

Farmacogenómica de Drogas Antiinfecciosas

Waldo H. Beloso

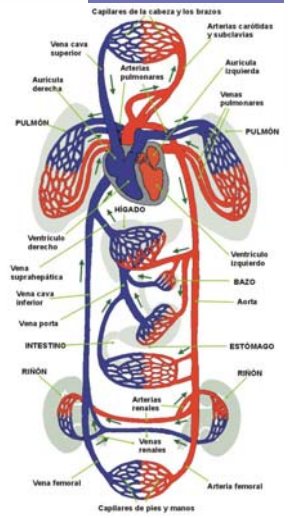
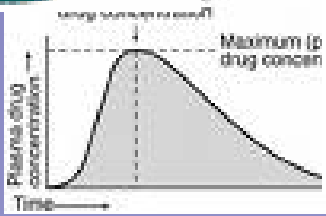
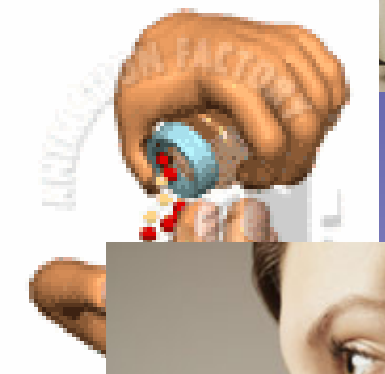
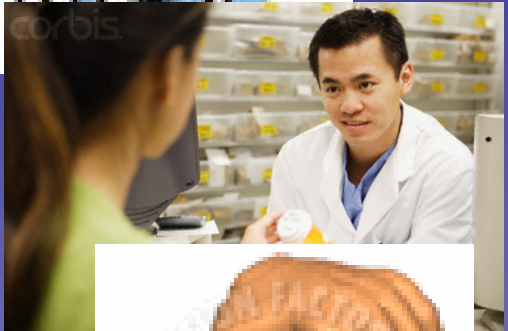
Jornadas Nacionales del Centenario de la SAP

Infectología Pediátrica, 2011

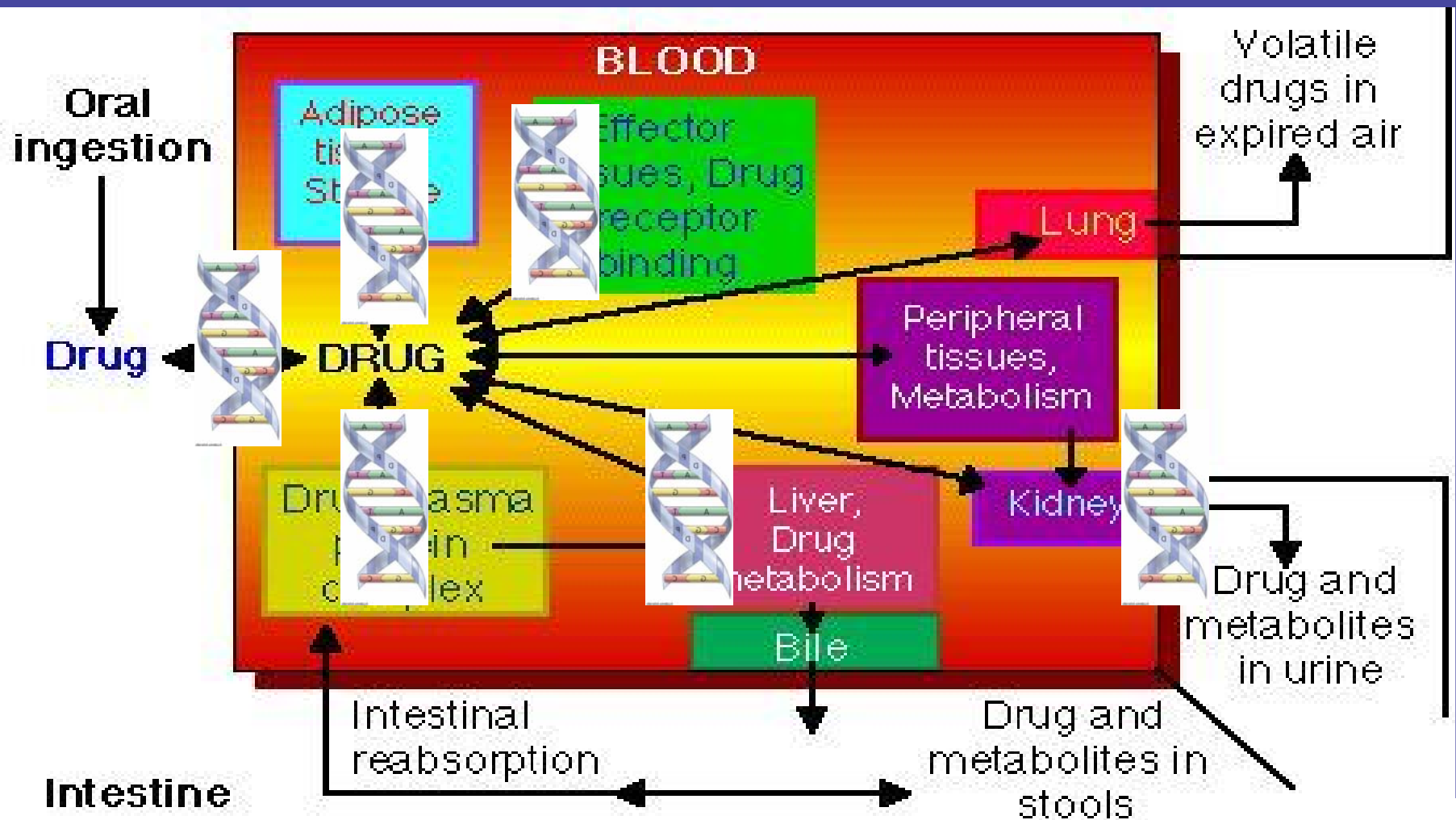
Prescripción “racional” (OMS)

- Apropriada para las **necesidades clínicas** del paciente
- En **dosis ajustadas** para su requerimiento individual
- En **períodos** de tratamiento adecuados
- Al **menor costo** para el paciente y su comunidad

Conferencia de Nairobi - 1985



Destino de las drogas en el organismo



Mecanismos de acción específica

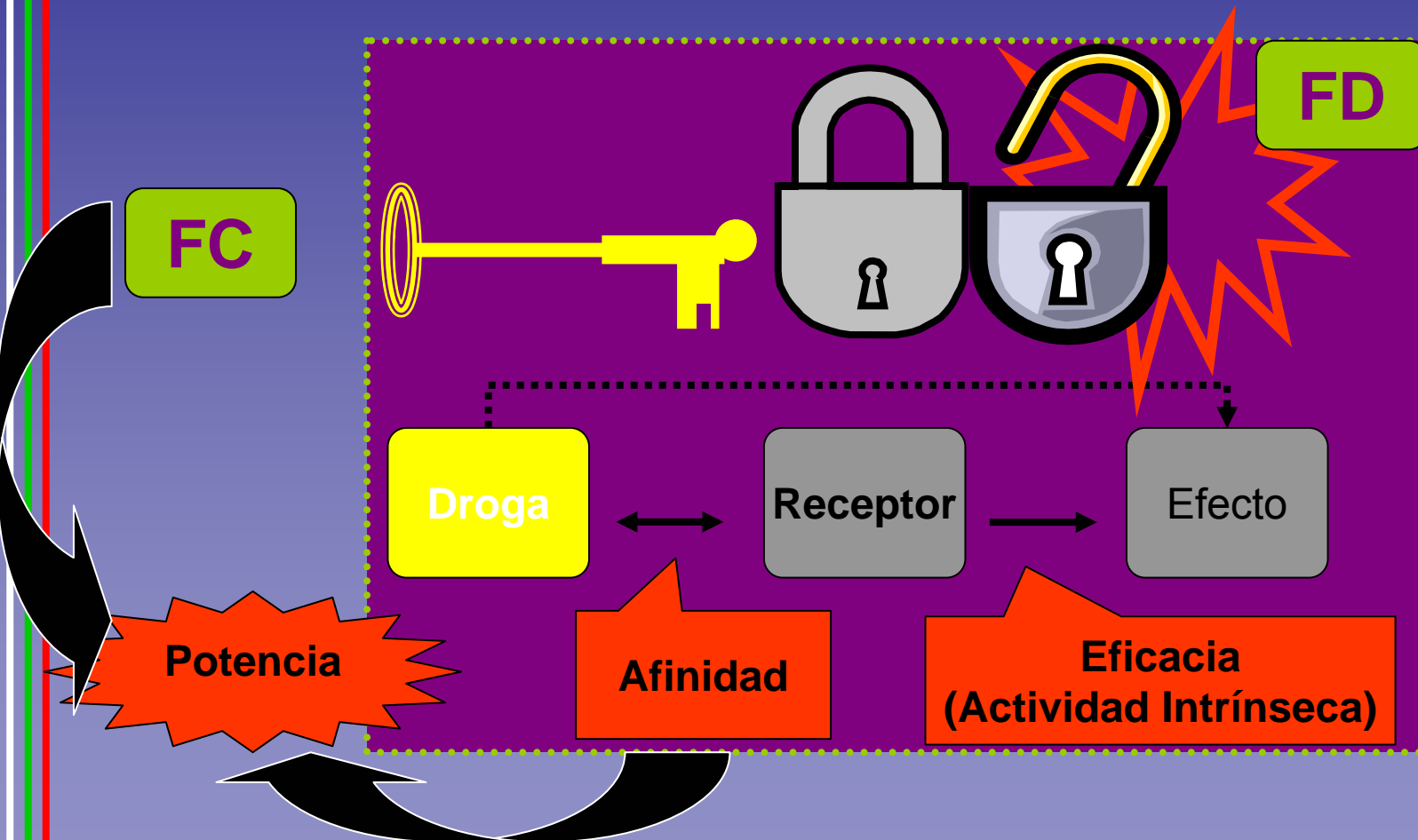
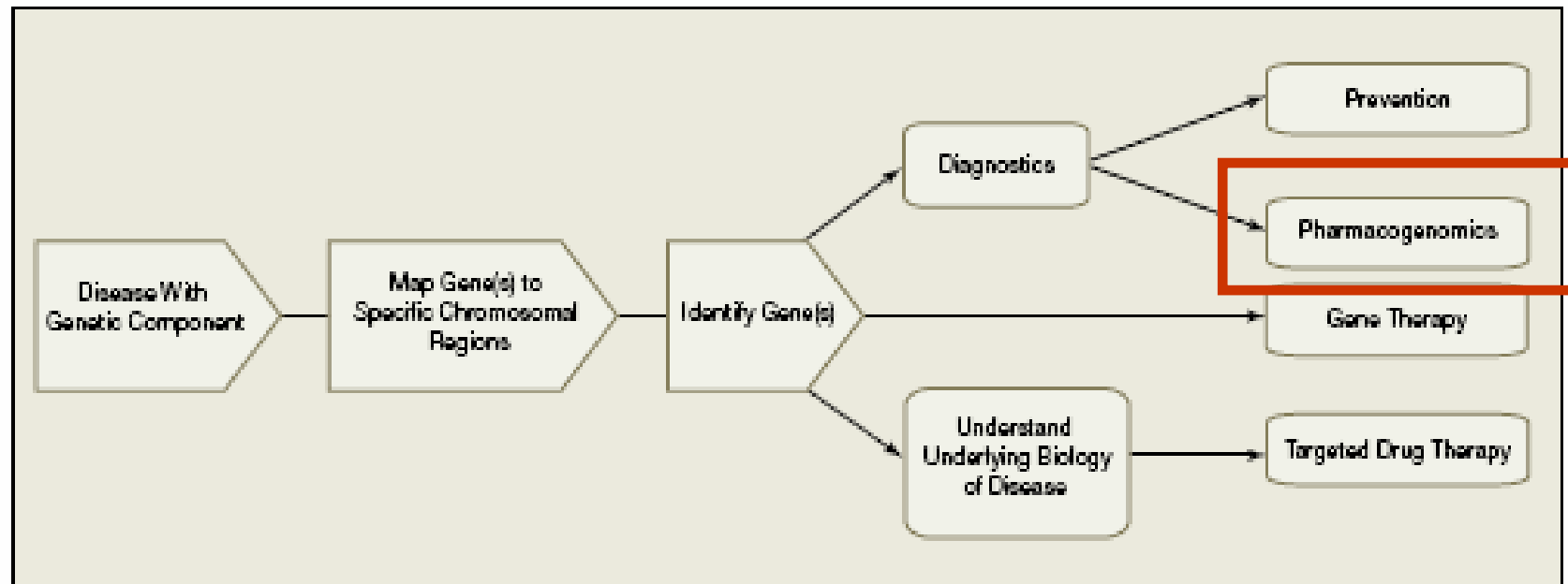


Figure. Steps Involved in a Genetic Approach to the Diagnosis and Treatment of Disease



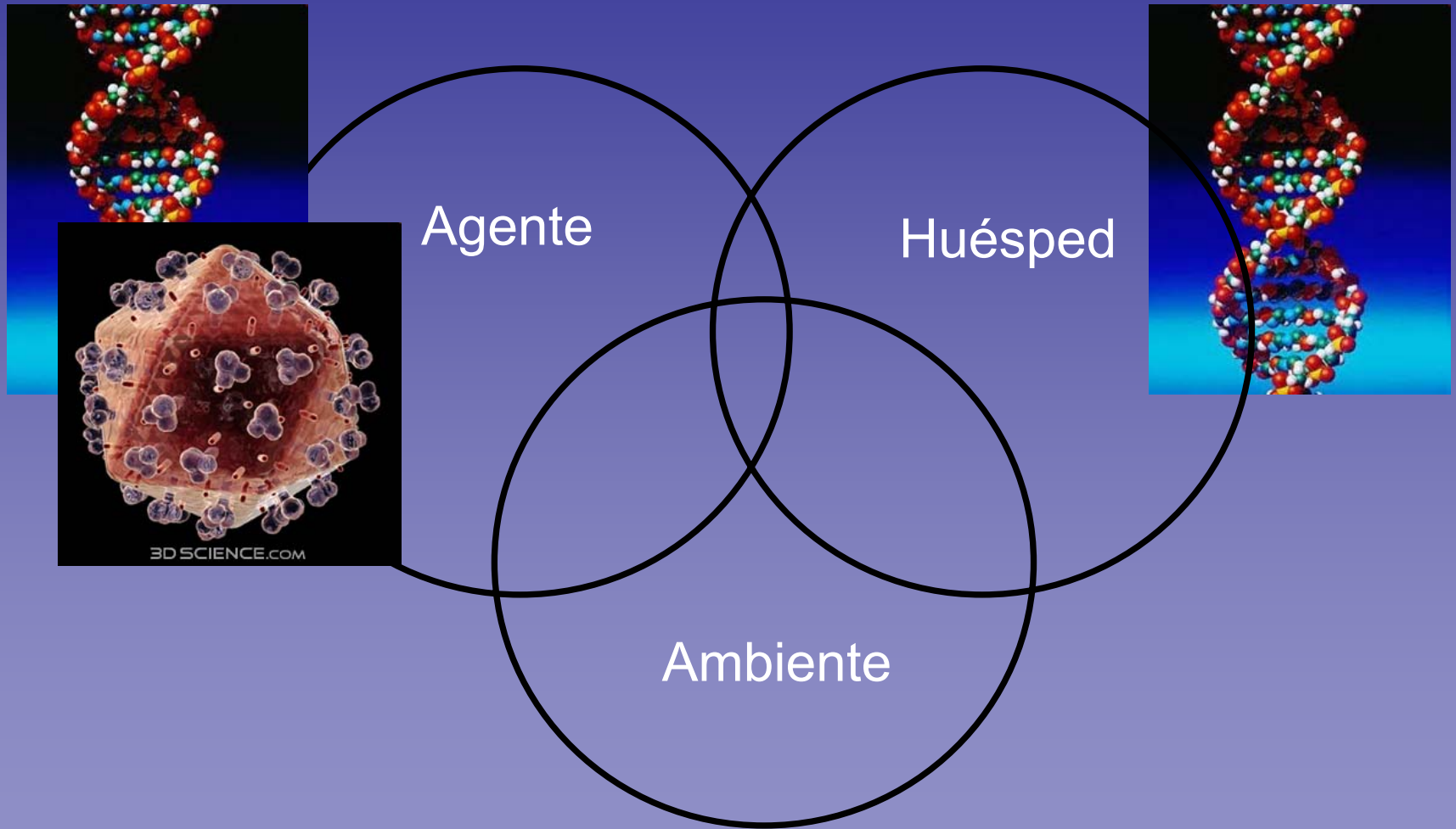
The rate of progress for applying a genetic approach to the diagnosis and treatment of each disease will be different depending on the research investment and the degree of biological complexity underlying the disease. First, the gene variants contributing increased disease risk must be identified by family studies and/or case-control studies. Diagnostic opportunities may then come along rather quickly, but will be of greatest clinical usefulness once prevention measures are developed that have proven benefit to those at high risk. Some gene variants will also show clinically useful associations with drug responsiveness (pharmacogenomics). In general, full-blown therapeutic benefits from identification of gene variants will take longer to reach mainstream medicine. In some instances, the gene itself will be the drug (gene therapy), while in others, a sophisticated knowledge of the underlying disease mechanism, built upon genetics, may allow the design of targeted and highly effective drug therapy.

