PHARMACOGENETIC OF ANTIRETROVIRALS
Toward a personalized antiretroviral therapy for HIV-infected patients

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Service de Toxicologie et Génopathies, Centre de Biologie Pathologie Génétique, CHRU Lille.
EA4483: « Impact de l’environnement chimique sur la santé »
Pôle Recherche, Faculté de Médecine, Lille.
Overall incidence of ADRs: 6.70 %
Incidence of fatal ADRs: 0.32 %

1994
- 2,216,000 hospitalized patients for "serious ADRs"
- 106,000 patients with fatal ADRs

<table>
<thead>
<tr>
<th>Leading cause of death in the US</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Heart disease</td>
<td>743,460</td>
</tr>
<tr>
<td>2 Cancer</td>
<td>529,904</td>
</tr>
<tr>
<td>3 Stroke</td>
<td>150,108</td>
</tr>
<tr>
<td>4 Pulmonary disease</td>
<td>101,077</td>
</tr>
<tr>
<td>5 Accidents</td>
<td>90,523</td>
</tr>
<tr>
<td>6 Pneumonia</td>
<td>75,719</td>
</tr>
<tr>
<td>7 Diabetes</td>
<td>53,894</td>
</tr>
</tbody>
</table>

Economic burden resulting from drug-related morbidity and mortality: 136.8 billion $US annually

Resistance to therapy
- 35 % of people do not respond to beta blockers
- 50 % do not respond to tricyclic antidepressants
- 30 % of schizophrenics do not respond to treatment by antipsychotics
- 50-60% do not respond to 5-FU combined with irinotecan and oxaloplatine for colorectal K
- The response rates for gefinitib or erlotinib in non-small cell lung cancer patients is 10-20%
MEDICAMENTS

EXPOSITION
Unique ou répétée
Seule ou Combinée

INHERENTS AU SUJET
• Facteurs physiologiques
• Facteurs pathologiques
• Facteurs environnementaux

Statut
GENETIQUE

PHARMACO GENETIQUE

PHARMACO GENOMIQUE

EFFETS
Absorption
Distribution
Métabolisme
Excrétion

Médicaments
Cinétique
Dynamie

GENES
PROTEINES

EFFETS
Almost ineffective monotherapy

20 years

Highly active combination multidrug regimens

Suppress HIV replication in most HIV-infected patients

HIV infection

Chronic disease requiring long-term antiretroviral treatment
ALMOST INEFFECTIVE MONOTHERAPY

20 years

HAART
HIGHLY ACTIVE COMBINATION MULTIDRUG REGIMENS

Suppress HIV replication in most HIV-infected patients

HIV INFECTION

CHRONIC DISEASE requiring Long-term antiretroviral treatment

Limited by the occurrence of
- Drug resistance
- Acute or chronic toxicities

Hypersensitivity reaction
Diabetes mellitus
Hepatotoxicity
Hyperbilirubinemia
Hypercholesterolemia
Hyperlipidemia
hyperlipoproteinaemia
Hypertriglyceridaemia
Lipoatrophy
Lipodystrophy
Neuropsychological toxicity
Pancreatitis
Peripheral neuropathy
Proximal tubulopathy
Skin rash
Response to HAART is a complex phenomenon which involves numerous proteins Limited by the occurrence of:

- Drug resistance
- Acute or chronic toxicities

HAART suppresses HIV replication in most HIV-infected patients.

CHRONIC DISEASE requiring long-term antiretroviral treatment:

- Hypersensitivity reaction
- Diabetes mellitus
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- Skin rash
HLA-B*5701 and Abacavir-induced Hypersensitivity Syndrome

**ABACAVIR** (Ziagen®; + lamivudine = Kivexa®):

- Potent and well tolerated NRTI of HIV-1
- 1 – 9% individuals → **HYPERSENSITIVITY REACTION**
- After a few weeks upon initiation
- Potentially lethal (0.03%)
- Unrelated to dose
- More severe in case of reexposure
- Multisystem involvement
- Rash, fever, gastrointestinal, constitutional and respiratory manifestations
Involvement of GENETIC FACTORS in abacavir hypersensitivity reaction

Involvement of GENETIC FACTORS in abacavir hypersensitivity reaction
Peyrère et al. Hypersensitivity related to abacavir in two members of the a family. Ann Pharmacother 2001; 35: 1291-1292

Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to abacavir
Mallal et al. Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcripase inhibitor abacavir. Ann Pharmacother 2002; 36: 727-732

HLA-B gene (short arm of chromosome 6) codes for a Class I HLA proteins which present peptides to CD8+ cytotoxic T lymphocytes

Prevalence of HLA-B*5701 alleles (%)
- India: 5-20%
- Thailand: 4-10%
- West Europe: 5-7%
- Mediterranean: 1-2%
- Subsaharan Africa: <1%
- China: 0%

P < 1x10^{-3}

OR: 117
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ASSOCIATION CONFIRMED in other cohorts of different ethnicities
Hughes et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some populations. 2004 Pharmacogenomics 5: 203-11.
Mechanism of the hypersensitivity reaction to abacavir
Clinical utility of HLA-B*5701 pharmacogenetic screening in preventing hypersensitivity to abacavir

Randomized, double-blind, prospective study

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Performance of HLA-B*5701 screening for hypersensitivity to abacavir in the control group

