore, D Sayer, A Castley, C Mamotte, D Maxwell, I James, F T Christiansen

### Summary

**Background** The use of abacavir—a potent HIV-1 nucleoside-analogue reverse-transcriptase inhibitor—is complicated by a potentially life-threatening hypersensitivity syndrome in about 5% of cases. Genetic factors influencing the immune response to abacavir might confer susceptibility. We aimed to find associations between MHC alleles and abacavir

**Interpretation** Genetic susceptibility to abacavir hypersensitivity is carried on the 57-1 ancestral haplotype. In our population, withholding abacavir in those with *HLA-B\*5701*, *HLA-DR7*, and *HLA-DQ3* should reduce the prevalence of hypersensitivity from 9% to 2-5% without inappropriately denying abacavir to any patient.

Lancet 2002; 359: 727-32

RESEARCH LETTERS

Research letters

Lancet March 30, 2002

## Genetic variations in *HLA-B* region and hypersensitivity reactions to abacavir

Seth Hetherington, Arlene R Hughes, Michael Mosteller, Denise Shorino, Katherine L Baker, William Spreen, Eric Lai, Kirstie Davies, Abigail Handley, David J Dow, Mary E Ring, Michael Stocum, Clive Bowman, Linda M Thurmond, Allen D Roses

**Hypersensitivity to abacavir affects about 4% of patients who receive the drug for HIV-1 infection. We did a retrospective, case-control study to identify multiple markers in the vicinity of *HLA-B***

occurred more frequently among patients than controls by Fisher's exact test. These included *HLA-B57* (39 [46%] of 84 or four of 112 [4%], odds ratio 22.6 [95% CI 8.0-70.0]

# A marker for Stevens–Johnson syndrome

**S**tevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication<sup>1–3</sup>. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen *HLA-B\*1502*, and Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possi-

Table 1 Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome

<i>HLA</i> allele	CBZ–SJS	CBZ-tolerant	Normal
<i>B*1502</i>	44 (100%)	3 (3%)*	8 (8.6%)†
<i>Cw*0801</i>	41 (93.2%)	17 (16.8%)	13 (14%)
<i>A*1101</i>	36 (81.8%)	51 (50.5%)	53 (57%)
<i>DRB1*1202</i>	33 (75%)	12 (11.9%)	18 (19.4%)
<i>B*1502, Cw*0801</i>	41 (93.2%)	3 (3%)	7 (7.5%)
<i>B*1502, A*1101</i>	36 (81.8%)	2 (2%)	6 (6.5%)
<i>B*1502, DRB1*1202</i>	33 (75%)	1 (1%)	5 (5.4%)
<i>B*1502, Cw*0801, A*1101, DRB1*1202</i>	29 (66%)	0 (0%)	3 (3.2%)

Frequencies (by number and percentage) of individual or combined loci of the *B\*1502* ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; *n* = 44), and in carbamazepine-tolerant (*n* = 101) and normal subjects (*n* = 93). For methods, see supplementary information.

\*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected *P* value *P*<sub>c</sub> = 3.13 × 10<sup>−27</sup>.

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); *P*<sub>c</sub> = 1.38 × 10<sup>−21</sup>.



## WARNING

### SERIOUS DERMATOLOGIC REACTIONS AND HLA-B\*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B\*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B\*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B\*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/LABORATORY TESTS).

## **WARNING**

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**Carbamazepine FDA Label Change December 2007**

PNAS 2005

# HLA-B\*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol

Shuen-lu Hung<sup>a,b</sup>, Wen-Hung Chung<sup>a,b,c,d</sup>, Lieh-Bang Liou<sup>e</sup>, Chen-Chung Chu<sup>f</sup>, Marie Lin<sup>f</sup>, Hsien-Ping Huang<sup>a</sup>, Yen-Ling Lin<sup>a</sup>, Joung-Liang Lan<sup>g</sup>, Li-Cheng Yang<sup>c</sup>, Hong-Shang Hong<sup>c</sup>, Ming-Jing Chen<sup>c</sup>, Ping-Chin Lai<sup>h</sup>, Mai-Szu Wu<sup>h</sup>, Chia-Yu Chu<sup>i</sup>, Kuo-Hsien Wang<sup>j</sup>, Chien-Hsiun Chen<sup>a</sup>, Cathy S. J. Fann<sup>a</sup>, Jer-Yuarn Wu<sup>a,k</sup>, and Yuan-Tsong Chen<sup>a,l,m</sup>

<sup>a</sup>Institute of Biomedical Sciences, Academia Sinica, Taipei 11529, Taiwan; Departments of <sup>c</sup>Dermatology, <sup>e</sup>Rheumatology, Allergy, and Immunology, and <sup>h</sup>Nephrology, Chang Gung Memorial Hospital, Taipei 10507, Taiwan; <sup>f</sup>Department of Medical Research, Mackay Memorial Hospital, Taipei 10449, Taiwan; <sup>g</sup>Department of Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung 40705, Taiwan; <sup>i</sup>Department of Dermatology, National Taiwan University Hospital, Taipei 10002, Taiwan; <sup>j</sup>Department of Dermatology, Taipei Medical University Hospital, Taipei 11031, Taiwan; <sup>k</sup>Department of Medical Research, China Medical University Hospital, Taichung 40447, Taiwan; <sup>l</sup>Department of Pediatrics, Duke University Medical Center, Durham, NC 27710; and <sup>m</sup>Molecular Medicine Program, Taiwan International Graduate Program, Academia Sinica and the School of Life Sciences, National Yang Ming University, Taipei 11529, Taiwan

## LETTERS

published online May 31 2009

nature  
genetics

## *HLA-B\*5701* genotype is a major determinant of drug-induced liver injury due to flucloxacillin

Ann K Daly<sup>1</sup>, Peter T Donaldson<sup>1</sup>, Pallav Bhatnagar<sup>1</sup>, Yufeng Shen<sup>2</sup>, Itsik Pe'er<sup>2</sup>, Aris Floratos<sup>2</sup>, Mark J Daly<sup>3</sup>, David B Goldstein<sup>4</sup>, Sally John<sup>5</sup>, Matthew R Nelson<sup>6</sup>, Julia Graham<sup>1</sup>, B Kevin Park<sup>7</sup>, John F Dillon<sup>8</sup>, William Bernal<sup>9</sup>, Heather J Cordell<sup>1</sup>, Munir Pirmohamed<sup>7</sup>, Guruprasad P Aithal<sup>10,11</sup> & Christopher P Day<sup>1,11</sup>, for the DILIGEN study<sup>12</sup> and International SAE Consortium<sup>12</sup>

## Associations may differ across race, phenotype, study design and underlying immune status

- HLA-DRB1\*0101 + CD4% > 25 and rash associated hepatitis (Martin et al AIDS 2005)
- HLA-Cw8-B14 haplotype in Sardinians (Littera et al AIDS 2006)
- HLA-Cw8 in Japanese (Gatanaga et al AIDS 2007)
- HLA-DRB1\*01 in French population with efavirenz

Pharmacogenetics & Genomics 2009

**HLA-B\*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients**

Soranun Chantarangsu<sup>a,b</sup>, Taisei Mushiroda<sup>a</sup>, Surakameth Mahasirimongkol<sup>e</sup>, Sasisopin Kiertiburanakul<sup>c</sup>, Somnuek Sungkanuparph<sup>c</sup>, Weerawat Manosuthi<sup>f</sup>, Woraphot Tantisiriwat<sup>g</sup>, Angkana Charoenyingwattana<sup>d</sup>, Thanyachai Sura<sup>c</sup>, Wasun Chantratita<sup>b</sup> and Yusuke Nakamura<sup>a</sup>

Genetic susceptibility conferred by *Class I MHC marker(s)* eg. HLA-B\*1402, HLA-Cw8, HLA-B\*3505

OR

Genetic susceptibility conferred by *Class II MHC marker(s)* eg. HLA-DRB1\*0101  
+ Sufficient levels of CD4+ T cells