Collins JAMA 2001;285:540-4

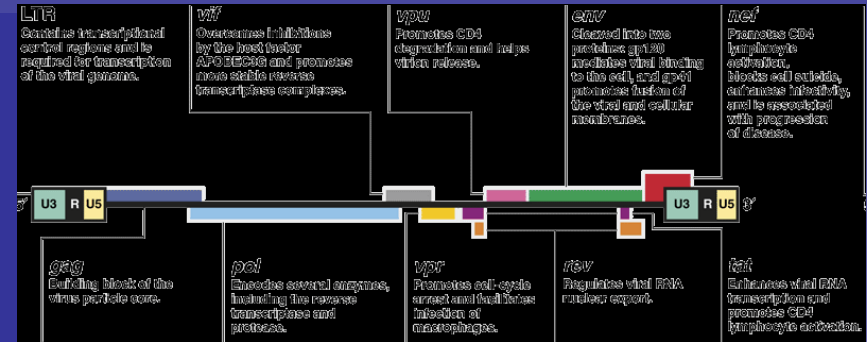
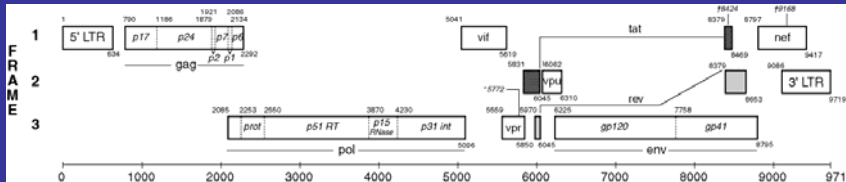
Medicina personalizada



Enfermedades infecciosas



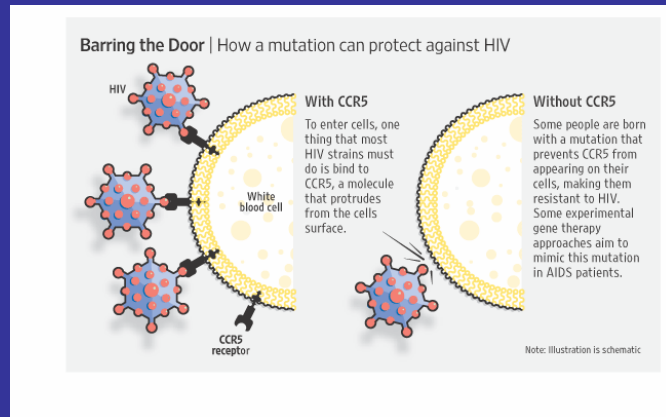
Genética del VIH



- Tests de resistencia
- Conocer determinantes patogénicos
- Identificar potenciales blancos de acción de fármacos
- Terapia génica?

Aspectos genéticos del huésped

- Susceptibilidad a la infección por VIH



- Determinantes de progresión?
- Determinantes de respuesta a fármacos
 - Eficacia
 - Toxicidad

Variabilidad del genoma

Mutaciones

Polimorfismos



Secuencia

Longitud

SNPs

Pirámide de la farmacogenética

SNPs que modifican desenlace clínico

SNPs que cambian respuesta a drogas

SNPs que cambian FC

SNPs que cambian actividad in vitro

Cambios no conservadores en Aa

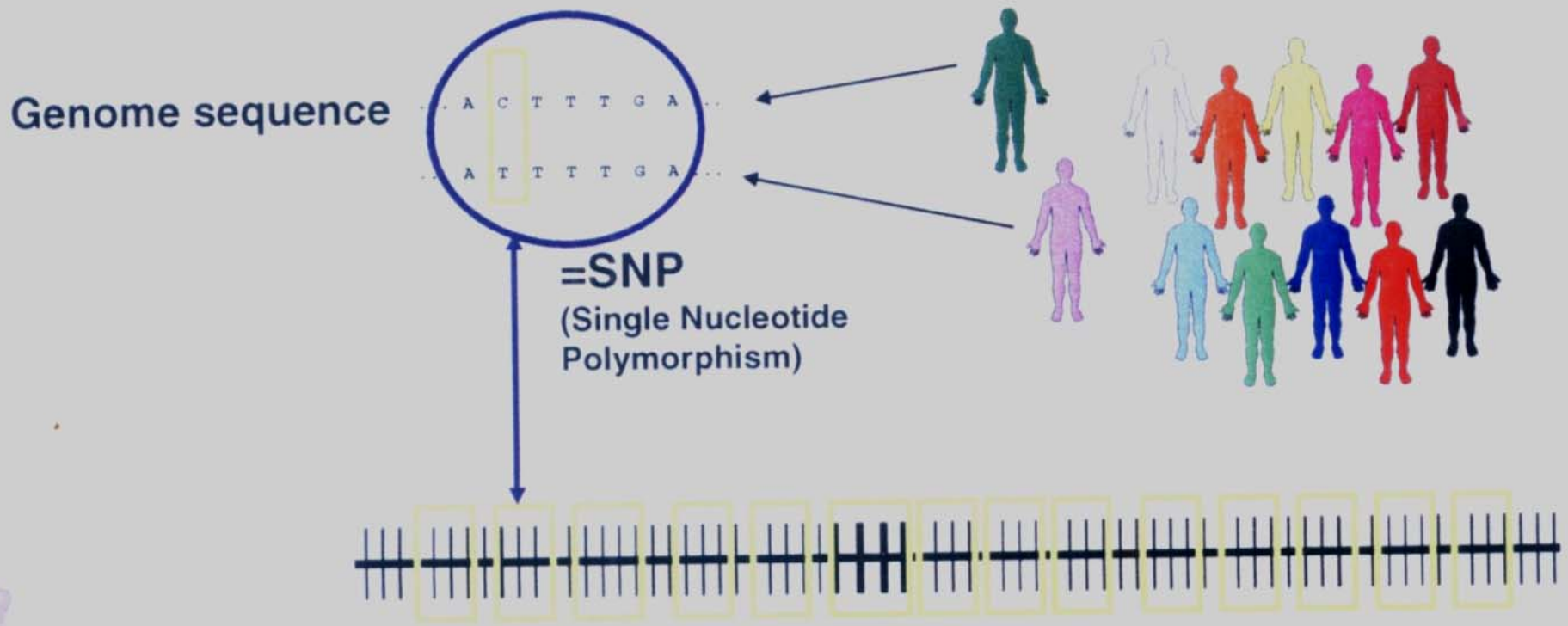
SNPs no sinónimos en exones

Cambios en exones

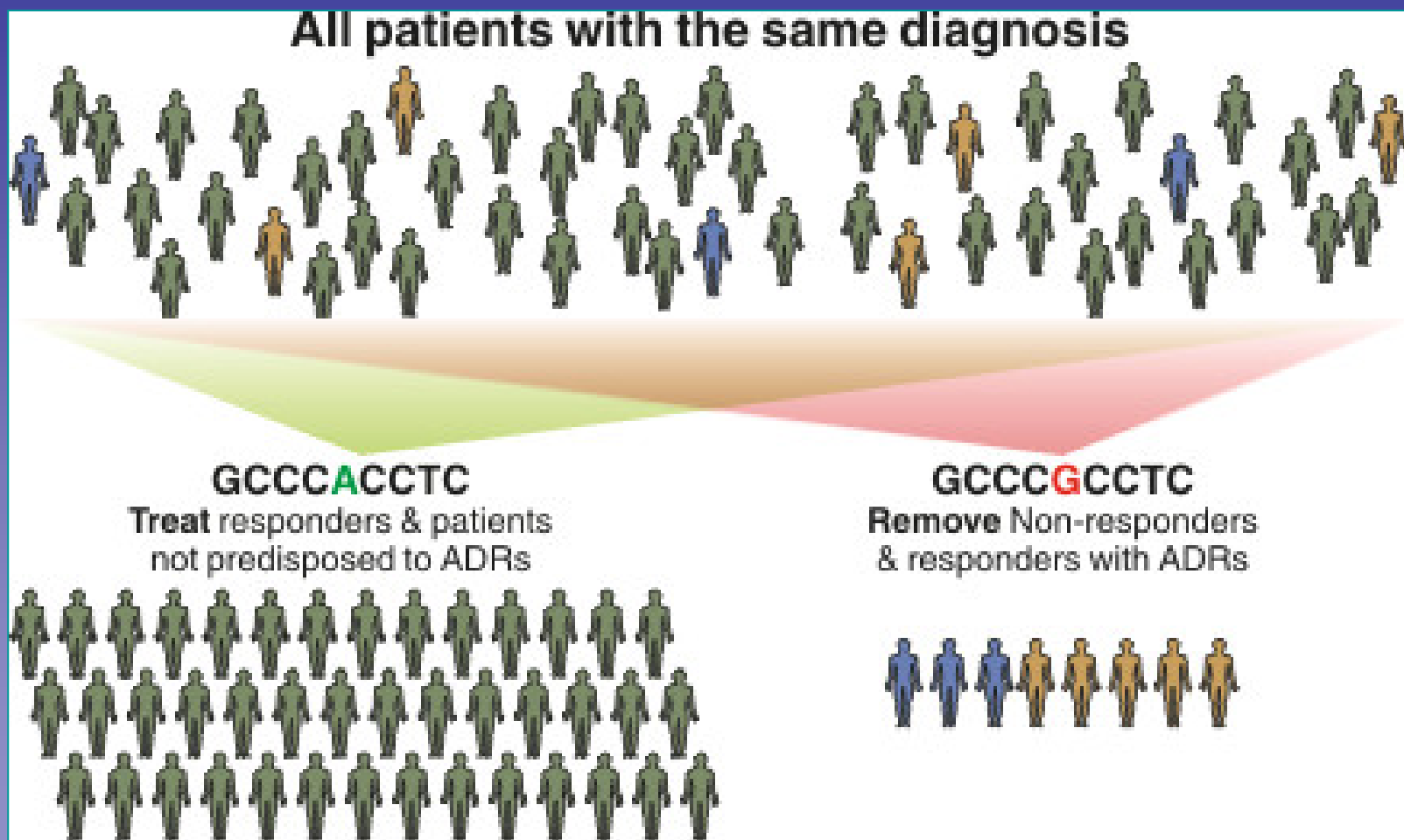
Todos los SNPs

SNPs

Single Nucleotide Polymorphisms are the spelling differences in the genome sequence...



Polimorfismo de SNPs



Farmacogenómica



Esta focalizada en elucidar el **Polimorfismo** de los genes involucrados en enzimas que:

- Metabolizan
- Transportan
- Receptores

DROGAS

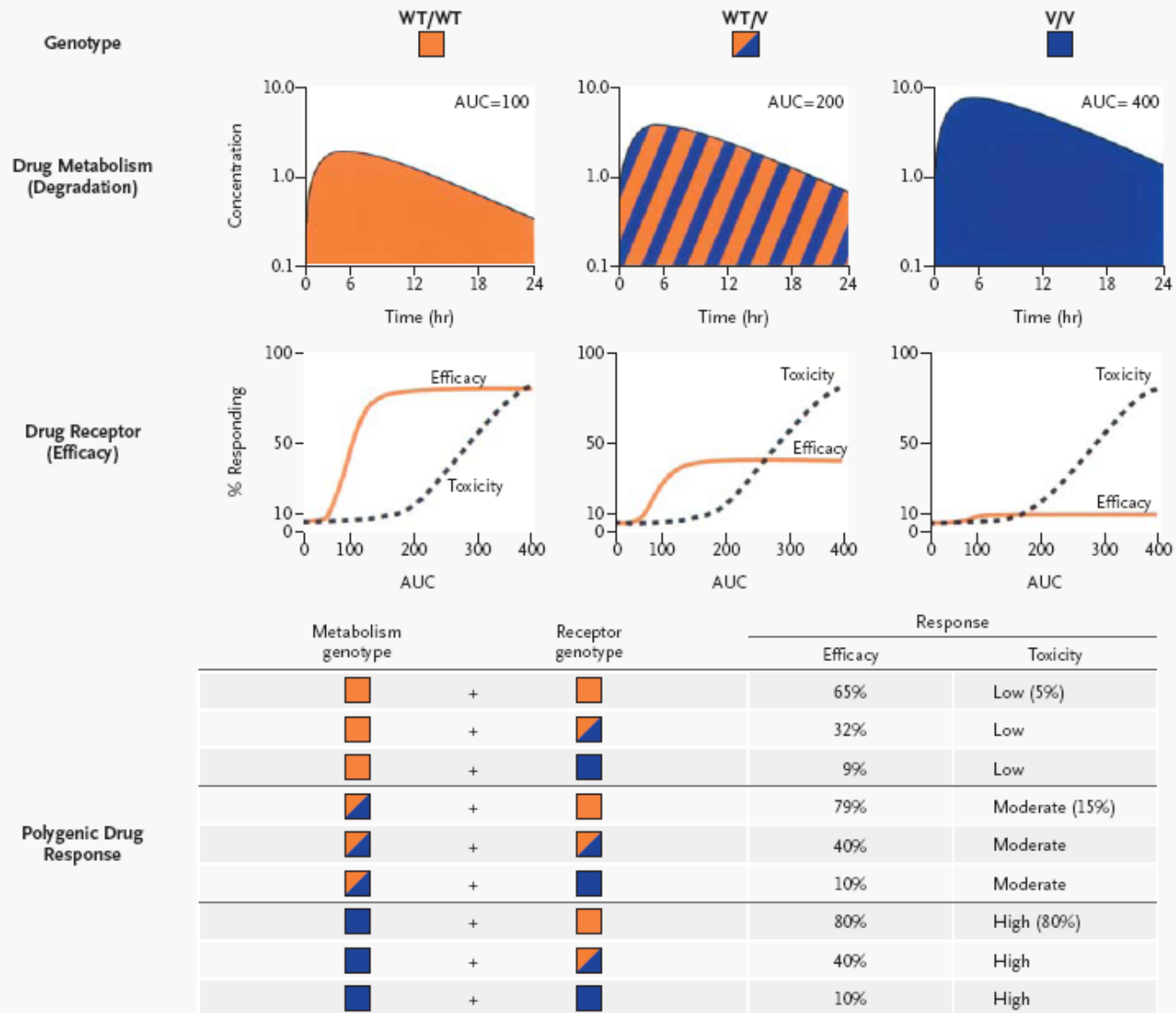
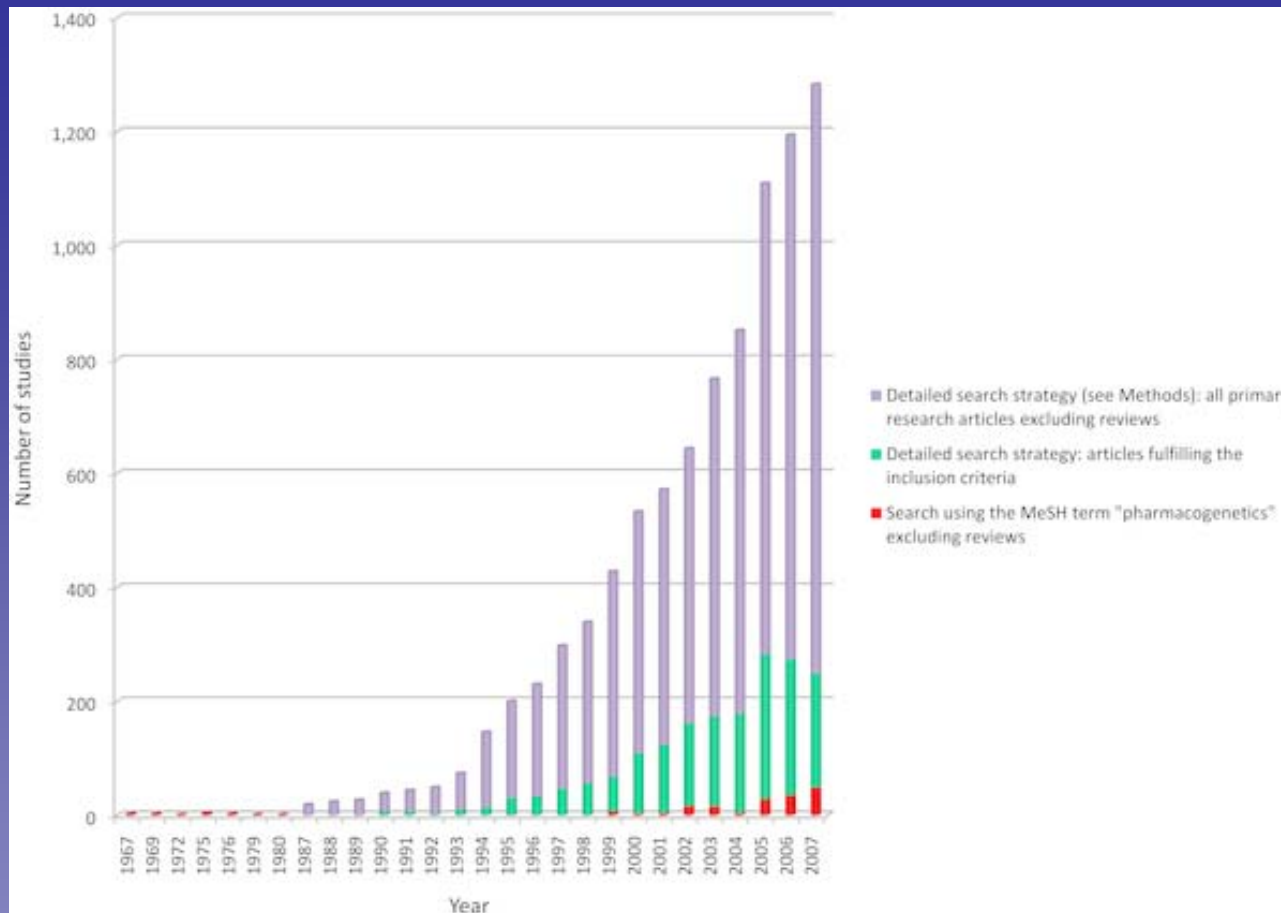


Figure 1. Polygenic Determinants of Drug Response.

The potential effects of two genetic polymorphisms are illustrated, one involving a drug-metabolizing enzyme (top) and the second involving a drug receptor (middle), depicting differences in drug clearance (or the area under the plasma concentration–time curve [AUC]) and receptor sensitivity in patients who are homozygous for the wild-type allele (WT/WT), are heterozygous for one wild-type and one variant (V) allele (WT/V), or have two variant alleles (V/V) for the two polymorphisms. At the bottom are shown the nine potential combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data at the top, yielding therapeutic indexes (efficacy:toxicity ratios) ranging from 13 (65 percent:5 percent) to 0.125 (10 percent:80 percent).



Publicaciones en el área de Farmacogenética entre 1967 y 2007

Holmes MV, PLoS One, 2009

Table 1

Notable advances between 1932 and 1995 in shaping the field of pharmacogenetics.^a

Observation	Key Reference
Phenylthiourea (PTU) nontaster trait ^b	(Snyder, 1932)
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	(Alving et al., 1956)
N-acetylation (NAT) polymorphism	(Knight et al., 1959; Evans et al., 1960)
<i>Federation Proceedings</i> of the Am. Soc. Exp. Biologists (FASEB): two symposia gave high visibility to the field.	(Kalow, 1965; O'Reilly and Aggeler, 1965; Armaly and Becker, 1965; Wigle, 1965; La Du, 1965; Eichelbaum, 1984; Spielberg, 1984; Vesell, 1984; Weber, 1984; La Du and Eckerson, 1984; Vesell and Penno, 1984; Weinshilboum, 1984a; Kalow, 1984a; Weinshilboum, 1984b; Kalow, 1984b)
Genetic variation in ethanol metabolism; mutation in aldehyde dehydrogenase (<i>ALDH</i>) gene	(Von Wartburg et al., 1964)
The aryl hydrocarbon receptor and [<i>Ahr</i>] gene battery	(Nebert et al., 1975)
Debrisoquine/sparteine oxidation polymorphism (<i>CYP2D6</i> gene)	(Mahgoub et al., 1977; Eichelbaum et al., 1979)
Thiopurine methyltransferase (<i>TPMT</i>) gene polymorphism	(Weinshilboum and Sladek, 1980)
Identification of the human <i>GSTM1</i> null allele; <i>GSTT1</i> null allele later	(Seidegård et al., 1986)
Molecular cloning of the <i>CYP2D6</i> gene and variant alleles	(Gonzalez et al., 1988)
Molecular cloning of the <i>NAT2</i> gene and variant alleles	(Blum et al., 1990)
Molecular cloning of the <i>CYP2C19</i> gene and variant alleles	(Goldstein and de Morais, 1994)
Molecular cloning of the <i>TPMT</i> gene and variant alleles	(Krynetski et al., 1995)

CYP

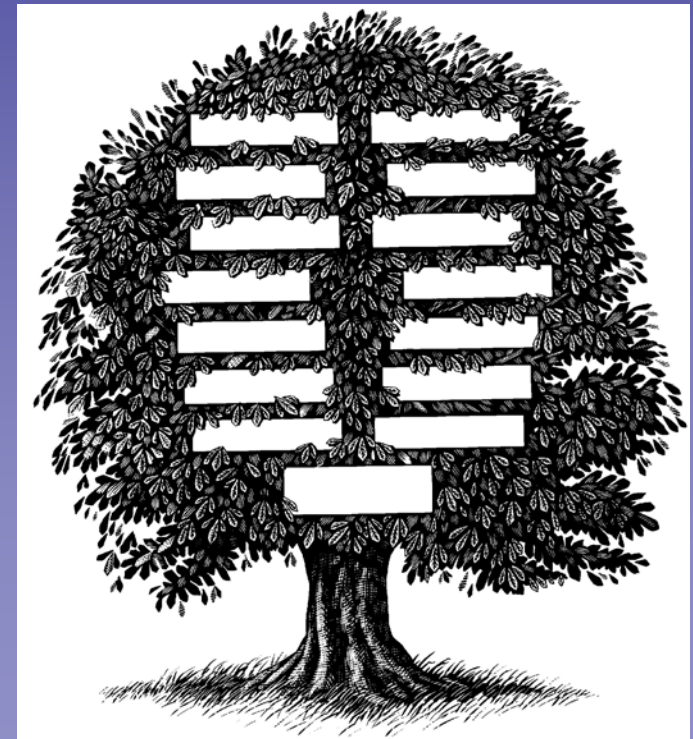
- Superfamilia muy diversa de hemoproteínas encontrada en bacterias, plantas y eucariontes.
- Involucradas en el metabolismo de enorme cantidad de compuestos endógenos y exógenos.
- Introducen cambios de reducción, oxidación o peroxidación sobre moléculas de diferente estructura química
- Contienen un núcleo hemo unido a la proteína a través de un ligando tiolato derivado de cisteína



- El estado estable de la proteína es con Fe³⁺ oxidado
- La unión del sustrato inicia una cadena de transporte de electrones y unión de oxígeno
- Otras proteínas (CYP450 reductasa, ferredoxina, Citocromo B5) proveen electrones para la reducción del hierro
- El oxígeno molecular es captado y separado, un átomo se consume en la monooxigenación del sustrato y el otro es reducido a agua.

Familia	Subfamilias
CYP1	1A1, 1A2, 1B1,
CYP2	2A6, 2A7, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2F1, 2J2, 2R1, 2S1, 2U1, 2W1.
CYP3	3A4, 3A5, 3A7, 3A43
CYP4	4A11, 4A22, 4B1, 4F2, 4F3, 4F8, 4F11, 4F12, 4F22, 4V2, 4X1, 4Z1.
CYP5	5A1
CYP7	7A1, 7B1
CYP8	8A1, 8B1
CYP11	11A1, 11B1, 11B2
CYP17	17A1
CYP19	19A1
CYP20	20A1
CYP21	21A2
CYP24	24A1
CTYP26	26A1, 26B1, 26C1
CYP27	27A1, 27B1, 27C1
CYP39	39A1
CYP46	46A1
CYP51	51A1

CYPs en humanos (familias y subfamilias de genes)



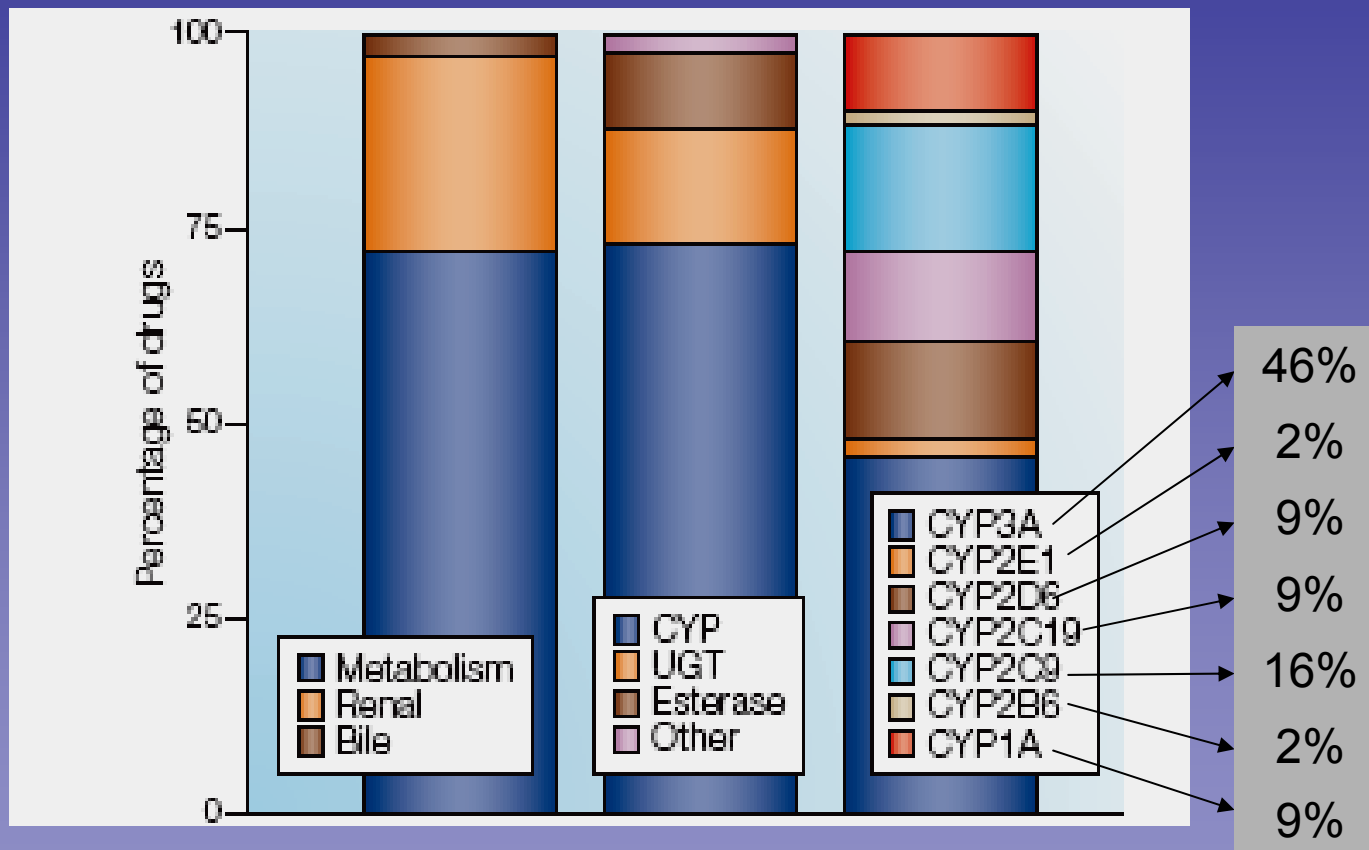
Isoenzimas de CYP en farmacología



Son todas importantes?