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Trial cohort PREDICT – 1

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Undergo abacavir use without HLA-B*5701 screening

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Clinical utility of HLA-B*5701 pharmacogenetic screening in preventing hypersensitivity to abacavir

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**Pharmacogenetic Based Therapeutic (dose) Recommendations**

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<tr>
<th>Drug (Gene)</th>
<th>Subjects (N)</th>
<th>Genotype or Phenotype</th>
<th>Level of evidence (0 → 4)</th>
<th>Clinical relevance (A → F)</th>
<th>Therapeutic (dose) recommendation</th>
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<tr>
<td>Abacavir</td>
<td>3791</td>
<td>HLA-B*5701 Positive</td>
<td>4</td>
<td>E</td>
<td>In the PRESENCE of HLA-B*5701 allele Select alternative drug</td>
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In the ABSENCE of HLA-B*5701 allele, abacavir can be safely prescribed but allergic events can still occur owing the concomitant drugs given to the patient.

Only 50% of patients carrying HLA-B*5701 allele will develop a hypersensitivity syndrome if abacavir has absolutely to be introduced, close medical supervision is essential.

**EMA and US FDA mandatory**  
Screening for HLA-B*5701 is recommended before starting an abacavir-containing regimen in all subjects.


**HLA-B*5701 genotyping in preventing abacavir hypersensitivity is COST-EFFECTIVE**  
EFAVIRENZ disposition and CENTRAL NERVOUS SYSTEM side effects

EFAVIRENZ (Sustiva®):
A first generation NNRTI
One of the preferred component of the first line treatment regimen of HIV infection worldwide
> 50% individuals → CENTRAL NERVOUS SYSTEM SIDE EFFECTS

During the first weeks of treatment
Abnormal dreams, dizziness, somnolence, mood disorder, insomnia, impaired concentration....
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EFAVIRENZ inactivated metabolites: 8-hydroxyefavirenz ++++, 7-hydroxyefavirenz, N-Glucuronoefavirenz (CYP3A4, CYP3A5, CYP2A6, UGT2B7).

Liver: CYP2B6 (Systemic clearance: 80%). Also expressed in brain (neuron and astrocyte).

GENETIC VARIABILITY
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**EFAVIRENZ** disposition and CENTRAL NERVOUS SYSTEM side effects

**Inactivated metabolites**

- 8-hydroxyefavirenz ++++
- 7-hydroxyefavirenz
- N-Glucuronoefavirenz

**CYP2B6**
(Systemic clearance: 80%)

Liver

**Modulator**
(31% of clearance variability)

**EXTENSIVE Metabolizer**
Carriers of 2 functional alleles
(~ 56% Caucasians)
(~ 31% Africans)

**INTERMEDIATE Metabolizer**
Heterozygotes for a non-functional allele
(~ 38% Caucasians)
(~ 49% Africans)

**POOR Metabolizer**
Carriers of 2 non-functional alleles
(~ 6% Caucasians)
(~ 20% Africans)

516G>T frequency
- Asian:17.4%
- West Europe: 21.4%
- Hispanic: 27.3%
- Subsaharian Africa: 45.5%
- African Americans: 46.7%

516G>T carriers
- Extensive: 39%
- Intermediate: 12.3%
- Poor: 6.7%

**Chromosome**
19q13.2

**Non functional Allelic variants Mutations**

- **CYP2B6*6**: 516G>T + 785A>G
- **CYP2B6*26**: 499C>G + 516G>T + 785A>G
- **CYP2B6*16**: 983T>C + 785A>G
- **CYP2B6*9B**: 983T>C
- **CYP2B6*27**: 593T>C
- **CYP2B6*28**: 1132C>T
Efavirenz concentration-time curve in CYP2B6 genotyped patients


- **POOR metabolizer (T/T)** and **INTERMEDIATE metabolizer (G/T)**
- **EXTENSIVE metabolizer (G/G)**

- **Prolonged half-life**
- **Excessive drug plasma level (OR:35)** 40% of Poors > 4 µg/ml
  20% of Intermediates > 4 µg/ml
- **Greater drug plasma exposure**
- **Higher intracellular concentrations in leucocytes**
- **More frequent and more severe CNS side effects**
- **Higher risk of resistance after treatment discontinuation**

- **Subtherapeutic drug plasma concentration (20% of EM < 1 µg/ml)**
- **Plasma exposure reduction by CYP2B6 efavirenz autoinduction** may influence the long-term therapy outcome
Efavirenz concentration-time curve in CYP2B6 genotyped patients

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  - Subtherapeutic drug plasma concentration (20% of EM < 1 µg/ml)
  - Plasma exposure reduction by CYP2B6 efavirenz autoinduction may influence the long-term therapy outcome

**Promising approach**
- Toward the prediction of efavirenz toxicity and resistance
- For individualizing efavirenz dose
  - Simulation: 35% EFV dose reduction in PM would maintain drug exposure within the therapeutic range
  - Successful EFV dose individualization

**CYP2B6 GENOTYPING**
- Clinical utility needs to be better defined
  - Useful adjuvant for a personalized therapy strategy based on measurements of plasma concentration
EFAVIRENZ disposition and CENTRAL NERVOUS SYSTEM side effects