Class I-restricted immune response to NVP-specific antigen

•Class II-restricted immune response to NVP-specific antigen

## NEVIRAPINE HYPERSENSITIVITY

(rash of varying severity, fever, hepatitis, multisystem disease)

**Sufficient** levels of relevant metabolite

(distinct from dose dependent or “Type A” adverse drug reactions)

•Nevirapine disposition (?Role of CYP3A4/CYP2B6/CYP2C9) and drug transporters (P-glycoprotein(MDR1)) and polymorphisms in drug metabolizing and drug transporter genes that differ across ethnicity

# Host-Drug-Infection Interactions: A Complex Dynamic

HOST

HLA  
Immune response genes  
Control of infection  
Vaccine design

Pharmacodynamics  
Pharmacokinetics  
Drug Efficacy  
Drug Toxicity

PATHOGEN

Chronic persistent DNA viruses  
(CMV, EBV, HHV-6, Herpes viruses)

HIV

DRUG

Drug resistance  
Drug Efficacy



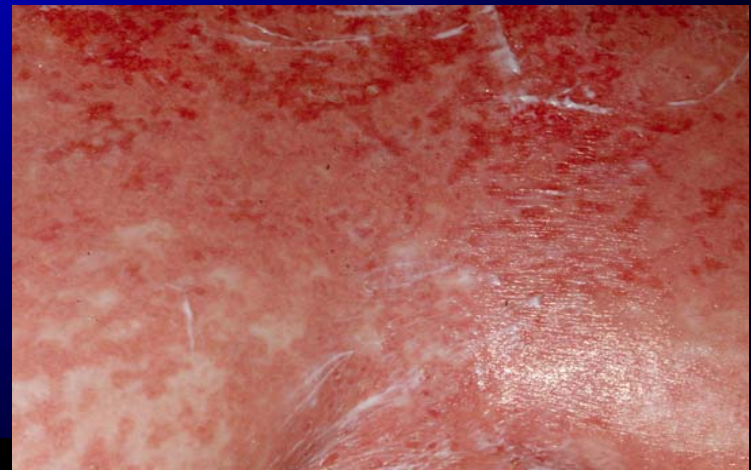
Classic 3 ring Target – HSV not drug



Atypical Target – 2 ring dusky center



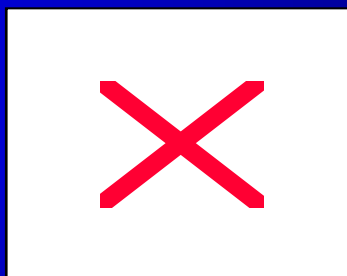
Mucositis & Atypical target



Blistering of TEN

# HLA-B\*1502 & Carbamazepine: Phenotype is Important

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis



-associated with severe skin syndromes (SJS/TEN in Han Chinese)

-NOT associated with drug hypersensitivity (fever/rash/internal organ involvement) or ?disease in Caucasians

# **Prerequisites for Widespread Incorporation of HLA Pharmacogenetic Testing**

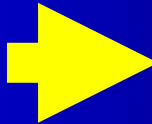
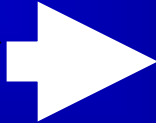
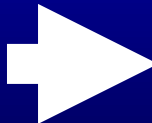
Implications differ according to drug...

Prerequisites	Drug/HLA association			
	ABC	CBZ	ALL	NEV
<b>Test</b> <ul style="list-style-type: none"> <li>HLA allele is strongly associated with the toxicity, and the negative predictive value of the test is high*</li> <li>The number of patients needed for testing to prevent a case of toxicity is low*</li> <li>HLA allele is prevalent in a large, non-disenfranchised population*</li> </ul>	+++	+++	++	++
<b>Drug</b> <ul style="list-style-type: none"> <li>Drug exhibits favorable attributes, such as good efficacy, convenience in dosing and administration, tolerability and pill burden*</li> <li>Alternative drug(s) that do not require pharmacogenetic testing are either absent or have negative attributes*</li> </ul>	++	+	++	+
<b>Drug toxicity</b> <ul style="list-style-type: none"> <li>Toxicity is severe and persistent* (ie, not isolated mild rash)</li> <li>Toxicity is readily and accurately phenotyped*</li> <li>An adjunctive diagnostic test, such as skin patch testing, can improve phenotypic precision</li> </ul>	++	++	++	++
<b>Environment</b> <ul style="list-style-type: none"> <li>Champions available (eg, clinical academics, industry [if drug not off patent*], professional bodies, regulatory agencies, guideline committees, patient advocacy groups, laboratory providers and the media), willing and able to drive pharmacogenetic test development and implementation</li> </ul>	+++	-	-	-
<b>Generation of high-level evidence</b> <ul style="list-style-type: none"> <li>Case-control studies with estimated predictive values based on the assumed prevalence of the HLA allele</li> <li>Population-based cohort studies with directly calculated predictive values of the test</li> <li>Open screening studies</li> <li>Supportive experimental data</li> <li>Blinded randomized controlled trials</li> <li>Evidence across ethnic groups and geographical areas to determine the clinical settings that the test may be applied to</li> <li>Cost-effectiveness data</li> </ul>	++	++	++	-
<b>Development and availability of appropriate laboratory support</b> <ul style="list-style-type: none"> <li>No patent restriction on use of the test</li> <li>Development of simple, inexpensive, robust, unambiguous laboratory tests</li> <li>Rapid and simple report and interpretation</li> <li>Development of reagents (eg, mAbs, PCR-based kits)</li> <li>Global distribution and commercialization of allele-specific test</li> <li>Allele-specific quality assurance targeted to avoid false-negative results and consequent morbidity or mortality</li> <li>Reimbursement of test</li> </ul>	++	-	-	-
<b>Design and implementation of appropriate clinical systems</b> <ul style="list-style-type: none"> <li>Education of clinicians, nurses, pharmacists, phlebotomists and patients</li> <li>Systems to ensure appropriate and routine triggering of ordering of the test</li> <li>Systems in the clinic to ensure the correct blood samples are sent to the correct laboratory for analysis</li> <li>Systems to ensure test results and correct interpretation is rapidly transmitted to, retained by and acted on by the healthcare team and patient</li> </ul>	++	-	-	-
	+	-	-	-
	+	-	-	-
	+	-	-	-

# Factors Favouring Clinical Uptake of a Pharmacogenetic Test

- **clinical outcome associated with the test has significant impact on patient well-being**
- **lack of alternative drug(s) with more favourable therapeutic/toxicity profile**
- **high predictive value of the genetic test**
- **ready availability of rapid, low cost test**
- **identification of clinical parameters that determine the usefulness of the test**
- **sufficient clinical utility to be incorporated into routine management, so that testing is performed prospectively without requiring specific ‘triggers’**

# Framework of Antiretroviral Therapy & Pharmacogenetics

- Define whether or not the drug should be used (dose independent toxicity)  Abacavir & HLA-B\*5701 screening
- Define the optimal dose of the drug for a specific patient or patient population (dose dependent toxicity & efficacy)  NNRTIs, protease inhibitors
- Avoid drug/drug & drug gene interactions
- Define or enhance understanding of the pathophysiology of drug toxicity  Metabolic complications, lipodystrophy, peripheral neuropathy, mitochondrial toxicities

# Translating Research in Genomic Medicine into the Clinic & Beyond

- **STEP 1 – The discovery & turning this into a health application** → 2002 – HLA-B\*5701 association in two independent groups

↓ *Imprecision of clinical phenotype (false positive clinical diagnosis) cast doubt on generalizability of HLA-B\*5701 to “all” abacavir HSR. Patch testing developed to identify those with true immunologically mediated HSR*

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- **STEP 2 - Development of high level clinical evidence (randomized) in support of test. Basic science to support biological plausibility** → 2002-present: genetic and cellular studies support plausibility of association  
2005-2008 – PREDICT-1, SHAPE & observational studies provide robust clinical evidence
- 