Sistemas enzimáticos y metabolismo de drogas

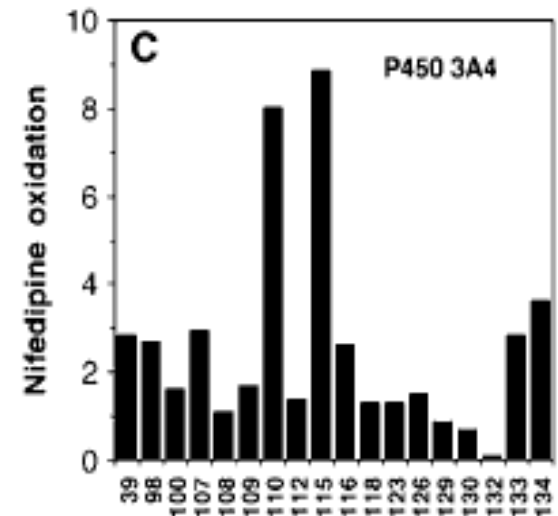
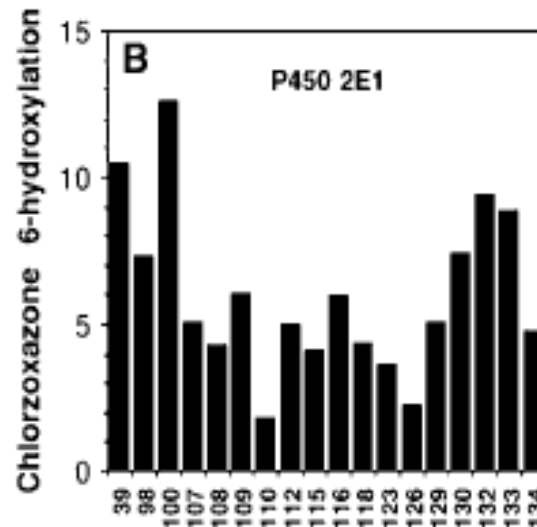
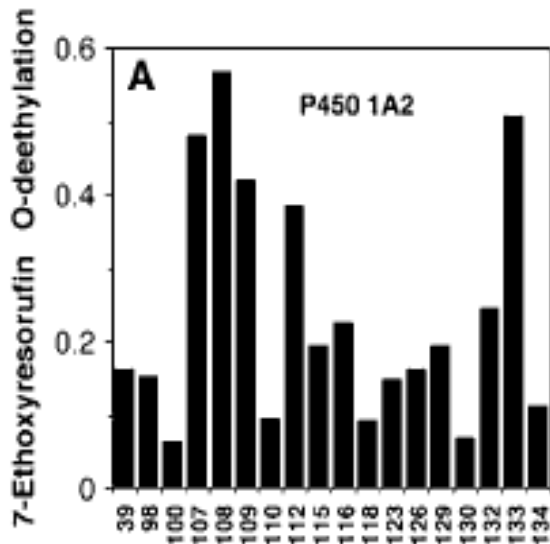


Ruta de eliminación de los 200 fármacos más prescritos en 2002 (EEUU)

Wienkers LC, *Nature Drug Discov* 2005, 4:825

Expresión de CYP

- A diferencia de las enzimas de CYP involucradas en el metabolismo de esteroides (en las que salvo ausencia por mutación genética la expresión es estable), la expresión de las isoenzimas del “metabolismo de xenobióticos” presenta gran variabilidad interindividual



Liver sample

Guengerich FP, AAPS Journal 2006, 8:E101

Desarrollos en pediatría

- Evaluación de la maduración del sistema CYP
- Farmacogenómica de TMPT

Review

Allergy Asthma Immunol Res. 2010 January;2(1):14-19.

doi: 10.4168/aa.2010.2.1.14

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AAIR
Allergy, Asthma & Immunology Research

Pharmacogenetics of asthma in children

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CYP1A2

Sustratos

Amitriptilina
Clomipramina
Cafeina
Clozapina
Estradiol
Fluvoxamina
Haloperidol
Imipramina
Mexiletina
Naproxeno
Olanzapina
Ondansetrón
Fenacetina
Propranolol
Ropivacaína
Tacrina
Teofilina
Verapamilo
R-warfarina
Zileuton
Ziprasidona

Inhibidores

- Amiodarona
- Cimetidina
- Ciprofloxacina
- Fluoroquinolonas
- Fluvoxamina
- Interferón
- Metoxsaleno
- Mibefradil

Inductores

- Brócoli
- Repollos de Bruselas
- Carne asada a carbón
- Insulina
- Modafinilo
- Nafcilina
- Omeprazol
- Tabaco

Cromosoma 15

CYP2B6

Sustratos

Bupropión
Metadona
Ciclofosfamida
Ifosfamida
Efavirenz

Inhibidores

Tiotepa
Ticlopidina

Inductores Inductores

- Fenobarbital
- Rifampicina

Cromosoma 19

3-4% polimorfismo en
caucásicos

CYP2C9

Sustratos

AINE

- Diclofenac
- Ibuprofeno
- Meloxicam
- Naproxeno
- Piroxicam
- Suprofen

ARBs

- Losartan
- Irbesartán

HGOrales

- Tolbutamida
- Glipizida
- Gliburida
- Glibenclamida
- Glimepirida
- Nateglinida

Amitriptilina
Rosiglitazona
Celecoxib
Fluoxetina
Fenitoína
Tamoxifeno
Warfarina

Inhibidores

- Amiodarona
- Fluconazol
- Voriconazol
- Fenofibrato
- Fluvastatina
- Lovastatina
- Fluvoxamina
- Isoniacida
- Fenilbutazona
- Probenecid
- Sertralina
- Sulfametoxazol
- Tenipósido
- Zafirlukast

Inductores

- Secobarbital
- Rifampicina

Cromosoma 10

1-3% polimorfismo en caucásicos

Sustratos

Inh Bomba Protones

- Omeprazol
- Lanzoprazol
- Pantoprazol
- Rabeprazol
- E-3810

Antiepilépticos

- Diazepam
- Fenitoína
- Mefenitoína
- Fenobarbitona
- Hexobarbital
- R-Mefobarbital

Amitriptilina

Ciclofosfamida

Carisoprodol

Citalopram

Clopidogrel

Clomipramina

Nelfinavir

Primidona

Progesterona

Proguanil

Propranolol

Talidomida

Tenipósido

R-warfarina

CYP2C19

Inhibidores

- Cloranfenicol
- Cimetidina
- Felbamato
- Fluoxetina
- Fluvoxamina
- Indometacina
- Ketoconazol
- Lanzoprazol
- Omeprazol modafinilo
- Oxcarbazepina
- Probenecid
- Ticlopidina
- Topiramato

Inductores

- Carbamazepina
- Noretindrona
- Prednisona
- Rifampicina

Cromosoma 10

3-5% polimorfismo en caucásicos

15-20% en asiáticos

Sustratos

Antidepresivos

- Amitriptilina
- Clomipramina
- Desipramina
- Imipramina
- Paroxetina
- Venlafaxina

Antipsicóticos

- Haloperidol
- Risperidona
- Tioridazina
- Fluoxetina

β -bloqueantes

- Carvedilol
- Metoprolol
- Timolol
- Propafenona

Opiáceos

- Codeína
- Dextrometorfano
- Tramadol

Flecainida

Encainida

Mexiletina

Odansetron

Metoclopramida

Tamoxifeno

Clorfeniramina

CYP2D6

Inhibidores

- Amiodarona
- Bupropion
- Clorpromazina
- Citalopram
- Cimetidina
- Cocaína
- Escitalopram
- Levomepromazina
- Metoclopramida
- Metadona
- Paroxetina
- Quinidina
- Ranitidina
- **Ritonavir**
- Sertralina
- Terbinafina

Anti H1

- Difenhidramina
- Clorfeniramina
- Hidroxicina
- Perfenazina
- Clemastina

Inductores Inductores

- Dexametasona
- Rifampicina

Cromosoma 22

5-10% polimorfismo en caucásicos

CYP3A4,5,7

Sustratos

Antibióticos macrólidos

- Claritromicina
- Eritromicina
- Diritromicina

Antiarrítmicos

- Quinidina

Benzodiazepinas

- Alprazolam
- Diazepam
- Midazolam
- Triazolam

Inmunomoduladores

- Ciclosporina
- Tacrolimus (FK506)

Antihistamínicos

- Clorfeniramina
- Terfenadina - astemizol

Proquinéticos

- Cisapride

Antirretrovirales

- Ritonavir
- Saquinavir
- Nelfinavir
- Indinavir
- Fosamprenavir
- Darunavir
- Tipranavir

Bloqueantes cálcicos

- Amlodipina
- Diltiazem
- Felodipina
- Nifedipina
- Nisoldipina
- Nitrendipina
- Verapamilo
- Lercandipina

Esteroides

- Hidrocortisona
- Fluticasona
- Estradiol
- Progesterona
- Testosterona

Estatinas

- Lovastatina
- Simvastatina
- Atorvastatina
- Cerivastatina

Alfentanilo

Aprepitant

Buspirona

Alcaloides del ergot

Cafeína

Cilostazol

Cocaína

Codeína

Dapsona

Dexametasona

Dextrometorfano

Docetaxel

Domperidona

Fentanilo

Finasteride

Halperidol

Lidocaína

Metadona

Ondansetron

Propranolol

Risperidona

Sildenafilafil

Sirolimus

Salmeterol

Tamoxifeno

Taxol

Trazodona

Vincristina

Ziprasidona

Zolpidem

Inhibidores

CYP3A4,5,7

Inductores Inductores

Antirretrovirales

- Indinavir
- Nelfinavir
- Ritonavir

Antibióticos

- Cloranfenicol
- Claritromicina
- Eritromicina
- Norfloxacin

Antimicóticos

- Fluconazol
- Ketoconazol
- Itraconazol
- Voriconazol

Aprepitant

Amiodarona

Verapamilo

Diltiazem

Cimetidina

Fluvoxamina

Norfluoxetina

Mibefradil

Nafazodona

Gestodeno

Mifepristona

Imatinib

Jugo de pomelo

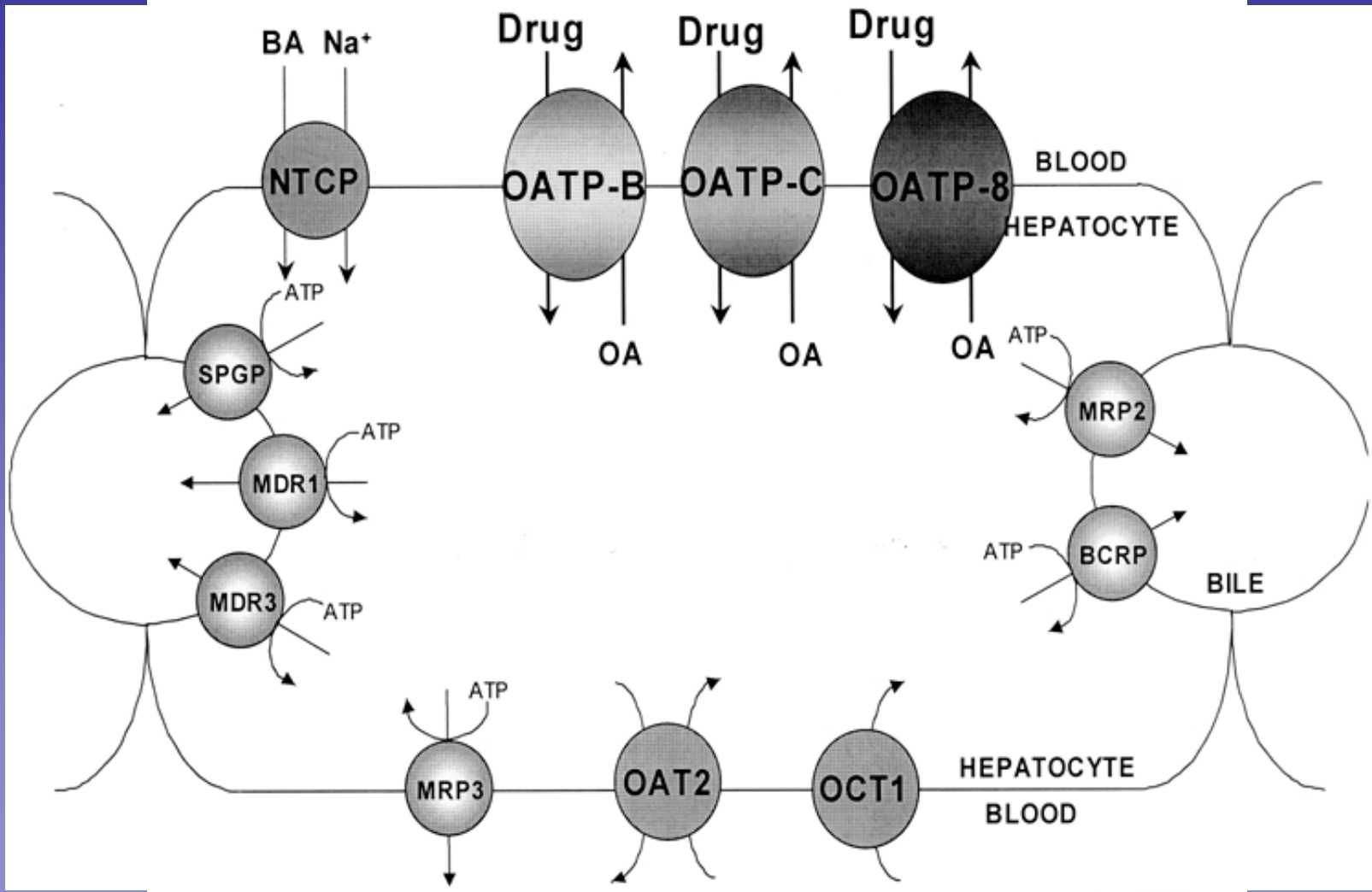
Antirretrovirales

- Nevirapina
- Efavirenz
- Barbitúricos
- Carbamazepina
- Glucocorticoides
- Modafinilo
- Nevirapina
- Fenobarbital
- Fenitoína
- Rifampicina
- Troglitazona
- Oxcarbazepina
- Pioglitazona
- Ipericum (hierba de San Juan)

Cromosoma 7

Sin polimorfismos importantes

Polimorfismos de transportadores III



Polimorfismo y transportadores

- ATP binding cassette family
- Ej: Glicoproteína p (MDR1/ABCB1)
- IPs: sustratos de Gp p

- Transportador de serotonina (SCL6A4) (cromosoma 17q). Región polimórfica asociada al gen de transporte de 5-HT (5-HTTLPR). Asociación de la variante larga (Alelo L) con mejor respuesta a IRSS

Polimorfismos de blancos de acción

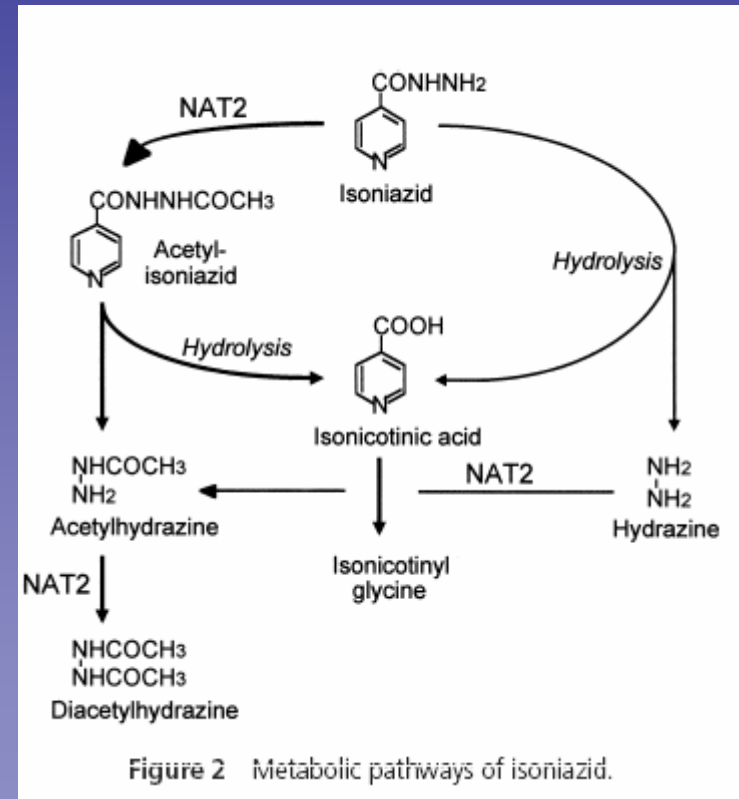
Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.*

Gene or Gene Product	Medication	Drug Effect Associated with Polymorphism
ACE	ACE inhibitors (e.g., enalapril) Fluvastatin	Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function ³²⁻⁴⁰ Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis ⁴¹
Arachidonate 5-lipoxygenase	Leukotriene inhibitors	Improvement in FEV ₁ ⁴²
β_2 -Adrenergic receptor	β_2 -Agonists (e.g., albuterol)	Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects ⁴³⁻⁵⁰
Bradykinin B2 receptor	ACE inhibitors	ACE-inhibitor-induced cough ⁵¹
Dopamine receptors (D2, D3, D4)	Antipsychotics (e.g. haloperidol, clozapine)	Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3) ⁵²⁻⁵⁶
Estrogen receptor- α	Conjugated estrogens Hormone-replacement therapy	Increase in bone mineral density ⁵⁷ Increase in high-density lipoprotein cholesterol ⁵⁸
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa	Aspirin or glycoprotein IIb/IIIa inhibitors	Antiplatelet effect ⁵⁹
Serotonin (5-hydroxytryptamine) transporter	Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)	5-Hydroxytryptamine neurotransmission, antidepressant response ⁶⁰⁻⁶²

Metabolismo de isoniácida: NAT2

- El metabolito principal – acetilisoniácida-, es el resultado de una acetilación por la enzima hepática (*n-acetiltransferasa-NAT-2*)
- Patrones de acetilación bi-trimodales, por diferencias en la actividad de NAT2:
 - Acetiladores Lentos
 - Acetiladores Intermedios
 - Acetiladores Rápidos

SUSCEPTIBILIDAD A POLIMORFISMOS GENÉTICOS



Determinación del tipo de acetilador según el genotipo para NAT2*

- AR: homocigota NAT2*4
- AL: se identificaron 3 mutaciones
 - 481C por T (NAT2*5)
 - 590G por A (NAT2*6)
 - 857G por A (NAT2*7)

Table 1 Frequency of the NAT2* genotype in Japanese tuberculosis patients and healthy population

Genotype	Health Subjects n (%)	Patients n (%)	Acetylator status
NAT2*4/*4	90 (46.4)	28 (36.4)	RA-type
NAT2*4/*5	5 (2.6)	2 (2.6)	
NAT2*4/*6	61 (31.4)	31 (40.2)	IA-type
NAT2*4/*7	21 (10.8)	9 (11.7)	
NAT2*5/*5	0 (0.0)	0 (0.0)	
NAT2*5/*6	2 (1.0)	1 (1.3)	
NAT2*5/*7	0 (0.0)	0 (0.0)	SA-type
NAT2*6/*6	5 (2.6)	2 (2.6)	
NAT2*6/*7	9 (4.7)	3 (2.9)	
NAT2*7/*7	1 (0.5)	1 (1.3)	
Total	194 (100)	77 (100)	

RA = rapid acetylator; IA = intermediate acetylator; SA = slow acetylator.