Inactivated metabolites
- 8-hydroxyefavirenz ++++
- 7-hydroxyefavirenz
- N-Glucuronoefavirenz

Genetic polymorphism
- CYP3A4, CYP3A5, CYP2A6, UGT2B7 (30% of clearance variability)

Modulator (60% of clearance variability)
- GENOTYPING CYP2B6
  + CYP3A4, CYP3A5, CYP2A6 and UGT2B7

More efficient strategy for identification of at risk patients

NEVIRAPINE-associated HYPERSENSITIVITY reaction and NNRTI-associated HEPATITIS

**NEVIRAPINE** (NNRTI of HIV-1, Viramune®):

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- **Higher frequency in:**
  - Naïve female patients with CD4⁺ cell count >250 cells/mm³
  - Naïve male patients with CD4⁺ cell count >400 cells/mm³

- **Lower frequency in:**
  - Patients with low CD4⁺ cell count before treatment (Protector factor)

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**ASYMPTOMATIC SERUM TRANSAMINASE ELEVATION**
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**ASYMPTOMATIC SERUM TRANSAMINASE ELEVATION**

**MECHANISM:** CD4+ T-Cell dependent immune response triggered by nevirapine-associated antigens + Genetic predisposition

Participation of HLA Class II allele

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<th>HLA-DRB1*0101 + CD4+ cell &gt; 25% → Higher risk (OR 17) of hypersensitivity (PPV: 40%, NPV: 96%)</th>
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**MECHANISM:** Genetic polymorphism of MDR1 (P-gp): a transporter that promotes active efflux of multiple drugs from human cells

- **ABCB1 (MDR1 gene) c.3435C>T mutation → Reduced risk of NNRTI-associated hepatotoxicity (OR 0.42)**
- **5% of Caucasians** (Alteration of the export activity of P-gp in the intestinal tract?)
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  - **HLA-Cw*8 (Japanese) →** Hypersensitivity (13% in patients with hypersensitivity vs 0% in tolerants)

**MECHANISM:** Genetic polymorphism of MDR1 (P-gp): a transporter that promotes active efflux of multiple drugs from human cells

ABC1 (MDR1 gene) c.3435C>T mutation → Reduced risk of NNRTI-associated hepatotoxicity (OR 0.42)

5% of Caucasians (Alteration of the export activity of P-gp in the intestinal tract?)

**GENOTYPING**

Promising approach toward a safer use of NNRTI

Clinical utility needs to be better defined & research is needed in non-Caucasian populations
<table>
<thead>
<tr>
<th>ATAZANAVIR (Reyataz®):</th>
<th>Most widely used PI due to its potency, low pill burden and favorable long-term tolerability</th>
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<td>INDINAVIR (Crixivan®):</td>
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6% clinical jaundice

**HYPERBILIRUBINEMIA**

**UGT1A1**

**BILIRUBINE**

**UDP-G acid**

**UDP acid**

**REDUCED activity**

**HETEROZYGOUS**

**INTERMEDIATE activity**

**NORMAL glucuronidation**

**GLUCUROCONJUGATED BILIRUBINE**

**Liver**

**Hyperbilirubinemia**

**A(TA)7TAA / A(TA)7TAA**

**UGT1A1*28 / UGT1A1*28**

**A(TA)6TAA / A(TA)6TAA**

**Normal UGT1A1 Expression**

**Normal glucuronidation**

**Expression**

**Low glucuronidation**

**Gilbert’s syndrome**

**Hyperbilirubinemia**

**~ 12 % Asia (UGT1A1*6)**

**~ 15 % Caucasians**

**~ 20 % Africans**

**Transcription factor IID**

**5, 6, 7 or 8 (TA) repeats**

**UGT1A1*6 (Asia)**

**~ 35 % caucasian**

**UPTAKE**

**CHROMOSOME 2q37**

**~ 51 % caucasian**
**ATAZANAVIR** (Reyataz®): Most widely used PI due to its potency, low pill burden and favorable long-term tolerability

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**HETERogenous Activity**

- **A(TA)₇TAA / A(TA)₇TAA**
  - UGT1A₁*28 / UGT1A₁*28
  - ~ 12% Asia (UGT1A₁*6)
  - ~ 15% Caucasians
  - ~ 20% Africans

- **A(TA)₆TAA / A(TA)₆TAA**
  - ~ 51% Caucasian

**Expression**

- Low glucuronidation
- Gilbert’s syndrome
- Hyperbilirubinemia

**Reduced activity**

- ~ 35% Caucasian
- ~ 51% Caucasian
- ~ 20% Africans

**Hyperbilirubinemia Jaundice**

**Competitive inhibition**

- UGT1A₁
- UDP-G acid
- UDP

**Glucuronic Acid**

- Conjugated bilirubine
- Liver

**Transcription factor IID**

- A(TA) repeats
- 5, 6, 7 or 8 (TA) repeats

**Promoter**

- 1 2 3 4 5

**UGT1A1**

- Chromosome 2q37

**Bilirubine**
**ATAZANAVIR** an **INDINAVIR** associated **HYPERBILIRUBINEMIA**

**ATAZANAVIR** (Reyataz®): Most widely used PI due to its potency, low pill burden and favorable long-term tolerability

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<th>ABCB1 c.3435T/T</th>
<th>Genotype</th>
<th>↓ Plasma level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>~ 5% caucasian</td>
<td></td>
</tr>
</tbody>
</table>