- **STEP 3 - Diffusion of research and delivery to clinic depends on efficiency and quality assurance of laboratory testing and reporting** → 2005 - PCR-based techniques readily applicable methodology (rapid, inexpensive)  
2005-2008 - HLA-B\*5701 quality assurance program roll-out  
2008 – HIV Treatment guidelines/product information change to incorporate recommendation for baseline testing & reimbursement
- 

- **STEP 4 – Evaluating performance of the test in real clinical practice** → 2008 + - Multiple observational studies  
Pharmacoeconomic evaluation  
Post “PREDICT-1” clinical quality assurance

# Pharmacogenetics & Antiretroviral Therapy: The Abacavir Example

- Guanosine nucleoside analogue used in antiretroviral therapy, approved by regulatory agencies 1998/1999
- Hypersensitivity syndrome characterized by fever, malaise +/- skin rash was characterized in pre-marketing phase, not fatal unless drug reintroduced; affected approximately 6- 8% of predominantly Caucasian population
- Robust clinical management program for drug
- Early clues such as familial case reports and rarity in Blacks suggested genetic association
- 2002 – two independent groups reported strong association with HLA-B\*5701
- 2008 – screening for hypersensitivity has rolled out into much of developed world

# HLA-B\*5701 and Abacavir Hypersensitivity: A Comparison of Two Studies

Mallal *et al*, 2002  
HLA-B\*5701

	Pos	Neg	
HSR	14	4	Sens 78%
No HSR	5	177	Spec 97%
	<b>Pos PV</b>	<b>Neg PV</b>	
	<b>74%</b>	<b>98%</b>	

Hetherington *et al*, 2002\*  
HLA-B57

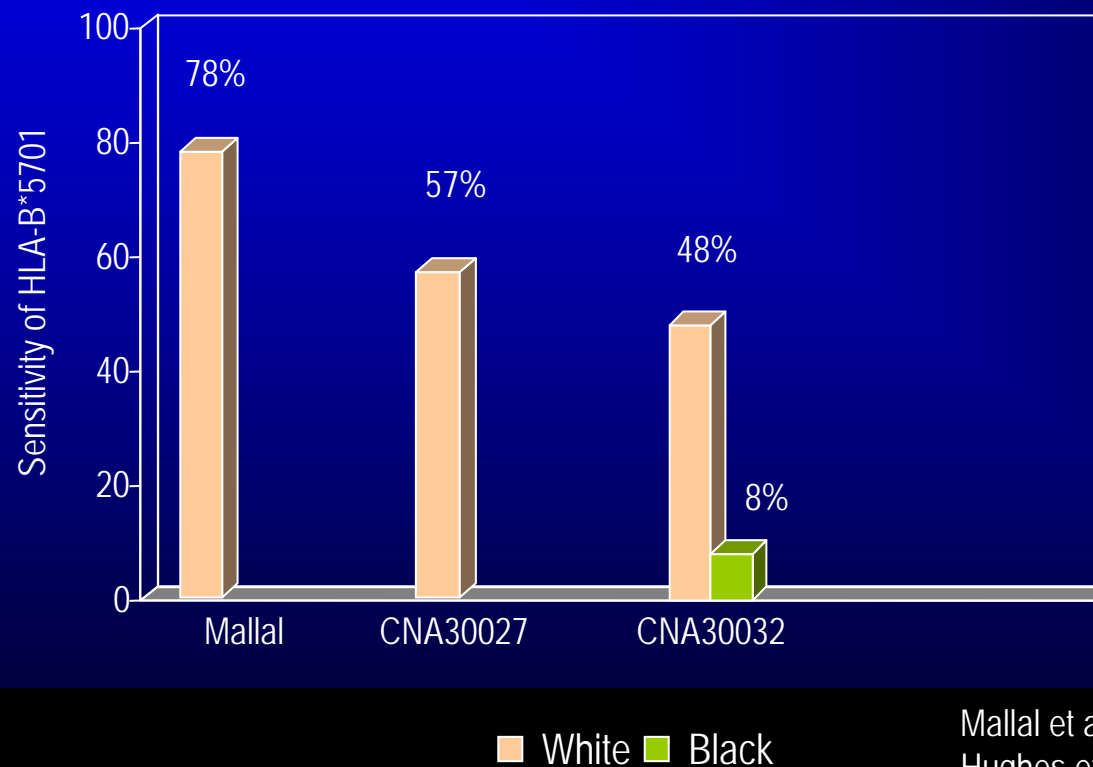
	Pos	Neg	
HSR	36	29	Sens 55%
No HSR	8	649	Spec 99%
	<b>Pos PV</b>	<b>Neg PV</b>	
	<b>82%</b>	<b>96%</b>	

\*Caucasians only  
Observed sensitivity and specificity  
PV assumes prevalence of ~9%

# Early Problems with “Phenotype”

- Early studies have observed variable sensitivity of *HLA-B\*5701*

- Definition of abacavir hypersensitivity reaction (ABC HSR) nonspecificity of clinical phenotyping → false positive clinical diagnosis
- Differences in white and nonwhite races



Mallal et al. Lancet 2002

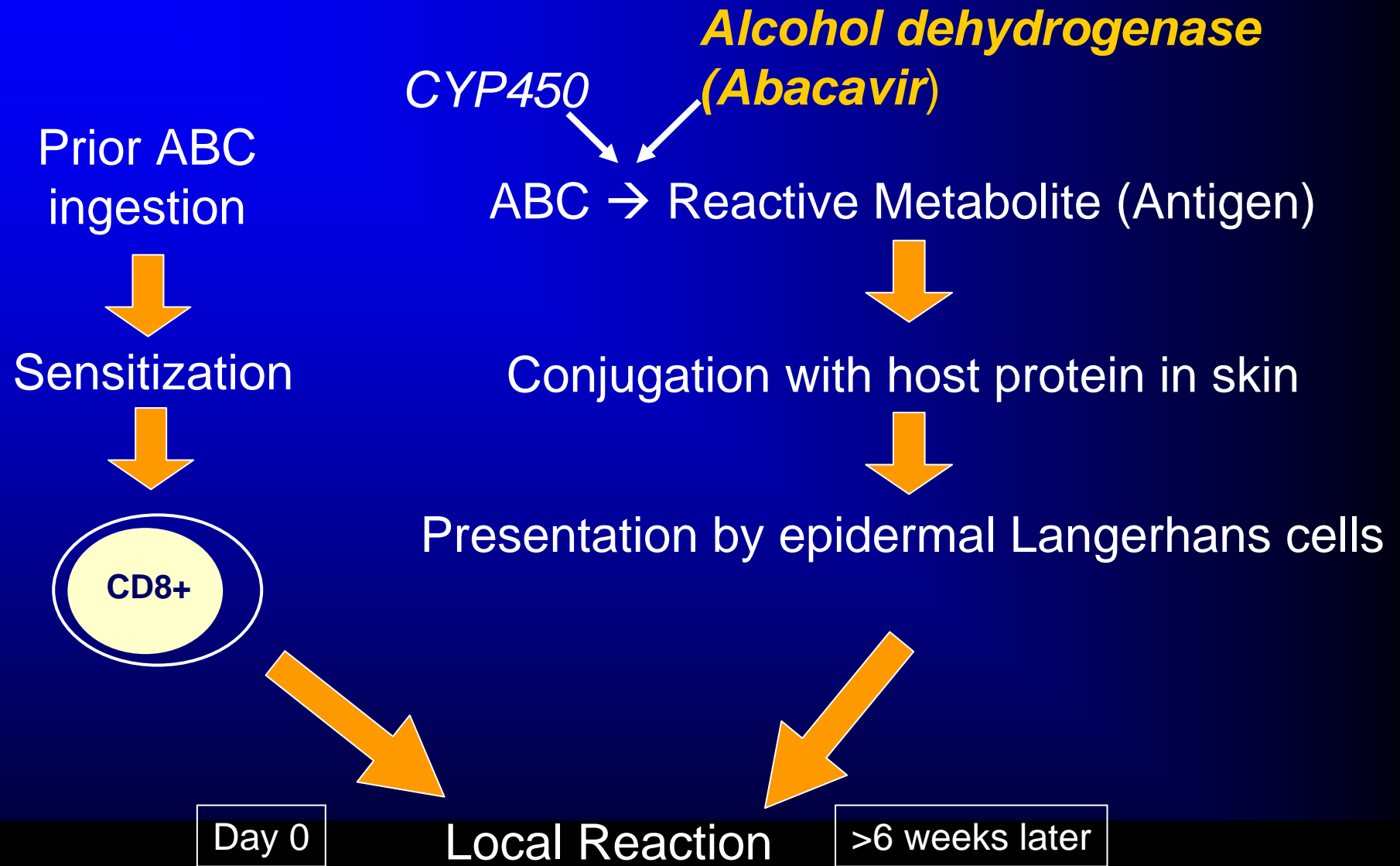
Hughes et al. Pharmacogenomics 2004

# Phenotypic Uncertainty of Abacavir HSR

Blinded Study	Abacavir Groups	Zidovudine or indinavir
CNA3005	19/268 (7%)	6/265 (2%)
CNA30024	27/324 (8%)	10/325 (3%)
Total Cases	46/592 (7.8%)	16/590 (2.7%)