Slow *N*-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity

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SUMMARY

SETTING: Japanese in-patients with pulmonary tuberculosis and normal liver function receiving treatment with isoniazid and rifampicin (INH + RMP).

OBJECTIVE: To elucidate the relationship between *N*-acetyltransferase 2 (NAT2) genotype and the incidence of isoniazid + rifampicin-induced hepatotoxicity.

DESIGN: Prospective study. After NAT2* genotyping, 77 patients were classified into three groups according to their NAT2* genotypes: rapid-type (a homozygote of NAT2*4), intermediate-type (a heterozygote of NAT2*4 and mutant alleles) and slow-type (a combination of mutant alleles). Their biochemical profiles of liver function test were investigated for 3 months to assess the development of serum aminotransferase elevation.

RESULT: Of the 77 patients, 18.2% developed adverse hepatic reaction within the first month of INH + RMP

treatment. A significant association was observed between hepatotoxicity and NAT2* genotype: compared with rapid-type, the relative risk was 4.0 (95%CI 1.94–6.06) for intermediate-type and 28.0 (95%CI 26.0–30.0) for slow-type. Especially in slow-type, the incidence of hepatotoxicity and serum aminotransferase elevation was significantly higher than in the other two types.

CONCLUSION: Slow NAT2* genotype significantly affected the development of INH + RMP-induced hepatotoxicity. This suggests the possibility that NAT2* genotyping prior to medication may be useful in evaluating patients with high risk for INH + RMP-induced hepatotoxicity.

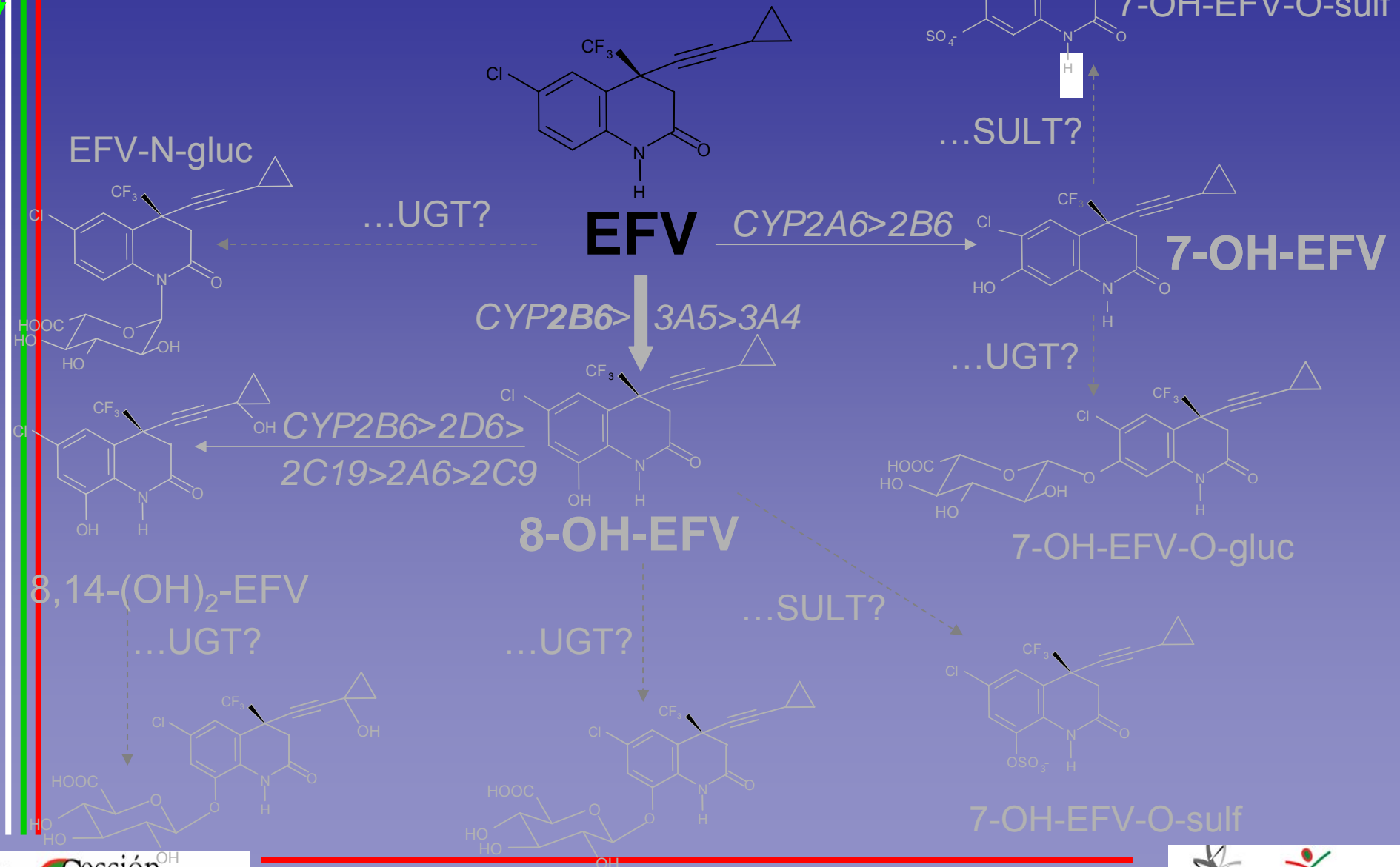
KEY WORDS: *N*-acetyltransferase 2 (NAT2); genotype; isoniazid; rifampicin; hepatotoxicity



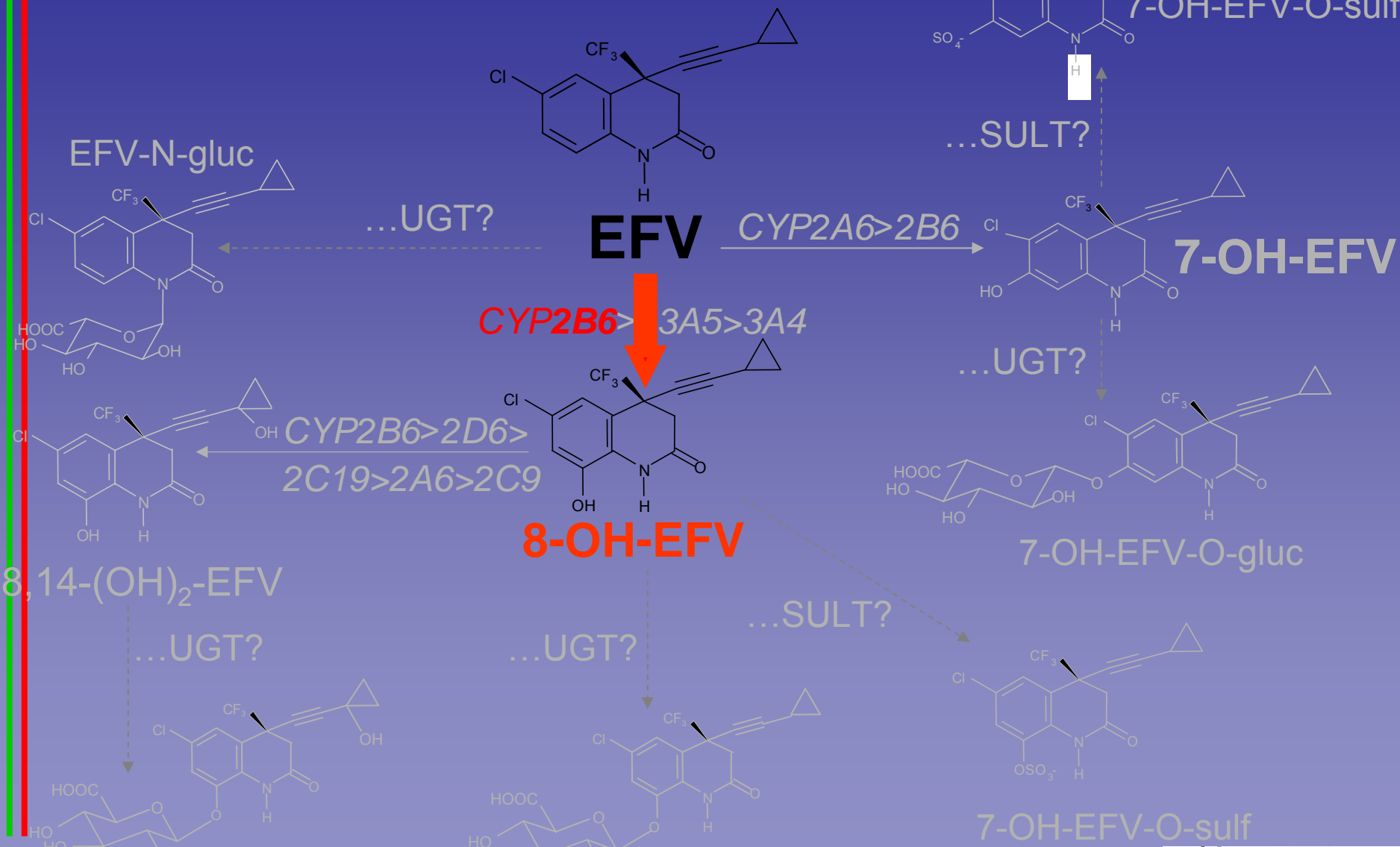
Farmacogenómica y Toxicidad de ARV

DROGAS CON MARCADORES GENETICOS	FENOTIPO	EFEECTO CLINICO
Efavirenz	↑ Conc plasma	Toxicidad SNC
Atazanavir	↑ Bilirrubina	Sind Gilbert
Lopinavir	↑ Lípidos	Enf. Cardiovascular
Tenofovir	Sind. Fanconi incompleto	Tubulopatía proximal
Abacavir		Hipersensibilidad

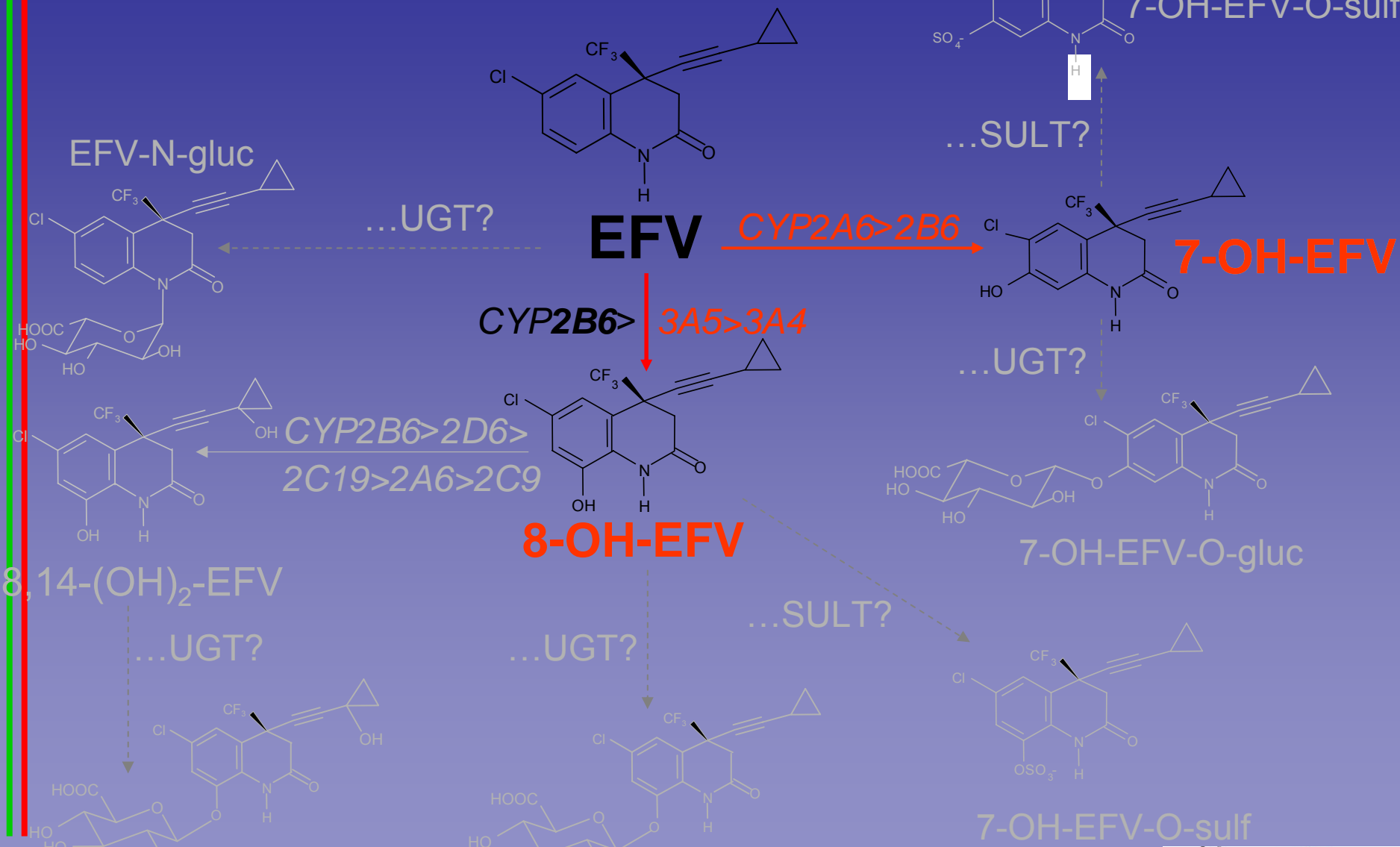
Efavirenz: vías metabólicas



Efavirenz: vías metabólicas



Efavirenz: vías metabólicas



Farmacogenética de EFV

- Los trastornos del SNC conducen a un 2-7% de suspensión
- En general efecto agudo, que resuelve dentro de las primeras 4-8 sem
- Trastornos del SNC relacionados con la exposición al EFV