**UGT1A1**

**BILIRUBINE**

**UDPG** acid

**UDP**

**GLUCURO CONJUGATED BILIRUBINE**

Liver

Hyperbilirubinemia

Jaundice

**Competition inhibition**

**Reduced activity**

**Transcription factor IID**

**A(TA)TAA** 5, 6, 7 or 8 (TA) repeats

**Promoter**

1 2 3 4 5

**ATG**

**TAG**

**Expression**

Low glucuronidation

**Gilbert’s syndrome**

Hyperbilirubinemia

**Normal UGT1A1 Expression**

Normal glucuronidation

**Hétérozygote** Intermediate activity

~ 51% caucasian

~ 35% caucasian

~ 12% Asia (UGT1A1*6)

~ 15% Caucasians

~ 20% Africans

~ 6% clinical jaundice

**Abbreviations**

* A(TA)6TAA / A(TA)6TAA
  * UGT1A1*28 / UGT1A1*28

* A(TA)7TAA / A(TA)7TAA
  * UGT1A1*28 / UGT1A1*28

* Gilbert’s syndrome

**Chromosome 2q37**

**UGT1A1**

~ 5% caucasian

↓↓ ↓↓

Plasma level
### ATAZANAVIR an INDINAVIR associated HYPERBILIRUBINEMIA

<table>
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<tr>
<th>Patients treated with atazanavir or indinavir</th>
<th>Asymptomatique Hyperbilirubinemia</th>
<th>Hyperbilirubinemia Grade 3-4 (&gt; 3.2 mg/ml)</th>
<th>At least 2 episodes of jaundice within a 6 years period of treatment</th>
<th>Total population</th>
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<tbody>
<tr>
<td>Homozygotes UGT1A1*28</td>
<td>90%</td>
<td>80%</td>
<td>67%</td>
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</tbody>
</table>

OR : 2.96

Severe hyperbilirubinemia

---

ATAZANAVIR an INDINAVIR associated HYPERBILIRUBINEMIA

Patients treated with atazanavir or indinavir

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Carrier of one UGT1A1*28 allele ~ 50% Caucasians

Severe hyperbilirubinemia

OR : 2.96


- Prospective UGT1A1 genotyping could be of value to identify patients at high risk of developing a severe hyperbilirubinemia and a clinical jaundice upon atazanavir or indinavir treatment

UGT1A1 (ABCB1) GENOTYPING

Theoretical impact of genotyping

Prior UGT1A1 genotyping

5.8% hyperbilirubinemia
In the jaundice range (> 2.5 mg/dl)

21.6% hyperbilirubinemia
the jaundice range (> 2.5 mg/dl)
### ATAZANAVIR an INDINAVIR associated HYPERBILIRUBINEMIA

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Severe hyperbilirubinemia

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### UGT1A1 (ABCB1) GENOTYPING

#### Theoretical impact of genotyping

- Prior UGT1A1 genotyping
  - 5.8% hyperbilirubinemia
  - In the jaundice range (> 2.5mg/dl)

- Prior UGT1A1 genotyping
  - 21.6% hyperbilirubinemia
  - In the jaundice range (> 2.5mg/dl)

- Risk is further increased by ABCB1 polymorphism
- Prospective UGT1A1 and ABCB1 genotyping could be more efficient

---

RALTEGRAVIR  
HIV integrase inhibitor

INACTIVATED METABOLITE  
N-Glucuronoraltigravir

Liver

UGT1A1

GENETIC VARIABILITY

Homozygotes UGT1A1*28 (N = 30)
Homozygotes UGT1A1*1 (N = 27)

Modest differences in raltegravir plasma concentrations

No dose adjustment required

Not clinically significant

Case-Control study

**TENOFOVIR associated RENAL TOXICITY**

| **TENOFOVIR (Viread®):** | NRTI among the most widely used anti-retroviral drug  
Efficient and well tolerated but: |
|--------------------------|--------------------------------------------------------------------------------|
| **RENAL PROXIMAL TUBULOPATHY** | 2% individuals  
Primary adverse effect of tenofovir  
Especially in advanced HIV Infection |
TENOFOVIR (Viread®): NRTI among the most widely used anti-retroviral drug
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Primary adverse effect of tenofovir
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**SYSTEMIC CIRCULATION**
- Glomerular filtration
- And
- Active tubular secretion
- **GENETIC VARIABILITY**

**URINE**
TENOFOVIR associated RENAL TOXICITY

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SYSTEMIC CIRCULATION
Glomerular filtration
And
Active tubular secretion
URINE

GENETIC VARIABILITY

Proximal tubule Cell
[ TENOFOVIR ]
(35%)

OCT2
OAT1
OAT2
OAT3
ABCC1
ABCC4
ABCC2
ABCB1

Tenofovir
Baso-lateral membrane
Apical membrane

Tenofovir Renal clearance ↓↓ ↓↓ 60%

ABCC4 knock-out mice

Mutation carriers

c.-24G>C
Mutation (OR: 4.2)
c.1249C>A
Tenofovir
Tenofovir
Tenofovir
Tenofovir

C.3463A>G
Mutation

Tenofovir
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OCT2
OAT1
OAT2
OAT3
ABCC1
ABCC2
ABCC4
ABCB1