Cases in CNA30024 as reported by Investigators in the ABC HSR CRF Module

# Patch Testing Following ABC Exposure



# Abacavir Skin Patch Testing



ABC HSR

## Patch testing

### Previously assigned cases

Carriers of 57.1 AH markers	9/9
Non-57.1 carriers (NNRTI+)	0/3
Non-57.1 carriers (NNRTI-)	1 patient unavailable



ABC non-HSR

### Previously assigned tolerant

Carriers of 57.1 AH markers 0/5

3 previously assigned cases had diagnosis revised

(1) Concurrent NNRTI therapy

(2) Negative patch test

# HLA-B\*5701 and Abacavir Hypersensitivity

*HLA-B\*5701*

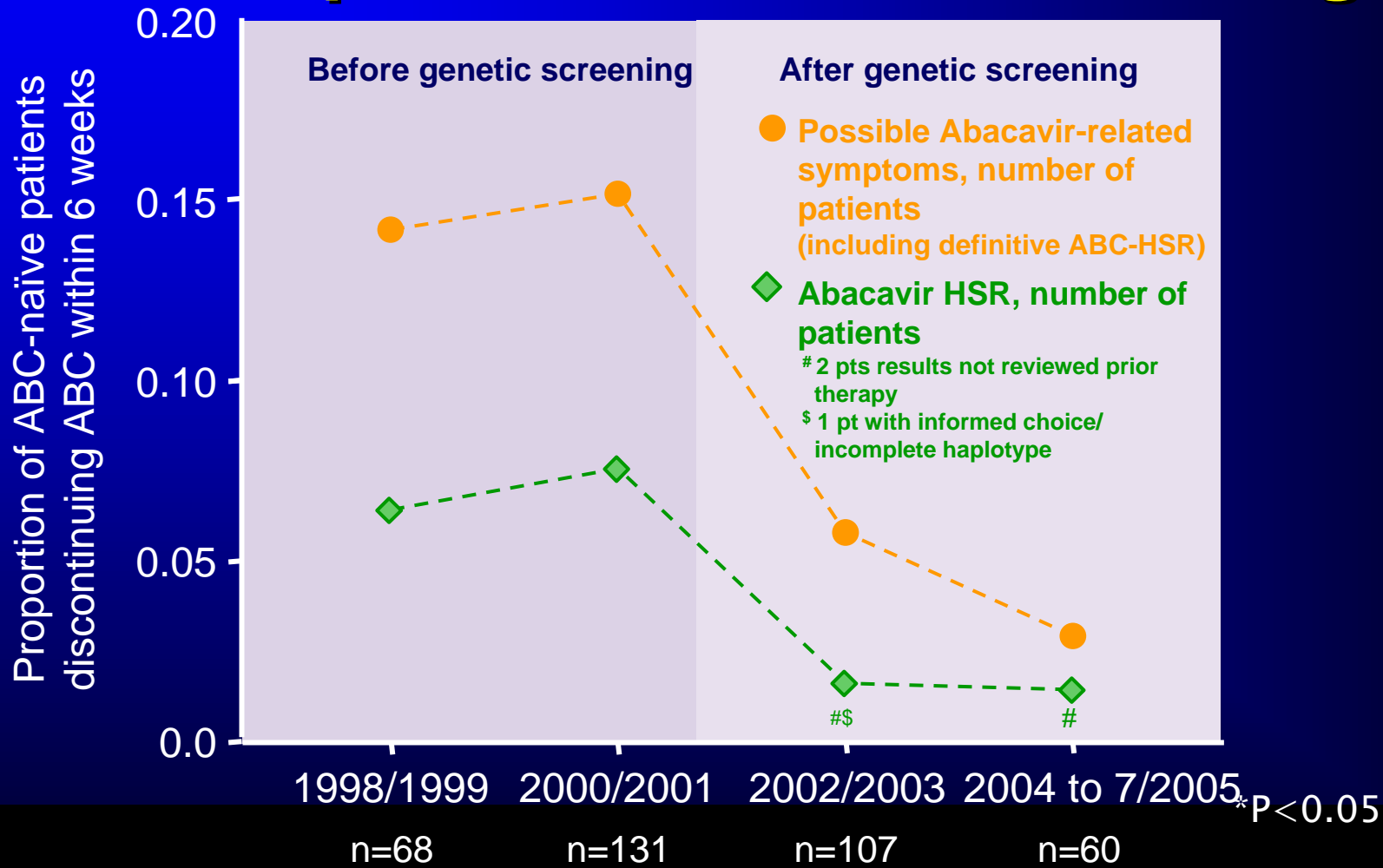
	Pos	Neg	
HSR	15	1*	Sens 93.8%
No HSR	4	180	Spec 97.8%
<b>Pos PV</b>		<b>Neg PV</b>	
<b>78.9%</b>		<b>99.4%</b>	

Reclassified first 200 patients (\*not available)

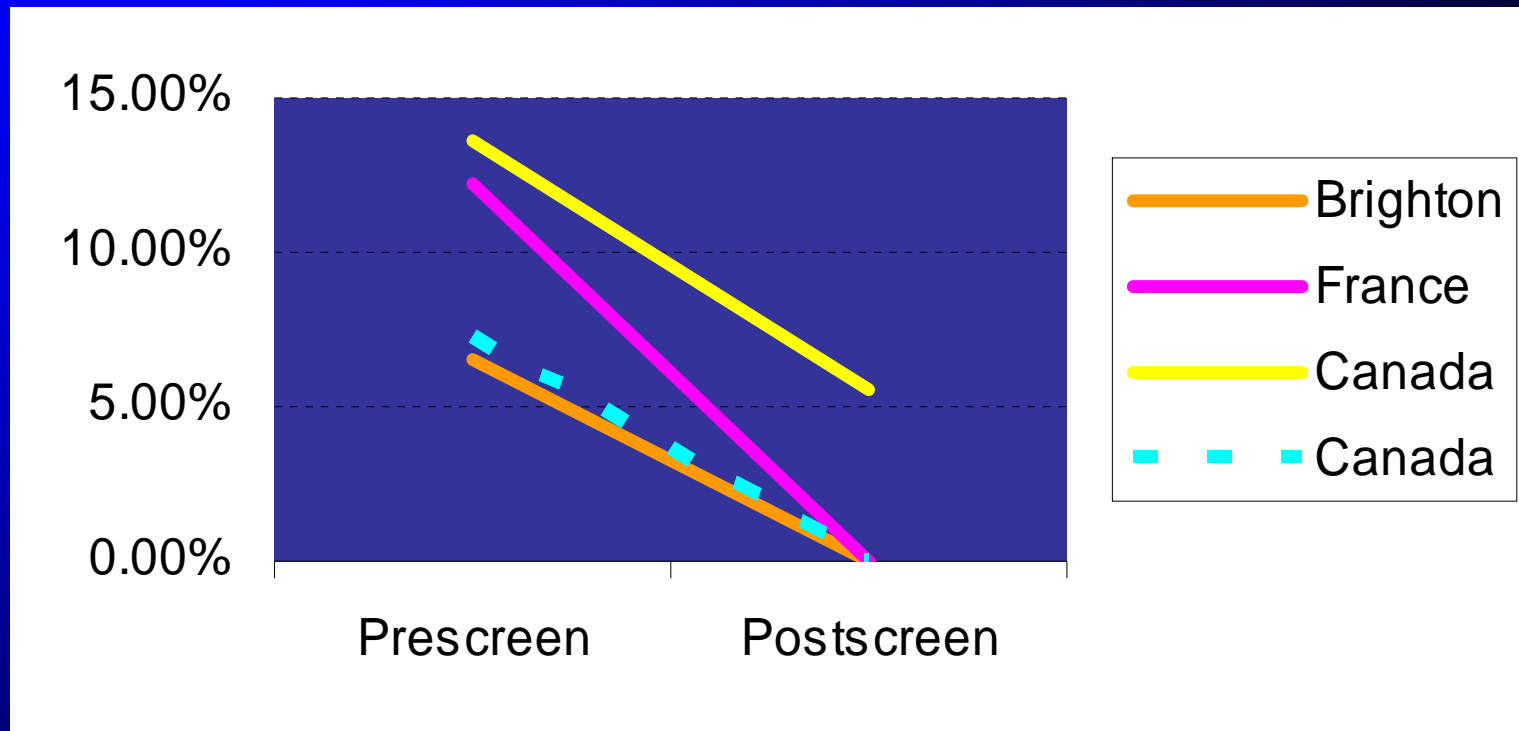
# Incorporation of a Pharmacogenetic Test into Clinical Practice