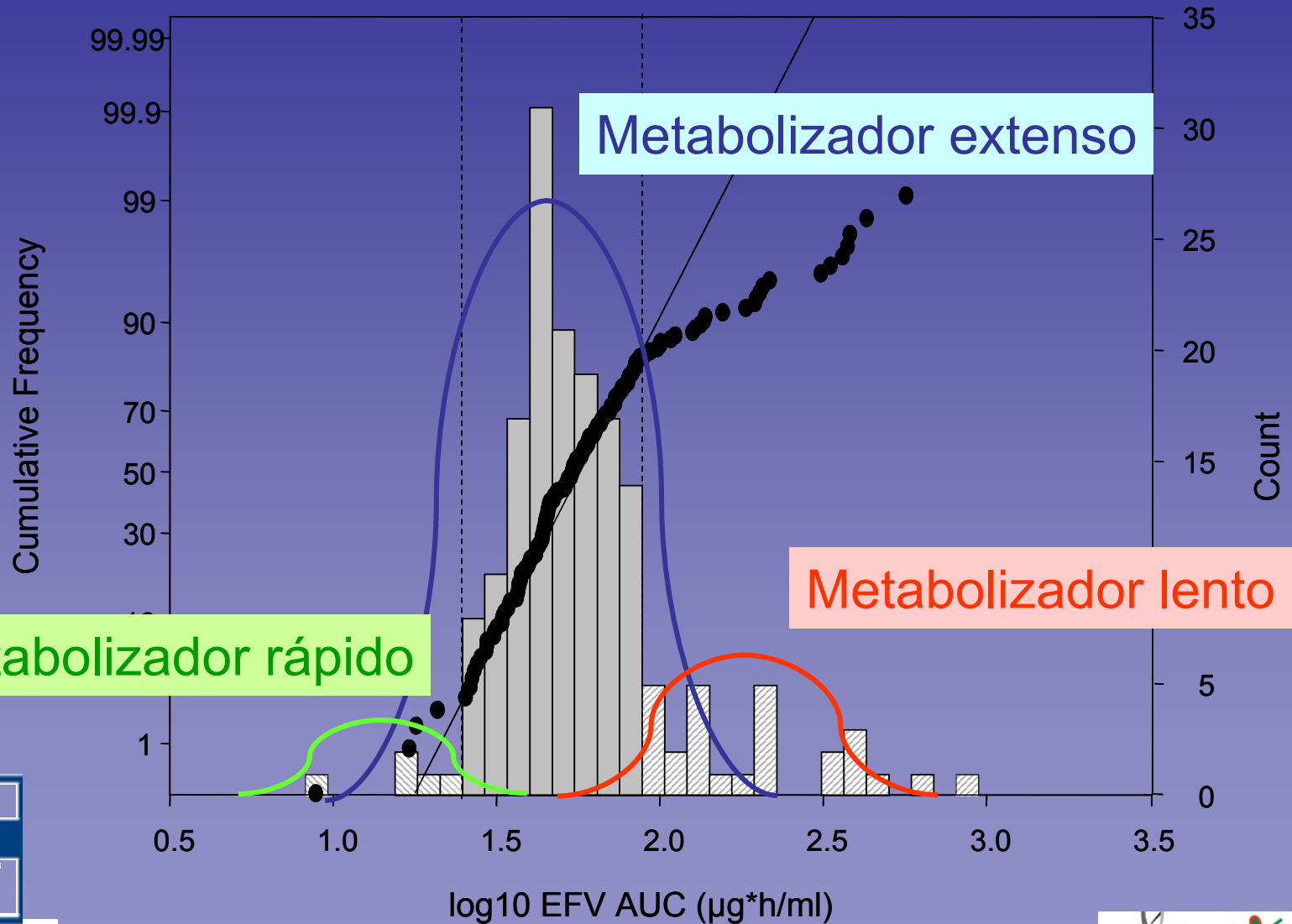
Parámetro	Blancos	Negros	Hispanos	P Valor
Mediana ABC ₀₋₂₄ , µg x hr/mL	46.4	58.3	66.1	< .0001
Mediana C _{max} , µg/mL	2.53	3.14	3.18	< .0001
Mediana C _{24h} , µg/mL	1.31	1.86	2.01	< .0001

- La exposición plasmática se asocia significativamente a CYP2B6 (G516T), CYP3A5 (A6986G), y CYP3A4 (A392G)
 - Clearance 54% menor para CYP2B6 516 T/T vs G/G ($P < .0001$)
 - Clearance 27% mayor para CYP3A5 6986 G/G vs A/A ($P = .014$)
- CYP2B6 G516T se asocia con aparición de síntomas SNC en Semana 1

Haas DW, et al. AIDS. 2004;18:2391-2400.

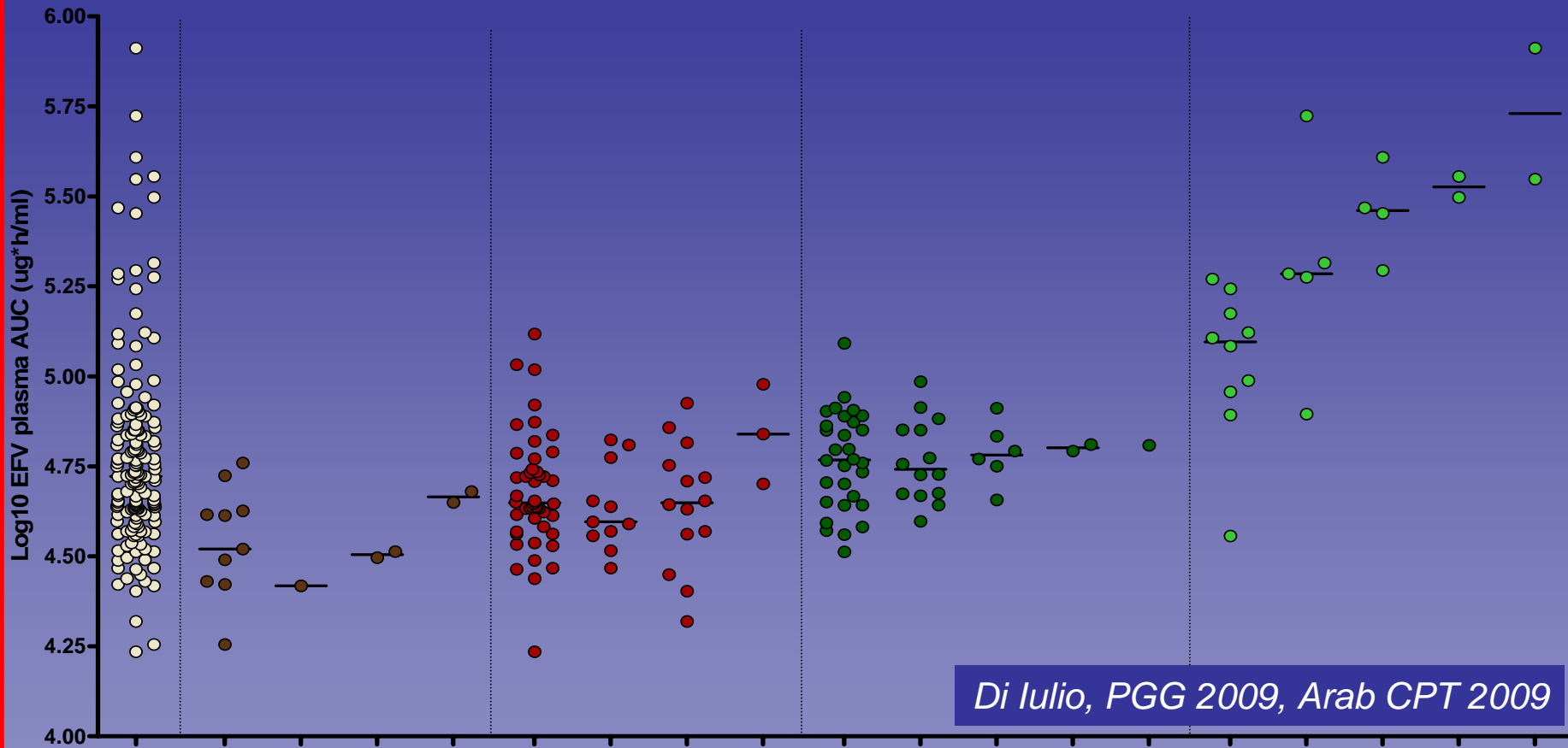
Distribución de ABC de Efavirenz

Rotger et al. Clin Pharm Ther 2007



SWISS
HIV
COHORT
STUDY

CYP2B6, CYP2A6, CYP3A4 y farmacocinética del Efavirenz



CYP2B6

CYP2A6/3A

2545 recibiendo EFV 600 mg por día

EFV ng/mL

4000
3000
2000
1000
10
0

Overall median
(IQR 25-75%)

2146

Marzolini K, et al. AIDS 2001; 15: 71-5

21.6%

60.9%

12.2%

5.3%

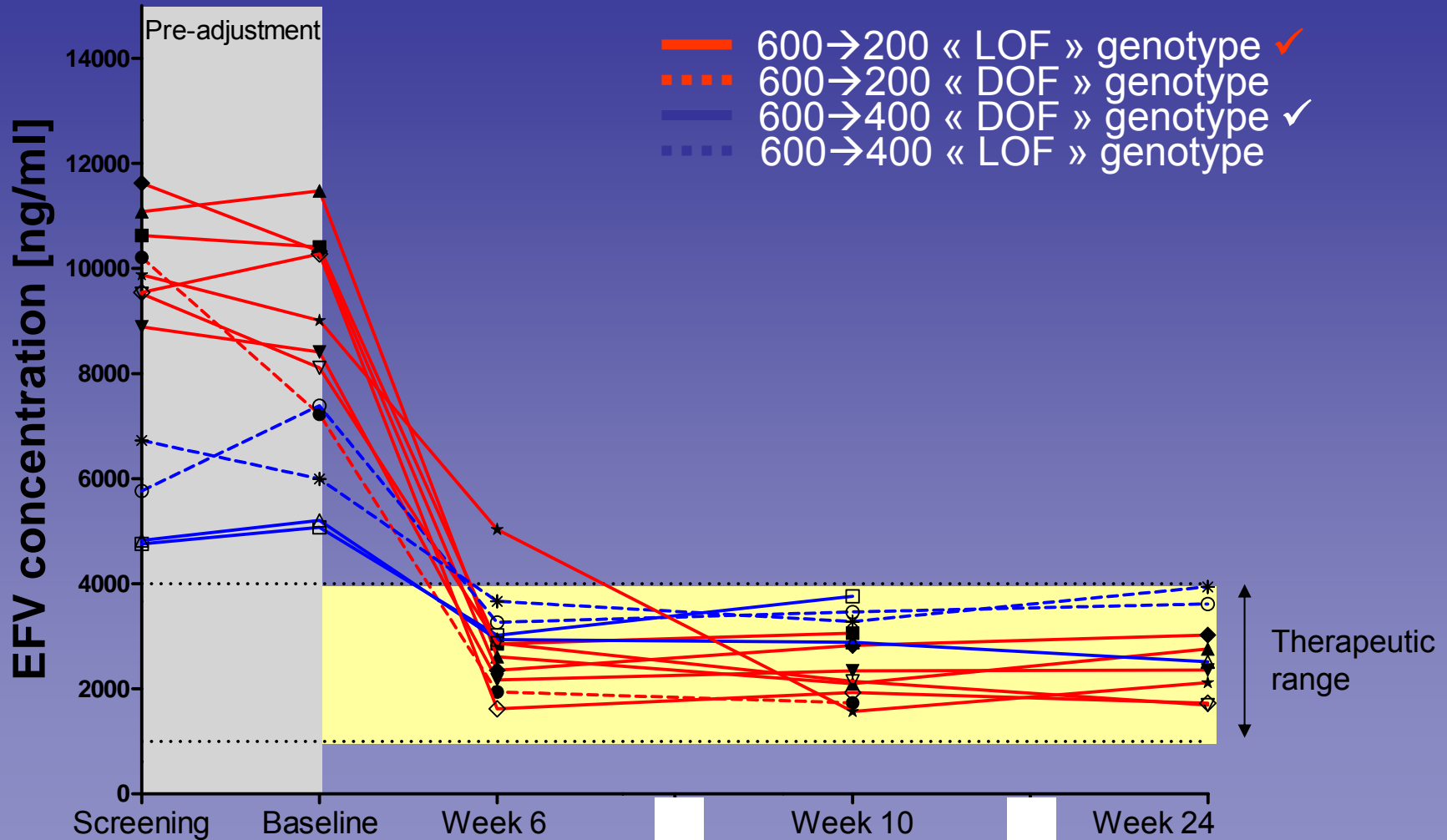
Efectos Adversos: 6% GI, 16% hiper TG, 33% SNC, 35% hepatotox, 10% otros

EFV reducción de dosis a 400, 300, 200 o 100 mg

EFV [c] llevada a rango normal con EAs residuales en 22% pacientes

Bensemmanne R, et al. Abstr P 48

Ajuste de dosis de efavirenz por TDM + genotipo

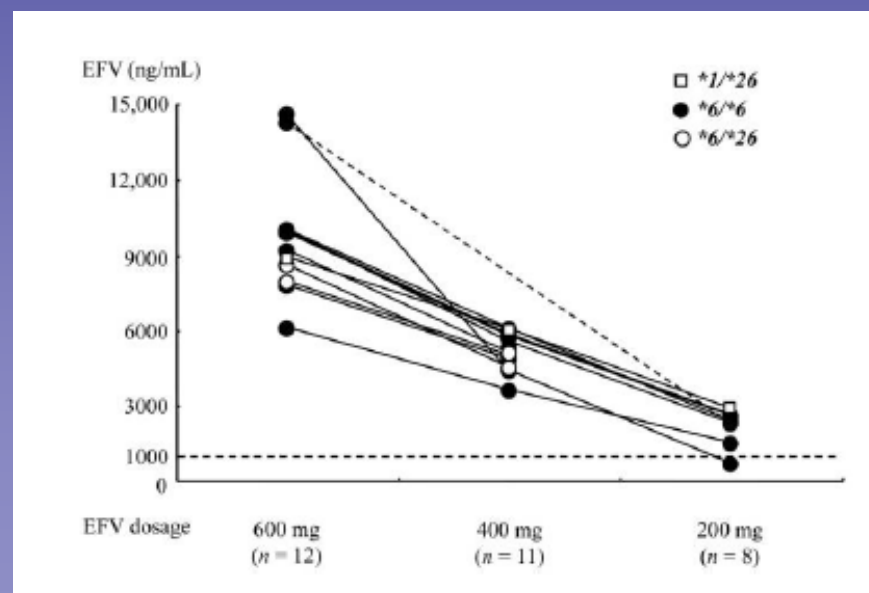
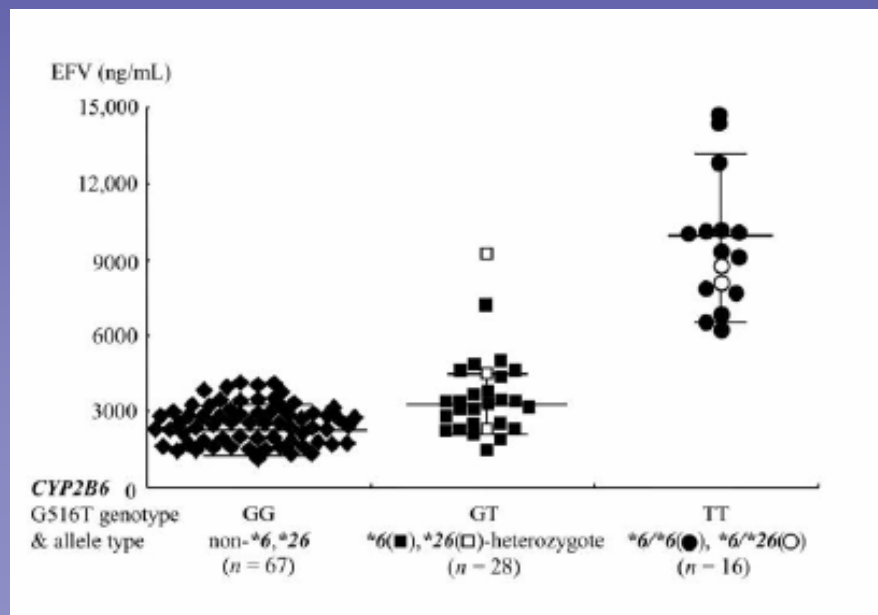