Tenofvir
Tenofvir
Tenofvir

To be confirmed
Further studies in this field are needed

NRTI associated PERIPHERAL NEUROPATHY

ACTG 384 Study

| Didanosine (Videx®) + Stavudine (Zérit®) | 108 (73%) | 3 years later | 147 (29%) |
| Zidovudine (AZT) + Lamivudine (Epivir®) | 39 (27%) | PERIPHERAL NEUROPATHY |

509 Patients
Accumulation of pyruvic and lactic acid

NRTI associated PERIPHERAL NEUROPATHY

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PERIPHERAL NEUROPATHY

and lactic acidosis Various effects

Various effects

Cellular energy production
Oxidative phosphorylation

MITOCHONDRIAL DEPLETION or DYSFUNCTION

MODULATOR GENETIC FACTOR

NRTI Inhibition

Mitochondrial DNA polymerase γ
NRTI associated PERIPHERAL NEUROPATHY

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NRTI

Inhibition

Mitochondrial DNA polymerase γ

POLγ gene deleterious mutation
845G>A (R964C)

Mitochondrial DNA
Haplotype T
ND5 region
7028C>T + 10398G>A + 13368G>A
MtND2(+) LHON 4917G
(OR: 5.4)

Mitochondrial depletion or dysfunction

Cellular energy production
Oxidative phosphorylation

Accumulation of pyruvic and lactic acid

Alteration of iron adsorption and transport

HFE gene mutation
845G>A (C282Y)
Protective (OR: 0.3)

Various effects

and lactic acidosis

Patients

108 (73%)

147 (29%)

39 (27%)
NRTI associated PERIPHERAL NEUROPATHY

ACTG 384 Study

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and lactic acidosis
Various effects

Mitochondrial DNA polymerase γ

Cellular energy production
Oxidative phosphorylation
MITOCHONDRIAL DEPLETION or DYSFUNCTION

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Protective (OR: 0.3)

To be confirmed
Further studies in this field are needed

Canter et al. The mitochondrial pharmacogenetic of haplotype T and antiretroviral therapy-associated peripheral neuropathy. 2008 Pharmacogenom J 8: 71-7
ZIDOVUDINE and LAMIVUDINE associated INTRACELLULAR DRUG LEVEL

**Clinical significance is to be determined**


NRTI associated PANCREATITIS

**Didanosine** (Videx®) + **Stavudine** (Zérit®)

- 4.5% pancreatic alterations
- 3.6% Asymptomatic hyperamylasemia
- 1.9% **PANCREATITIS**

**Gene**
- **SPINK-1**
  - **Encoded protein**: Serine protease inhibitor kazal-1 (trypsin inhibitor in the cytoplasm of pancreatic acinar cells)
- **CFTR**
  - **Encoded protein**: Cystic fibrosis transmembrane conductance regulator (Cl- channel which also conducts thiocyanate ions)

**Mutations**
- **Swiss cohort**: 40% of patients with acute pancreatitis vs 14% in controls

**Associated disorders**
- **Pancreatitis**
- Cystic fibrosis, Male infertility, Pancreatitis

Further studies in this field are needed

*Felley et al. The role of CFTR and SPINK-1 mutations in pancreatic disorders in HIV-positive patients. A case-control study. 2004 AIDS 18: 1521-7*
NRTI, particularly Stavudine (Zérit®) → LIPOATROPHY

Peripheral fat loss
Thinning of face, extremities and buttocks
Stigmatize the patient and affect his quality of life
NRTI associated LIPOATROPHY

NRTI, particularly Stavudine (Zérit®)

LIPOATROPHY

Peripheral fat loss
Thinning of face, extremities and buttocks
Stigmatize the patient and affect his quality of life

Genetic risk factors for developing lipoatrophy have been identified

- **TNF-α** -238G>A within the promoter region (controversial)
- **APOC3** -455CC genotype
- **ADRB3** 64TT genotype
- **Fas** -670GG genotype

<table>
<thead>
<tr>
<th>Gene</th>
<th>Why?</th>
</tr>
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<tbody>
<tr>
<td><strong>TNF-α</strong></td>
<td>Tumor necrosis factor alpha</td>
</tr>
<tr>
<td></td>
<td>Cytokine promoting adipocyte apoptosis</td>
</tr>
<tr>
<td></td>
<td>High level of expression in adipose tissue of HIV patients</td>
</tr>
<tr>
<td><strong>APOC3</strong></td>
<td>Apolipoprotein C3</td>
</tr>
<tr>
<td></td>
<td>Involved in lipid metabolism, located on VLDL</td>
</tr>
<tr>
<td><strong>ADRB3</strong></td>
<td>Beta-3 Adrenergic receptor,</td>
</tr>
<tr>
<td></td>
<td>G-protein coupled receptor for catecholamines</td>
</tr>
<tr>
<td></td>
<td>Major role in lipolysis in subcutaneous fat</td>
</tr>
<tr>
<td><strong>Fas and FasL</strong></td>
<td>Main genes that control apoptosis in the immune system</td>
</tr>
<tr>
<td><strong>IL-1β, PPARγ, FIZZ-3</strong></td>
<td></td>
</tr>
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</table>