- High level evidence generalisable to diverse clinical settings
- Widespread availability of cost-effective and reliable laboratory tests
- Effective strategies to operationalise testing into routine clinical practice

# Fall in Early Discontinuation of Abacavir after Introduction of Prospective Genetic Screening\*



# Other Observational Data

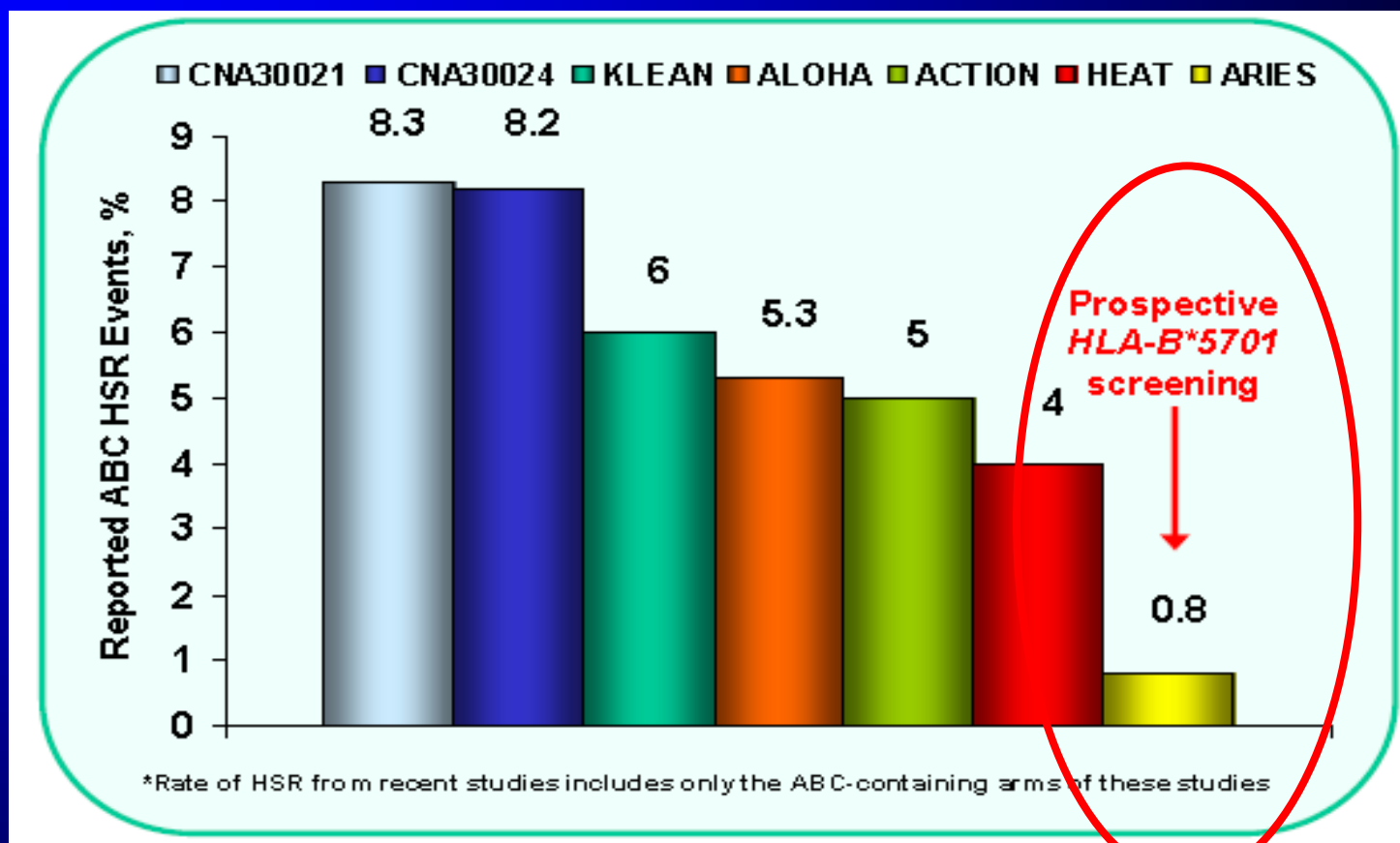


\*Trottier et al abacavir early discontinuation decreased from 13.6% to 5.6% after screening, IAS 2007, abstract MOPEB002)

+HLA-B\*5701 + HSR from 12.2% to 0% (Zucman et al JAIDS 2007; epub March 8)

^ABC HSR 6.5% historically to 0% post screening (Reeves et al HIV Medicine March 2006)

# Abacavir Hypersensitivity in Clinical Trials



\*All 4/725 (0.8%) patients in ARIES study clinical diagnosed with HSR were patch test negative