CDB076 – Calmy et al -Therapeutic drug monitoring (TDM) enables efavirenz dose reduction in virologically-controlled patients

Successful Efavirenz Dose Reduction in HIV Type 1-Infected Individuals with Cytochrome P450 2B6 *6 and *26

Hiroyuki Gatanaga,¹ Tsunefusa Hayashida,¹ Kiyoto Tsuchiya,¹ Munehiro Yoshino,² Takeshi Kuwahara,² Hiroki Tsukada,⁴ Katsuya Fujimoto,⁵ Isao Sato,⁶ Mikio Ueda,⁷ Masahide Horiba,⁹ Motohiro Hamaguchi,⁹ Masahiro Yamamoto,¹⁰ Noboru Takata,¹¹ Akiro Kimura,¹² Takao Koike,⁵ Fumitake Gejyo,⁴ Shuzo Matsushita,¹³ Takuma Shirasaka,³ Satoshi Kimura,¹ and Shinichi Oka¹

CID 2007;45 (1 November) • HIV/AIDS



CYP2B6, CYP2A6 and UGT2B7 genetic polymorphisms are predictors of efavirenz mid-dose concentration in HIV-infected patients

Awewura Kwara^{a,b}, Margaret Lartey^c, Kwamena W.C. Sagoe^c, Ernest Kenu^d and Michael H. Court^e

AIDS 2009, 23:2101–2106

Nevirapina

Associations between *CYP2B6* Polymorphisms and Pharmacokinetics after a Single Dose of Nevirapine or Efavirenz in African Americans

David W. Haas,^{1,2} Tebeb Gebretsadik,³ Gail Mayo,¹ Usha N. Menon,^{1,4} Edward P. Acosta,⁵ Ayumi Shintani,³ Michael Floyd,⁵ C. Michael Stein,^{1,4} and Grant R. Wilkinson^{1,4}

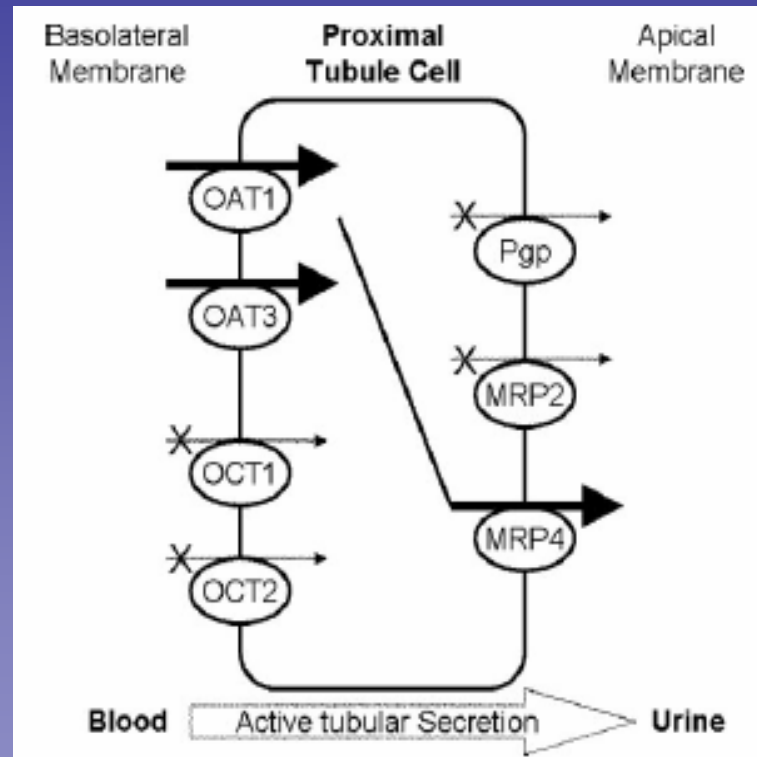
Departments of ¹Medicine, ²Microbiology and Immunology, ³Biostatistics, and ⁴Pharmacology, Vanderbilt University School of Medicine, and ⁵Department of Medicine, Meharry Medical College, Nashville, Tennessee; ⁶Department of Medicine, University of Alabama at Birmingham, Birmingham

JID, Marzo 2009

Los principales metabolitos de la NVP son la 12-OHNVP y 4 CarboxiNVP, producto de la acción de CYP3A4, más que 2-OHNVP secundario a CYP 2B6

Fan-Havard 5th IAS Conference P WEPEB257

Eflujo tubular del TDF

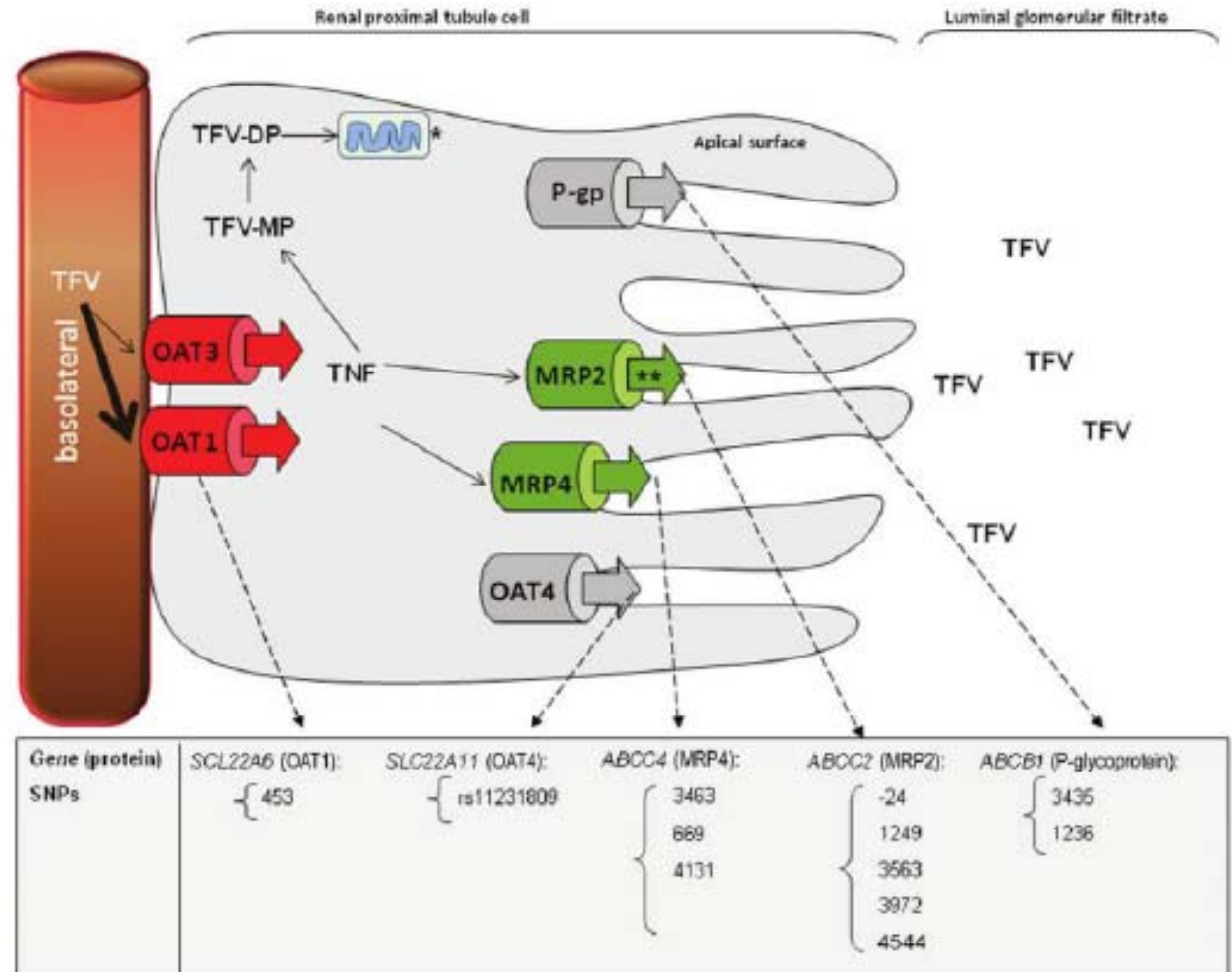


Ray AS, Antimicrob Agents Chemother 2006

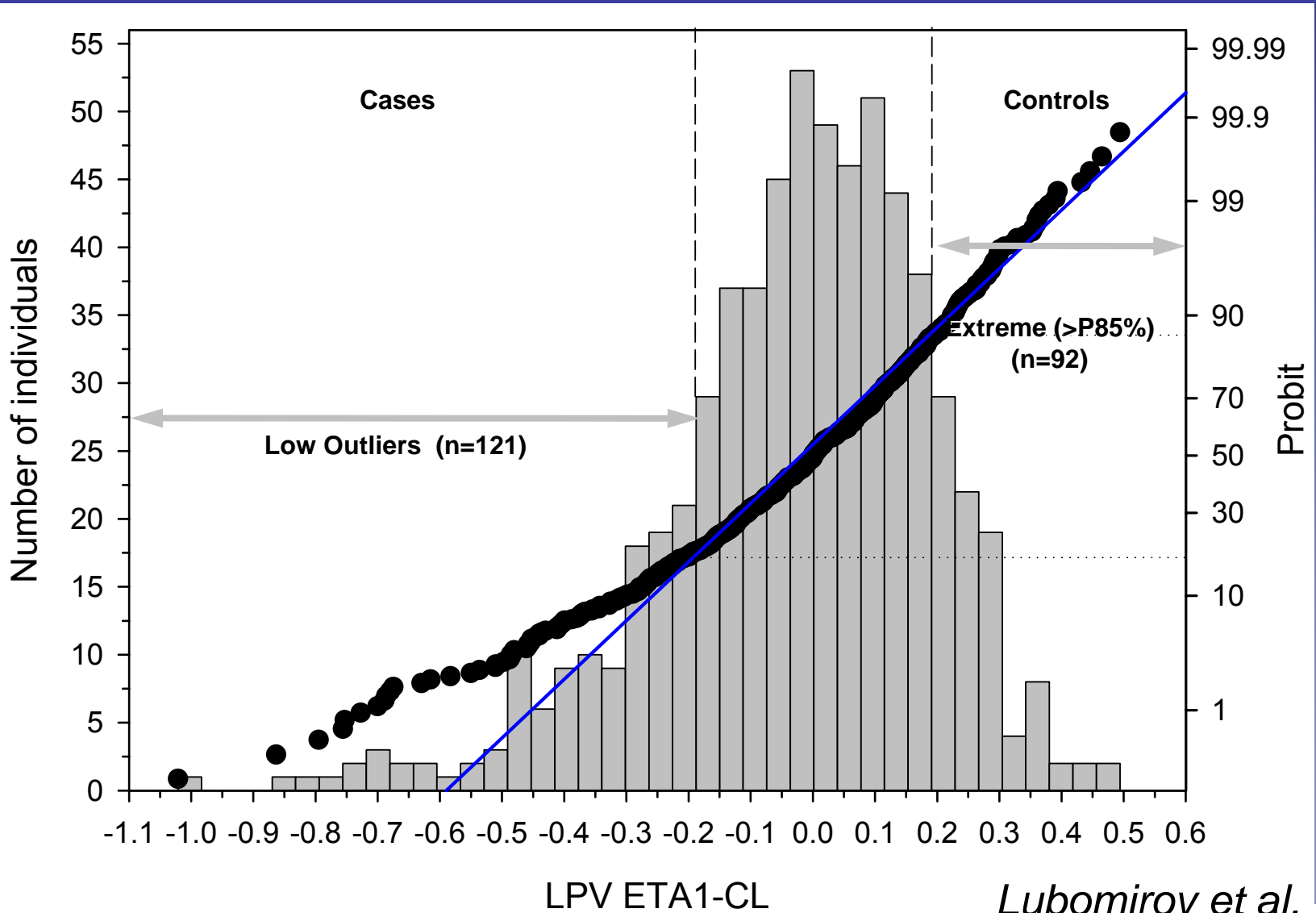
Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with Tenofovir: A Pharmacogenetic Study

Clinical Infectious Diseases 2009; 48:e108-16

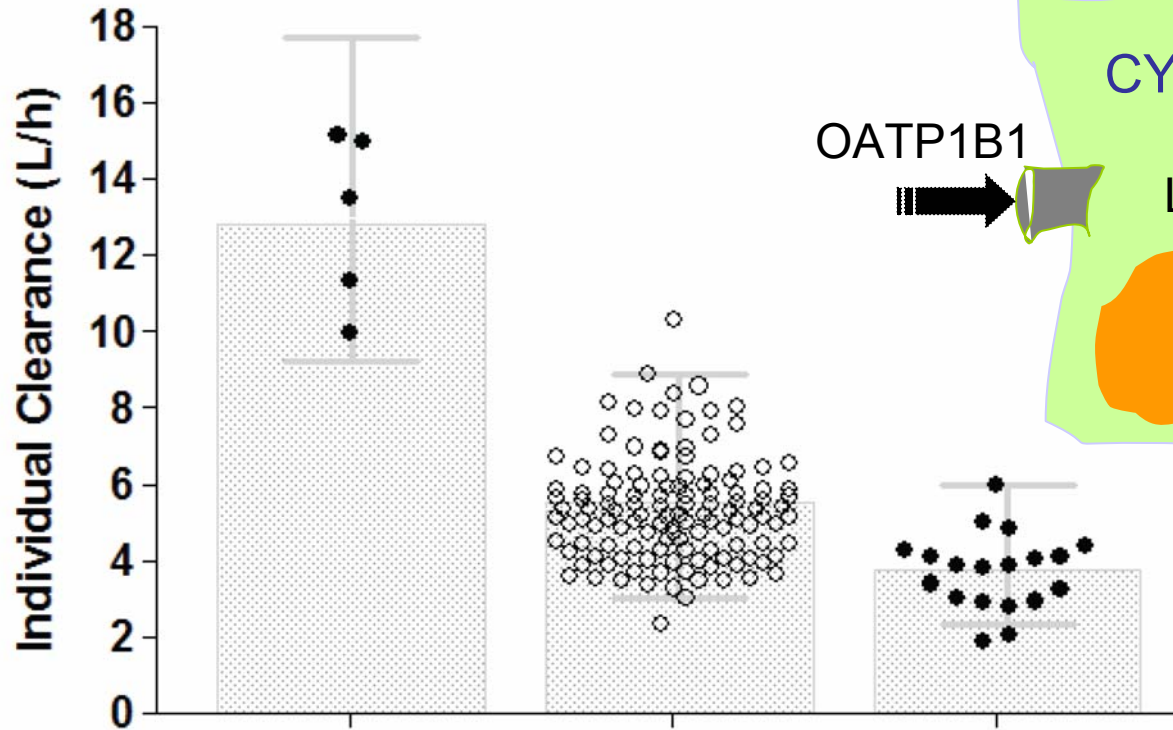
Sonia Rodríguez-Nóvoa,¹ Pablo Labarga,¹ Vincent Soriano,¹ Deirdre Egan,² Marta Albalater,² Judit Morello,¹ Lorena Cuenca,¹ Gema González-Parto,¹ Saye Khoo,² David Back,² and Andrew Owen²