To date, genetic predisposition of fat loss is not possible

PI-associated METABOLIC and MORPHOLOGICAL ABNORMALITIES

**METABOLIC abnormalities**
- Lipid metabolism
- Hyperlipidemia (very common)
- Glucose metabolism
- Insulin resistance
- Diabetes (5% of patients)

**MORPHOLOGICAL abnormalities**
- Fat accumulation
  - Visceral (20-70% of patients)
  - Subcutaneous (trunk, dorsocervical)
  - "Buffalo hump"

- Affect quality of life, adherence to treatment
- Increase the risk of cardiovascular disease

**MUTATIONS**
- APOC3 + APOC3: Severe hypertriglyceridemia
- APOA5: Severe hypertriglyceridemia
- APOC3: Hypertriglyceridemia protection (Hispanic, not black or white)
- ABCA1 + APOA5 + APOC3 + APOE + CTEP: Plasma triglyceride and HDL plasma level
- APOC3 + APOC3 + TNF-α: Lipoatrophy
- ADRB2: Fat accumulation
- IL1-β: Lipodystrophic syndrome

**GENE**
- **APOA1**: Apolipoprotein A1
  - Encoded protein: Apolipoprotein A1
  - Rational: Involved in lipid metabolism
  - Function: Involved in lipid metabolism
  - High level of expression in adipose tissue of HIV patients

- **APOA5**: Apolipoprotein A5
  - Encoded protein: Apolipoprotein A5
  - Rational: Involved in lipid metabolism

- **APOC3**: Apolipoprotein C3
  - Encoded protein: Apolipoprotein C3
  - Rational: Involved in lipid metabolism

- **APOE**: Apolipoprotein E
  - Encoded protein: Apolipoprotein E
  - Rational: Involved in lipid metabolism

- **TNF-α**: Tumor necrosis factor alpha
  - Encoded protein: Tumor necrosis factor alpha
  - Rational: Cytokine promoting adipocyte apoptosis

- **CTEP**: Cholesteryl ester transfer protein
  - Encoded protein: Cholesteryl ester transfer protein
  - Rational: Facilitates the transport of CE and TG between lipoproteines

- **ABCA1**: ABC transporter A1
  - Encoded protein: ABC transporter A1
  - Rational: Associated with plasma lipid level

Genetic factors may influence the development of lipid abnormalities during PI treatment
Genetic profiling may contribute to identify at risk patients
Most relevant GENETIC DETERMINANTS of antiretroviral drug adverse effects

<table>
<thead>
<tr>
<th>DRUG</th>
<th>GENE</th>
<th>REPORTED ASSOCIATION</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td>• Abacavir</td>
<td>HLA-B*5701</td>
<td>Hypersensitivity reaction</td>
<td>Genotyping before prescription is recommended by all guidelines</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Genotyping is cost-effective</td>
</tr>
<tr>
<td>• Tenofovir</td>
<td>ABCC2</td>
<td>Renal proximal tubulopathy</td>
<td>To be confirmed in # ethnies</td>
</tr>
<tr>
<td>• Lamivudine, Zidovudine</td>
<td>ABCC4</td>
<td>Intracellular exposure of active metabolite</td>
<td>Uncertain clinical significance</td>
</tr>
<tr>
<td>• NRTIs</td>
<td>TNF-α</td>
<td>Earlier onset of lipoatrophy</td>
<td>Controversial</td>
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<td>• NRTIs</td>
<td>Mitochondrial DNA</td>
<td>Peripheral neuropathy</td>
<td>Tissue-specific mt DNA depletion</td>
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<td>May also play a role</td>
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<td>SPINK-1</td>
<td>Pancreatitis</td>
<td>Also in general population</td>
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<td>• Nevirapine</td>
<td>HLA-DRB1*0101</td>
<td>Hypersensitivity / Hepatotoxicity</td>
<td>Low CD4+ attenuates the risk</td>
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<td>HLA-Cw8</td>
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<td>ABCB1</td>
<td>Hepatotoxicity</td>
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<td>CYP2B6</td>
<td>Plasma exposure / CNS toxicity</td>
<td>Successfull EFV dose individualization</td>
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<td>CYP2B6</td>
<td>↑↑↑↑ risk of Plasma exposure</td>
<td>To be confirmed in other populations</td>
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<td>Genotyping prior TRT proposed</td>
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<td>ABCB1</td>
<td>Hyperbilirubinemia and jaundice</td>
<td>Greater plasma level</td>
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<tr>
<td>• Nelfinavir</td>
<td>CY2C19</td>
<td>↑↑↑↑ risk of drug exposure</td>
<td>To be confirmed in # ethnies</td>
</tr>
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<td>• Indinavir</td>
<td>CYP3A5</td>
<td>Faster oral clearance</td>
<td>To be confirmed in # ethnies</td>
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<td>APOA5</td>
<td>↑↑↑↑ risk of hyperlipidemia</td>
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<td>APOE</td>
<td>↑↑↑↑ risk of hyperlipidemia</td>
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<td>• PIs</td>
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<td>• Raltegravir</td>
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<td>• Maraviroc</td>
<td>CCR5</td>
<td>No effect on virological response</td>
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### Natural History Modifiers

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<td>TLR9</td>
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### Treatment Response

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Pharmacogenomics Databank

This databank enables you to search our comprehensive database in a variety of different ways, for example by gene, metabolising enzyme, drug transporter, toxicity type or treatment response.