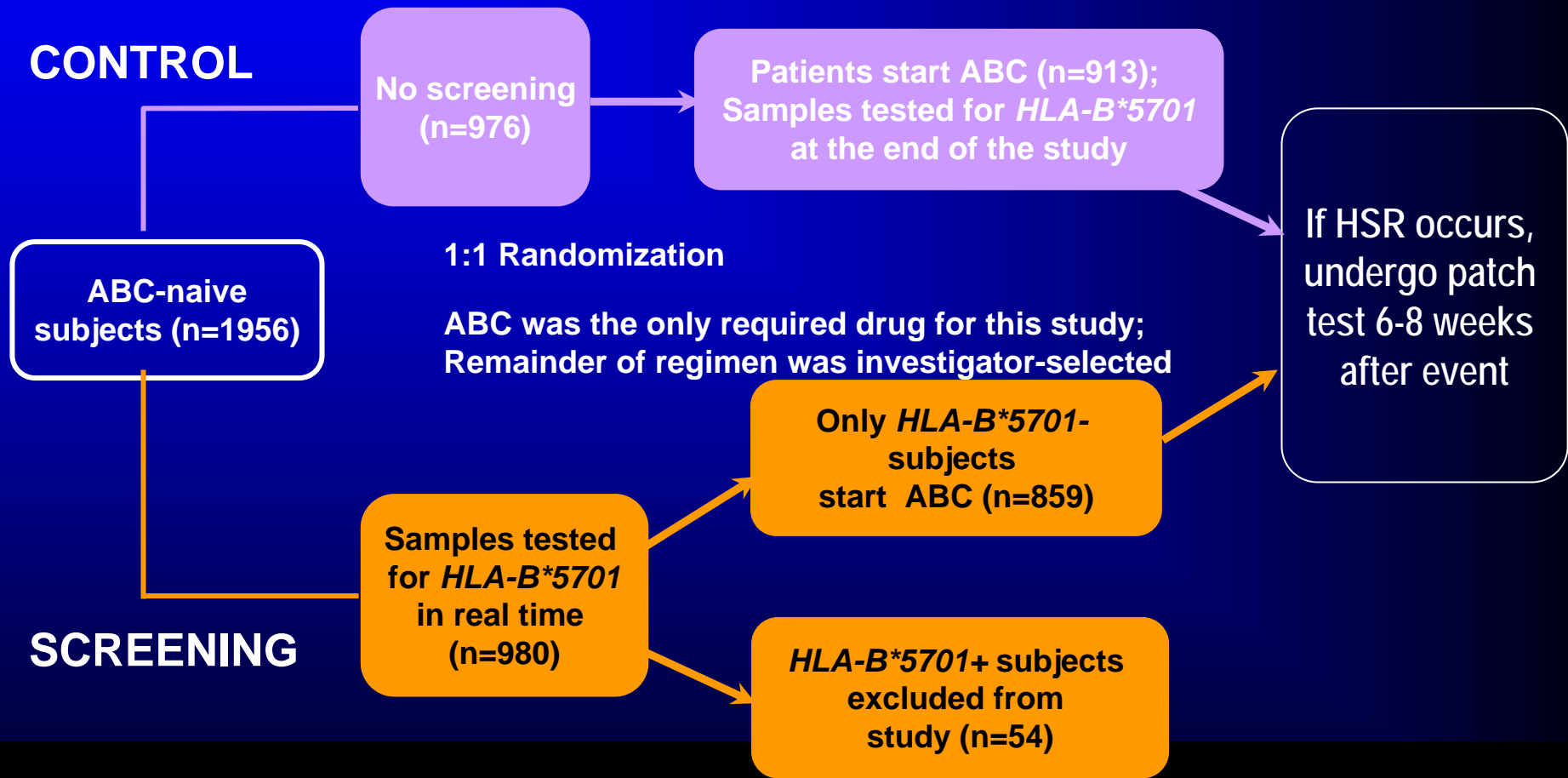
## HLA-B\*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team<sup>2\*</sup>

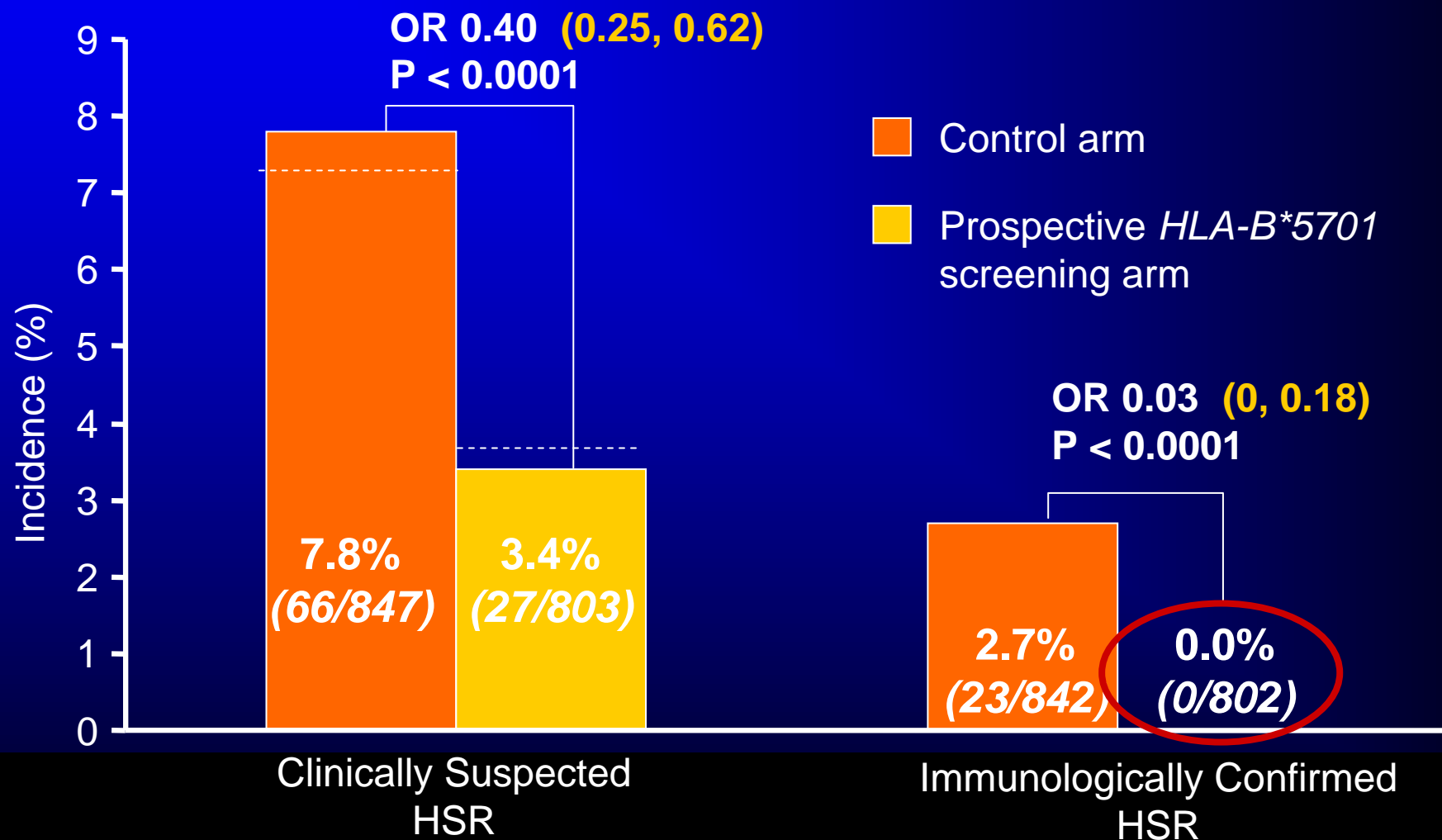
- First RCT to look at clinical utility of a pharmacogenetic test to prevent a specific drug toxicity
- Problem of false positive clinical diagnosis of abacavir hypersensitivity was overcome by using strategy of skin patch testing (100% specific) to define the phenotype of true immunologically mediated abacavir hypersensitivity