Farmacocinética – Genética de Lopinavir/r



Farmacocinética – Genética de Lopinavir/r

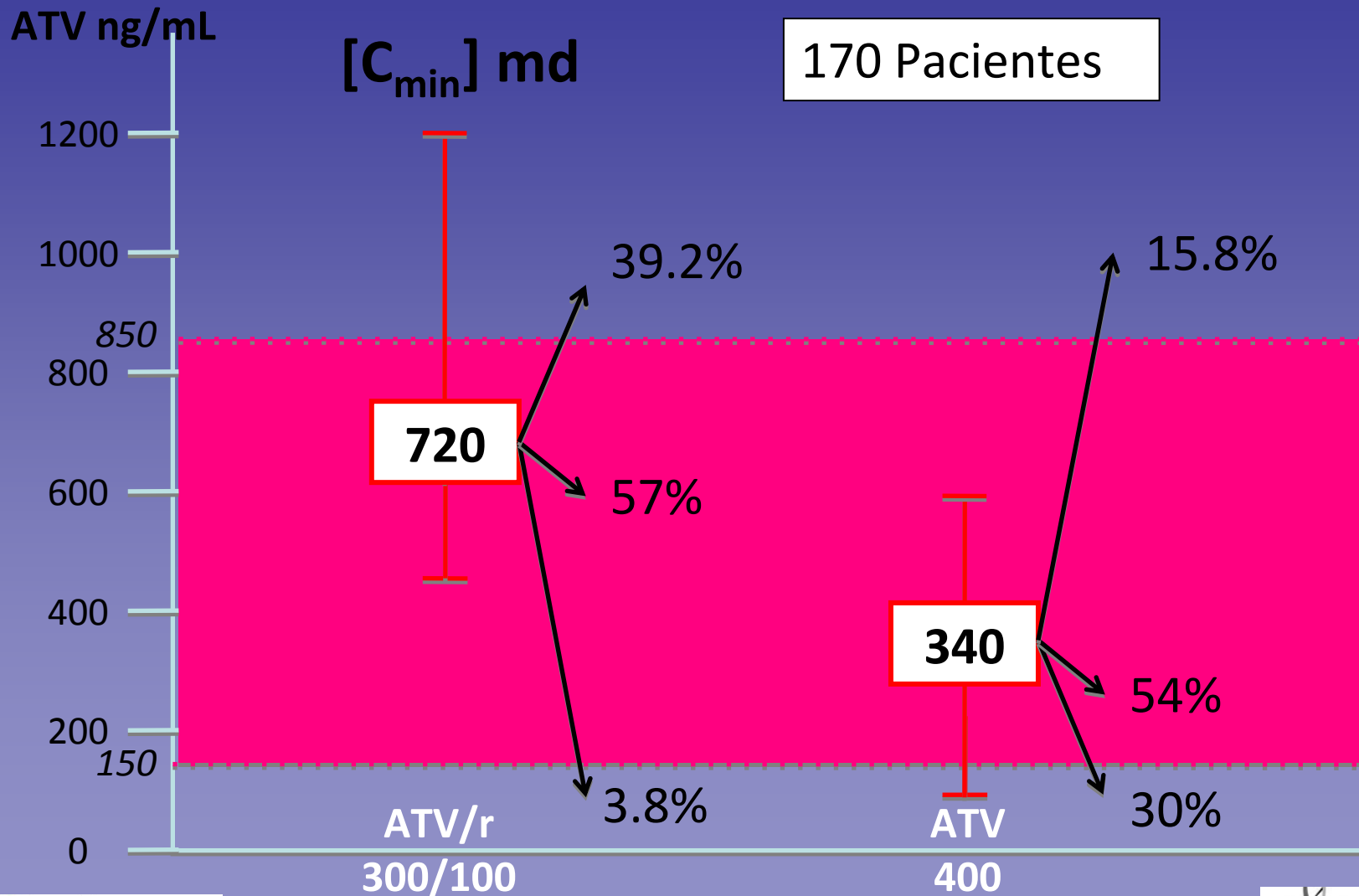


<i>SLCO1B1</i> *4 rs11045819	2	0, 1	0
<i>SLCO1B1</i> *5 rs4149056, <i>ABCC2</i> rs717620 or <i>CYP3A</i> rs6945984	0	0, <2	≥2
n	5	124	19

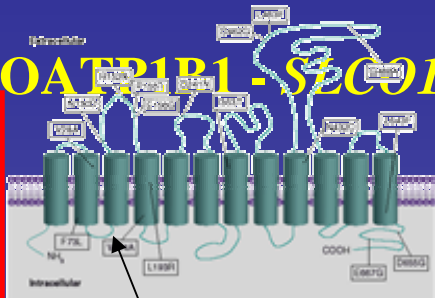
Lubomirov et al.

Atazanavir (\pm ritonavir) terapéutico

Rango

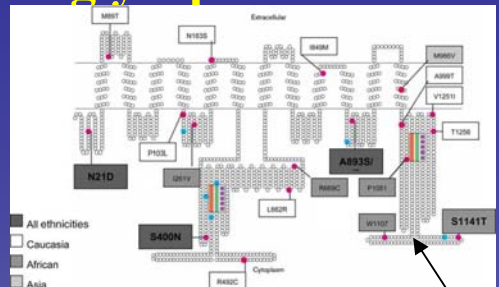


OATP1B1 - *SLCO1B1*



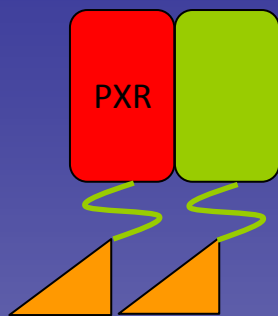
521T>C

P-glycoprotein - *ABCB1*

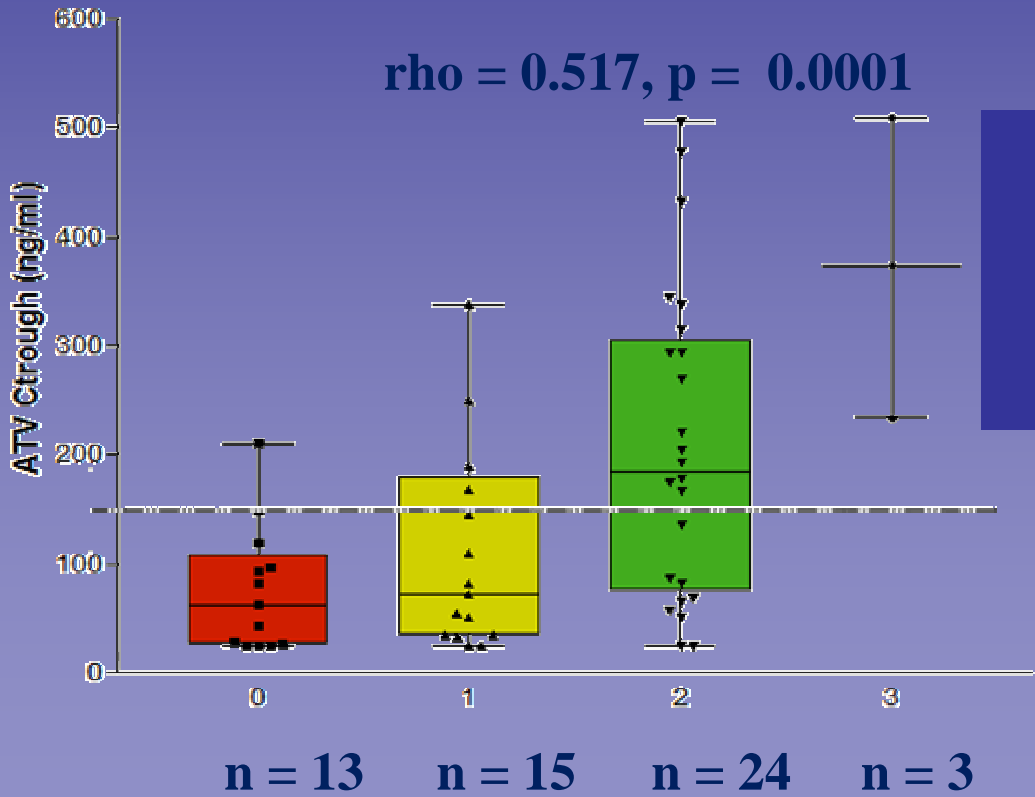


3435C>T

Pregnane X receptor 63396 C>T



$\rho = 0.517, p = 0.0001$



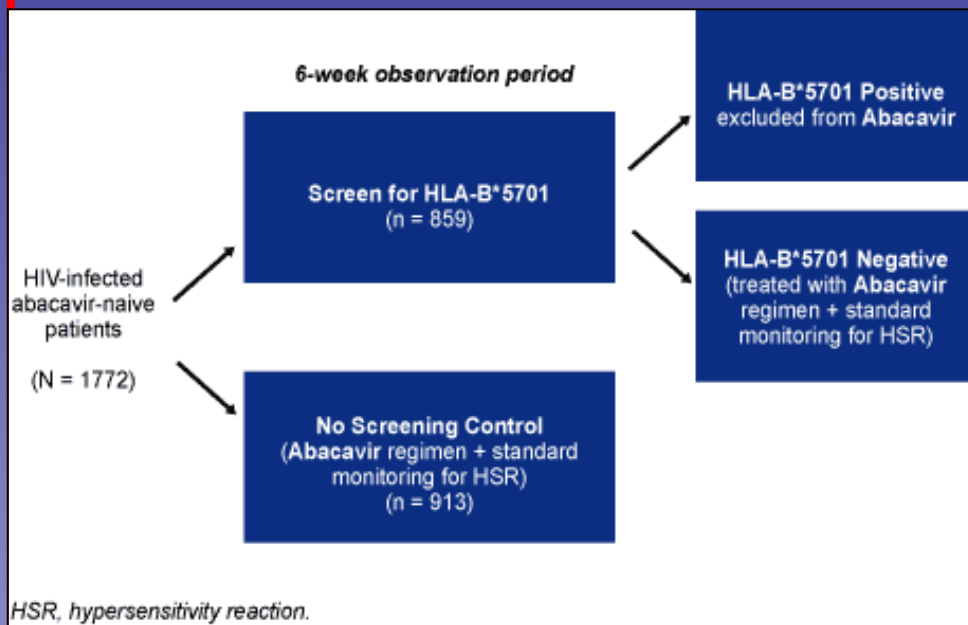
Farmacogenómica y Niveles plasmáticos de Atazanavir
Siccardi M, et al. Abstr. N. O 4

UDP-glucuronosil transferasa

- Principal vía de eliminación de xenobióticos, hormonas (estradiol) y bilirrubina, haciéndolos mas polares, mas solubles en bilis y orina.
- La variante de **UGT1A1*28** esta asociada a reducción de la capacidad de glucuronización
- *Esta variante de UGT1A1 contiene en la zona promotora 7 secuencias TA timina-adenosina (Sdre. Gilbert) en lugar de 6 (wild type)*

Estudio Predict-1

HLA-B*5701 e Hipersensibilidad por ABC



- Especificidad confirmada por test cutáneo
- Episodios con sospecha clínica (%): 3,4 (test) vs 7,8 ($p < 0.001$)
- Confirmados (%): 0 (test) vs 2,7% ($p < 0.001$)

VPN: 100% - VPP: 48%

Mallal S y col, IAS 2007

HSA - Mecanismo postulado

Reconocimiento antigénico



metabolitos del ABC por HLA B 5701

(antes de la activación a Carbovir 3P)



Ly T α/β o Ly T γ/δ



Reacción de Hipersensibilidad

HIBA - Resultados

- 128 pacientes tipificados hasta abril 2010
- PCR – SSP

HLAB 57 Negativo \Rightarrow B 5701(-) n=120

HLAB 57 Positivo \Rightarrow Secuenciación

4/8 Tenían rash
Previo al test

B 5701(+)
n=8

HIBA - Resultados II

Reacción de hipersensibilidad	HLA B 5701 +	HLA B 5701 -	
Positiva	4	0	4
Negativa	1	120	121
No evaluable (no recibieron ABC)	3	0	3
TOTALES	8	120	128

Valor predictivo negativo 100%

Guías de tratamiento antirretroviral

Con qué empezar

- Regímenes preferidos



- AZT/3TC + EFV

Pharmacogenetics and the potential for the individualization of antiretroviral therapy

Elizabeth J. Phillips^a and Simon A. Mallal^b

- | |
|---|
| ✓ Test is clinically relevant* |
| ✓ Clinical and cost-effectiveness data to support reimbursement |
| ✓ Early and routine initiation of the test |
| ✓ System to ensure correct blood sample to the correct lab |
| ✓ Maintenance of sample and data integrity |
| ✓ Robust assay |
| ✓ Assay specific laboratory quality assurance programs |
| ✓ Rapid, simple report and interpretation |
| ✓ Education of healthcare workers and patients |
| ✓ Information needs to be transmitted to, retained and acted on by healthcare team (clinicians, pharmacists, nurses and patients) |

Current Opinion in Infectious Diseases 2008,
21:16–24

Pharmacogenomics. 2009 May ; 10(5): 837–852. doi:10.2217/PGS.09.25.

Application of pharmacogenomics to vaccines

Gregory A Poland^{1,2,3,†}, Inna G Ovsyannikova^{1,2}, and Robert M Jacobson^{1,3,4}

¹Mayo Vaccine Research Group, MN, USA

²Program in Immunovirology & Biodefense, Mayo Clinic, College of Medicine, 611C, Guggenheim Building, 200 First Street, SW Rochester, MN, 55905, USA

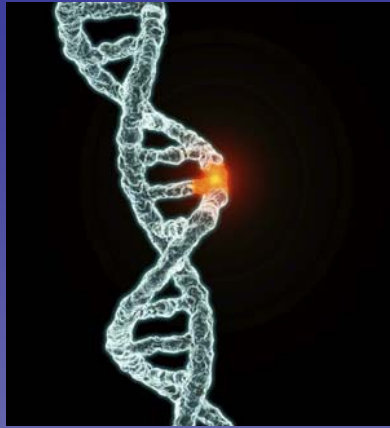
³Department of Medicine, Mayo Clinic, MN, USA

⁴Department of Pediatric & Adolescent Medicine, Mayo Clinic, MN, USA

Farmacogenómica, farmacoproteómica

- Etapas iniciales de desarrollo
- No es un fin en si mismo
- Instrumento útil para la identificación de la droga y la dosis más beneficiosas para el paciente
- Interés creciente: Senado EEUU (2002) Genómica y Medicina Personalizada establecimiento del Programa GPS (Genetic Prescribing System)





“Si no fuese por la gran variabilidad entre los individuos la medicina sería sólo ciencia y no arte”

Sir William Osler, 1892.