The intuitive, dynamically driven process helps you to navigate the wealth of existing pharmacogenomic information to access the specific information you require. The drill-down search facility is based on an easy to follow, step-by-step approach. To further help you, links to all currently available supporting references are displayed for your particular search request.

Please use the Show/hide menu option (top left) if you want to expand the width of the results table.

Search the databank

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SEQUENCAGE COMPLET DU GENOME HUMAIN

3.5 $10^9$ Nucléotides
23 000 Gènes
20 $10^6$ SNP (single nucleotide polymorphism)
800 000 Fréquence significative
150 000 Affectent la séquence codante de gènes
60 000 Ont une conséquence fonctionnelle

Probablement beaucoup plus
(Constitutional) COPY NUMBER VARIATIONS (CNV)

- Very common phenomenon: 1447 CNV, 360 Mb, 12% of the human genome
- Enzyme involved in xenobiotic metabolism

Deletion: CYP2A6, CYP2B6 (partial), CYP2D6, GSTM1, GSTT1, SULT1A1, SULT1A3, UGT2B7, UGT2B10, UGT2B11, UGT2B17

Amplification: CYP2A6, CYP2D6, SULT1A1, SULT1A3
EPIGENETIC MECHANISMS

Histone modification

- Kinases
- Phosphatases
- Protein arginine methyltransferases
- Histone acetyltransferases
- Histone deacetylases
- Histone demethylases

DNA methylation

- DNA methyltransferases
- Methylation
- Phosphorylation
- Acetylation

Epidemiology

- DNA Methylation
- Histone modification
- Micro RNA

Environmental factors

- Nickel
- Chrome
- Arsenic
- Cadmium
- Tabac, alcool, Thé vert

Gene expression

- Oncogenes
- Tumor suppressor genes
- Genes involved in cellular disposition of xenobiotics

Dietary factors

- Folic acid
- S-adenosyl methionine
- Methionine
- 5, 10 methylene THF

Pathways

- MTHFR
- BHMT
- SAM
- SAHH
- THF
- GHMT
- MAT
- Diethylstilbestrol
Micro ARN

Gene

↓↓ ↓↓

Gene expression

↑↑ ↑↑

Gene expression

GENES

- Prolifération cellulaire
- Apoptose
- Différenciation cellulaire
- Réparation ADN
- Morphogenèse
- Enzymes
- Transporteurs
- Xénosensors

} Prise en charge cellulaire des xénobiotiques
Transgenerational Epigenetic Inheritance of Xenobiotic Effects

**XENOBIOTIC EXPOSURE**

Diethylstilbestrol
First 3 months of pregnancy

MOTHER

Aberrant methylation pattern of the promoters of estrogen-responsive genes associated with the development of reproductive organs

DAUGHTER

Aberrant Methylation Pattern Transfer

Reproductive tract abnormalities
+ Vaginal and cervical cancer at young age

GRAND DAUGHTER
ANNOUNCEMENTS

MONDAY APRIL 11, 2011
New Sequence Data is available

Additional sequence data from the 1000 Genomes full project are now available. The current sequence.index file can be found at [20110411.sequence.index](20110411.sequence.index)

Data access links: EBI / NCBI / Instructions for data download and Aspera

Sequence index and Statistics files

Sequence index file format

---

MONDAY FEBRUARY 28, 2011
New Sequence Data is available

Additional sequence data from the 1000 Genomes full project are now available. The current sequence.index file can be found at [20110228.sequence.index](20110228.sequence.index)

Data access links: EBI / NCBI / Instructions for data download and Aspera

Links to additional information: Sequence index file format

---

WEDNESDAY FEBRUARY 16, 2011
Release of Full Project Phased Alignments
The New

GS Junior

Instrument & Workflow
Data Analysis
Research Applications
Publications & Resources

Contact Us

Simplify Amplicon Sample Prep
Fluidigm

Watch the GS Junior Launch Video

Now Available!
### Initial Information

Is this patient new to WarfarinDosing.org?
- [ ] New patient
- [ ] Existing patient

Warfarin doses taken so far*: -Select-

*Required

### Required Patient Information

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-Select- Accept Terms of Use - ESTIMATE WARFARIN DOSE
Problèmes d'organisation au plan national

- Dispersée
- Fractionnée
- Manque de visibilité
- Manque de coordination

Problèmes économiques

- Selon la région, l'hôpital
- Hétérogénéité des modes de financement et de fonctionnement

Inégalités

- d'accès aux tests
- de prise en charge et de paiement
- de qualité et fiabilité des analyses
Considérations éthiques, légales, sociales et économiques

Proposition du test

Prospectif ou Rétrospectif

- Connaissances
- Médecin
- Patient
- Informations scientifiques
- Fréquence des phénotypes, pénétrance
- Recommandations
- Autorités
- Industriels
- Médiacment / pathologie
- Facilités à réaliser le test
- Coût de l'analyse
- Responsabilités
- Médicales
- Autorités

Consentement éclairé écrit du patient

Au cas par cas

- Dépend de l'information que transporte le test
  - Pharmacogénétique
    - Révélatrice d'une pathologie
    - Facteur de risque pathologique ou autre
- Contenu va dépendre
  - Capacité du patient à comprendre l'information et ses conséquences
  - Effet psychologique du résultat du test
  - Informations complémentaires devront être données
Considérations éthiques, légales, sociales et économiques

Réalisation de l'analyse

Qui doit faire les tests et dans quels conditions ?
• Vide juridique
• Professionnel de la santé agréés dans des structures autorisées
  • Possibilité d'information touchant à la santé
  • Difficultés d'interprétation et de fiabilité des tests

Résultats et interprétation de l'analyse

Fournis au prescripteur
• Toxicologue ?
• Pharmacologue ?
• Généticien ?
• Conseil génétique ?