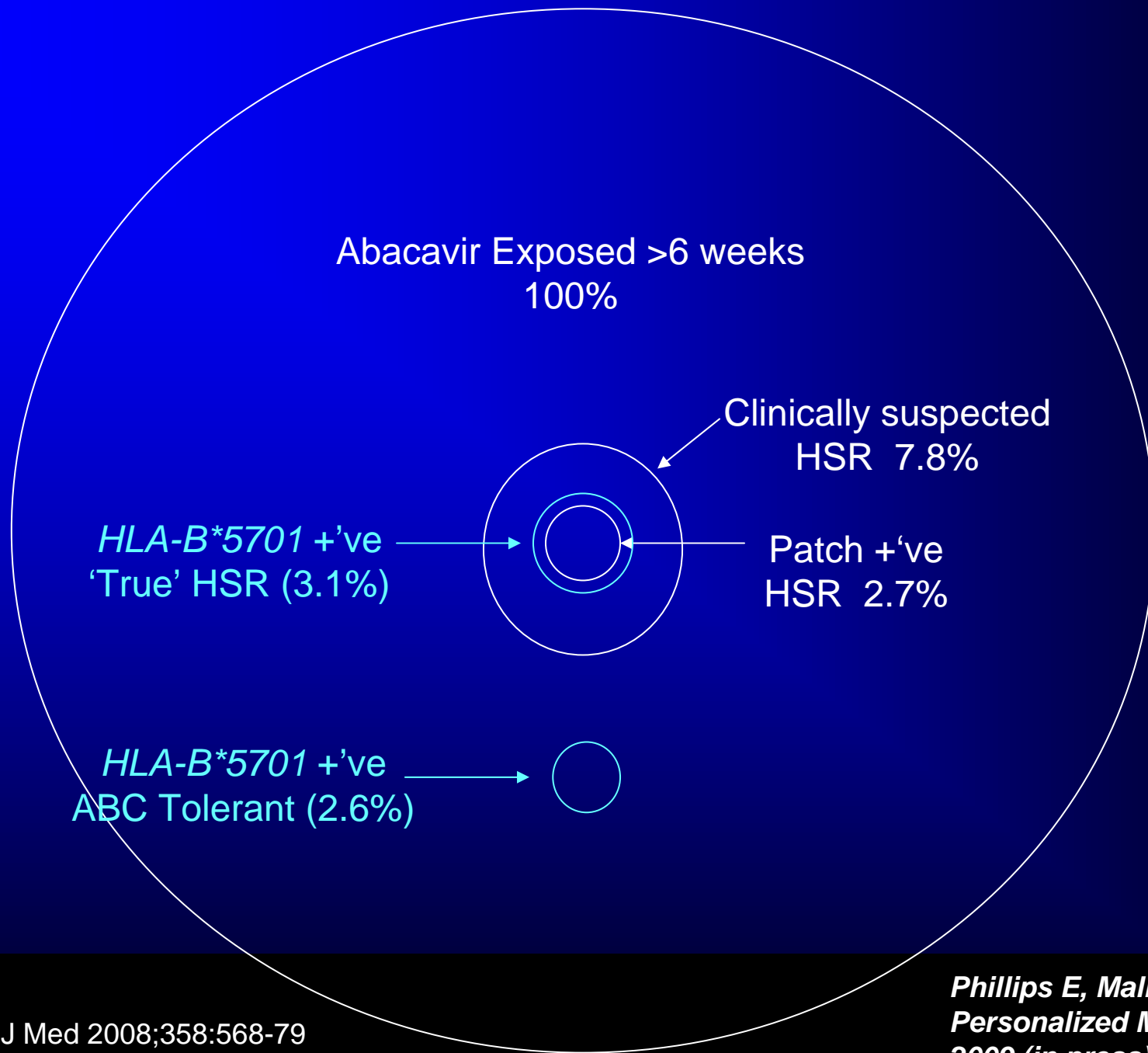
# PREDICT-1

Prospective, randomized (1:1), double-blind, multicenter study with 6-week observation period (>90% of HSR cases)

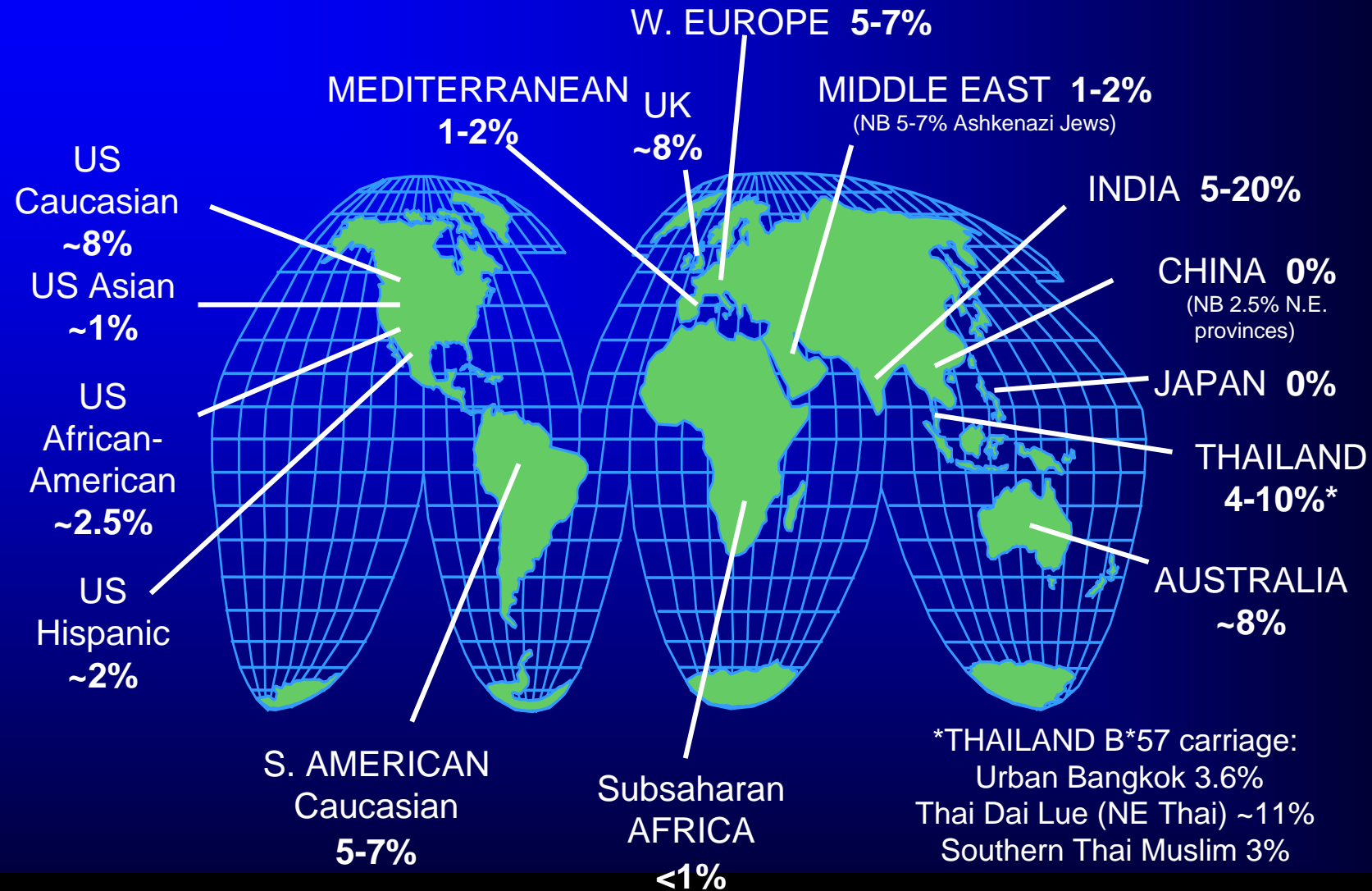


# Clinically Suspected and Immunologically Confirmed HSR in ITT evaluable population



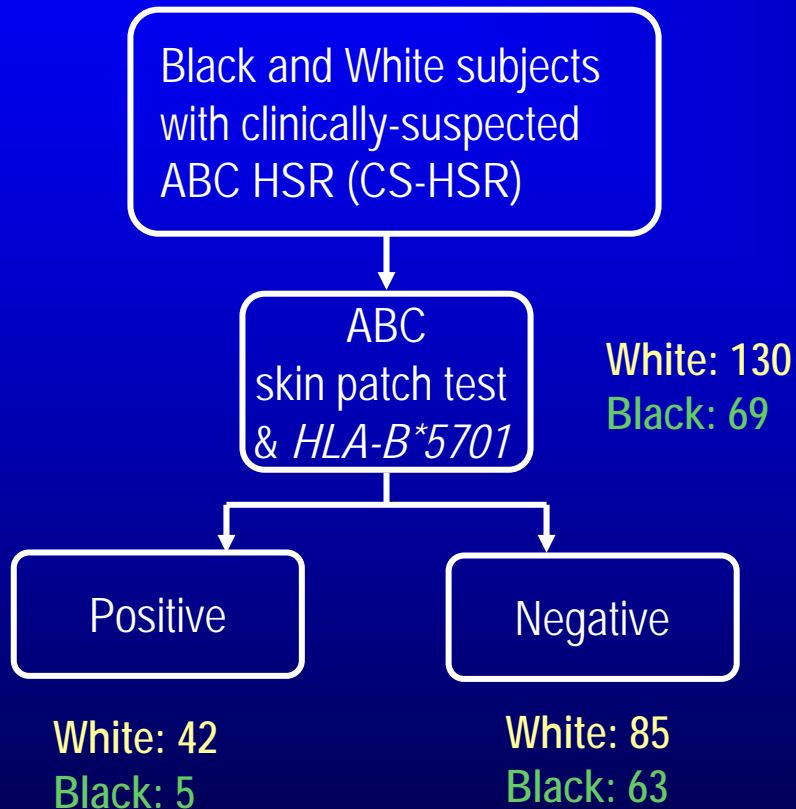


# HLA-B\*5701 Carriage Frequency



# SHAPE Study Design

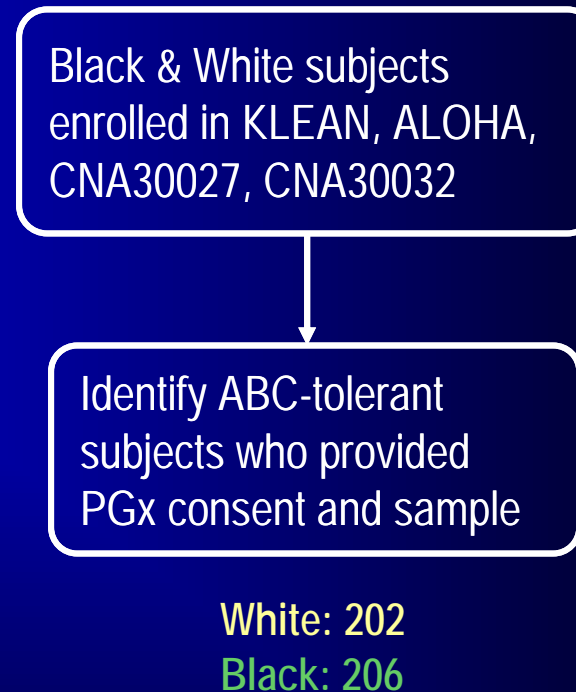
## CASES



*HLA-B\*5701* results available for all but one case  
Skin patch test results unavailable for 3 Whites, 1 Black

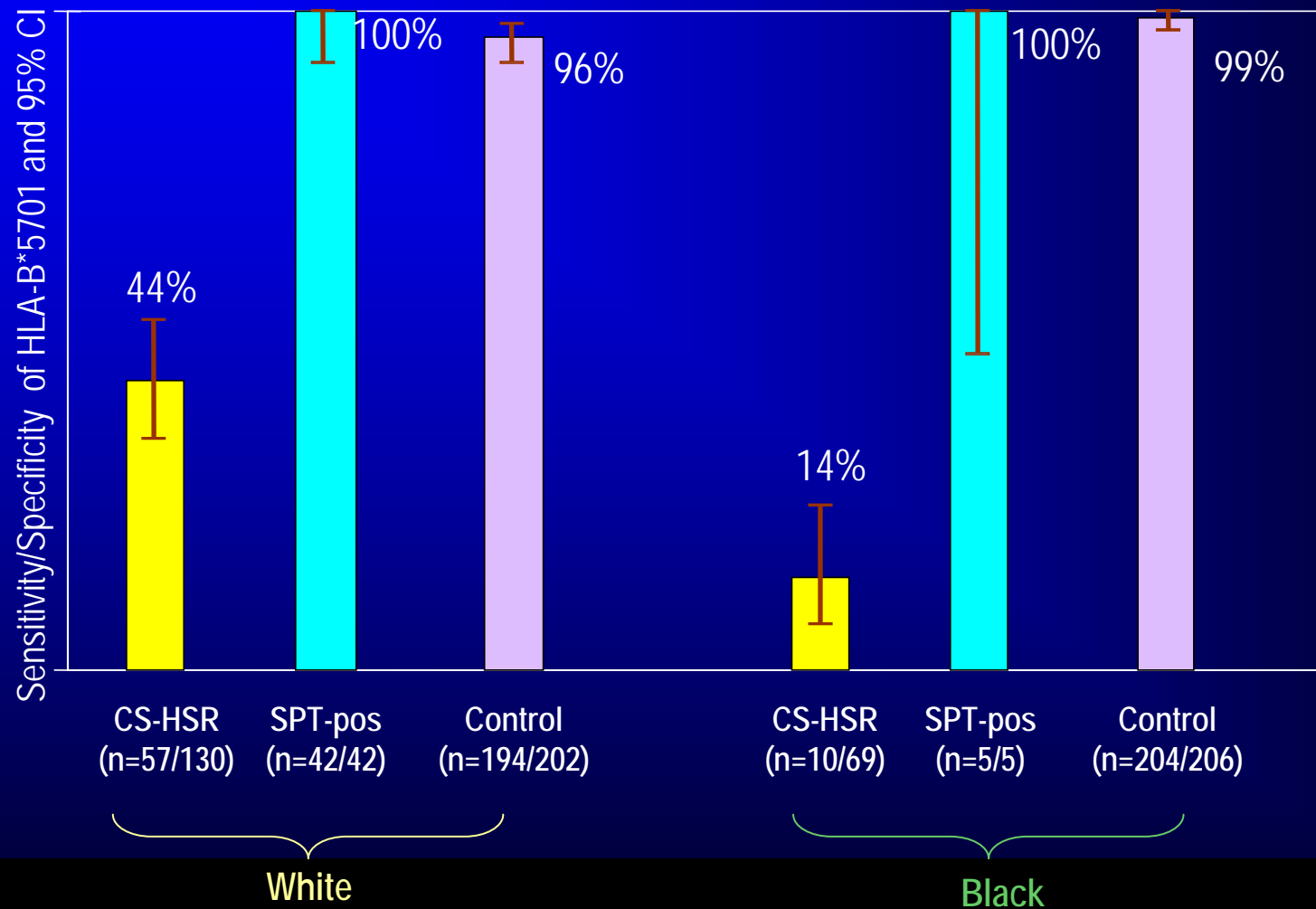
\*Saag et al Clin Infect Dis 2008;46:1111-18

## CONTROLS



*HLA-B\*5701* results available for all control subjects

# High Negative Predictive Value of HLA-B\*5701 Generalised Across Race



OR: White IC-HSR 1945 [110-34352]; CS-HSR 19[8-48]

Black IC-HSR 900 [30-21045]; CS-HSR 17[4-164]

# Major Treatment Guidelines Revised to Reflect HLA-B\*5701 Screening

Preferred		
NNRTI	EFV	ABC/3TC (for HLA-B*5701 negative patients) or TDF/FTC
PI	FPV/r BID LPV/r BID ATV/r	ABC/3TC (for HLA-B*5701 negative patients) or TDF/FTC

DHHS Guidelines: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>: Jan 2008.

IAS Guidelines: JAMA 2008;300(5):555-70

# Prerequisites for Successful Integration of HLA Pharmacogenetic Testing into Routine Clinical Care: Laboratory Aspects

- IP- freedom to operate
- development of simple,  
inexpensive,  
robust,  
yes/no laboratory tests  
and associated reagents (eg monoclonal antibodies)
- rapid and simple report and interpretation
- global distribution and commercialization of allele specific test
- quality assurance of allele specific test
- reimbursement of test

# Available Technologies

	Cost	Turn-around-time	Feasibility
High resolution HLA B typing	High	Long (2 weeks or more)	Not feasible unless specialty laboratory
PCR-based techniques	Moderate (<\$100 USD)	Moderate (<2 week)	Feasible for labs with molecular technologies
B17-monoclonal Flow Cytometry	Low	Low (mandated by need for fresh cells)	For labs doing CD4+/8

# Pharmacogenetics and HLA: Predicting the Unpredictable?

- Type A reactions are predictable based on their pharmacological action therefore pharmacogenetic factors will only explain a proportion of the variability in drug response
- Type B adverse drug reactions such as hypersensitivity reactions and severe skin syndromes are immunogenetically mediated
- HLA associations are promising for prediction and hence prevention of these types of reactions but abacavir is currently the only drug where high level evidence exists and widespread screening has been implemented
- Numerous clinical and laboratory hurdles must be overcome for successful integration of pharmacogenetic testing into a clinical setting.

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