Interprétés par le labo et le prescripteur
• Traitement / emploi alternatif ou non
• Thérapeutique / exposition "off-label"
• Balance bénéfice / risque

Utilisation du résultat
• Dépend de nb facteurs
Considérations éthiques, légales, sociales et économiques

Propriété et confidentialité de l'information

Pour le sujet
- Résultats inclus dans le dossier médical
- Information disponible à l'ensemble du personnel médical directement responsable de sa santé mais appréhende la possibilité d'un accès à ces informations par d'autres groupes sociaux

Pour la famille
Informations donnés par le médecin aux patients avec ses conséquences
- Conséquences possibles Information PG+++ ex: situation d'urgence
  Susceptibilité à une pathologie ou autres
- Réponse ? Il est évident que dans certaines circonstances le médecin doit encourager le patient à donner ces informations au reste de la famille.

Autres groupes sociaux
- Inconvénients Patient "difficile à traiter " "cher à traiter" ou "maladie sérieuse intraitable 
  - Informations associées (maladie, addictions)

- Avantages Patient pourra être traité efficacement, mieux que la population générale

- Problème de l'information révélée indirectement
Polymorphic enzymes and polymorphic transmembrane transporters involved in the disposition of antiretroviral drugs

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<td>2C19, 3A4/3A5</td>
<td>B1, C1</td>
<td>G2</td>
<td>-</td>
<td>OCT1, OCT2, SLCO2B1</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>3A4/3A5</td>
<td>B1, C1, C2</td>
<td>G2</td>
<td>-</td>
<td>OCT1, OCT2, SLCO2B1</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>3A4/3A5</td>
<td>B1, C1, C2</td>
<td>G2</td>
<td>SLCO1A2, 1A3, 1B1</td>
<td>OCT1</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>3A4/3A5</td>
<td>B1</td>
<td>-</td>
<td>-</td>
<td>SLCO2B1</td>
</tr>
<tr>
<td><strong>CCR5 antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>3A4/3A5</td>
<td>B1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>-</td>
<td>B1</td>
<td>-</td>
<td>SLC22A6</td>
<td>-</td>
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</tbody>
</table>
**HLA-B*5701 and Abacavir-induced Hypersensitivity Syndrome**

**ABACAVIR** (Ziagen®): Potent and well tolerated NRTI

1 – 9% individuals → **HYPERSENSITIVITY REACTION**

- Potentially lethal (0.03%)
- Multisystem involvement
- Rash, fever, gastrointestinal, constitutional and respiratory manifestations

**Involvement of genetic factors in abacavir hypersensitivity reaction**

Peyréére et al. Hypersensitivity related to abacavir in two members of the a family. Ann Pharmacother 2001; 35: 1291-1292

**Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to abacavir**

Mallal et al. Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcripase inhibitor abacavir. Ann Pharmacother 2002; 359: 727-732

**Association confirmed in other cohorts of different ethnicities**

Peyréére et al. Hypersensitivity related to abacavir in two members of the a family. Ann Pharmacother 2002; 359: 1291-1292

**Mechanism of the hypersensitivity reaction to abacavir**

**Clinical utility of HLA-B*5701 screening in preventing hypersensitivity to abacavir**


**HLA-B*5701 genotyping in preventing abacavir hypersensitivity is cost-effective**

Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to abacavir

Prevalence of HLA-B*5701 alleles (%)

Hypersensitivity to abacavir

Tolerant to abacavir

p < 1x 10^{-3}

OR: 117
HLA-B*5701 and Abacavir-induced Hypersensitivity Syndrome

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1 – 9% individuals → **HYPERSENTIVITY REACTION**

After a few week upon intiation
Potentially lethal (0.03%)
Multisystem involvement
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<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>5-20%</td>
</tr>
<tr>
<td>Thailand</td>
<td>4-10%</td>
</tr>
<tr>
<td>West Europe</td>
<td>5-7%</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>1-2%</td>
</tr>
<tr>
<td>Subsaharan Africa</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>China</td>
<td>0%</td>
</tr>
</tbody>
</table>

Prevalence of HLA-B*5701 alleles (%)

Assosciation Confirmed in other cohorts of different ethnicities


Hughes et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some populations. 2004 Pharmacogenomics 5: 203-11.

TENOFVIR associated RENAL TOXICITY

TENOFVIR (Viread®): INTI among the most widely used anti-retroviral drug

RENAL PROXIMAL TUBULOPATHIE: Primary adverse effect of tenofovir
Especially in advanced HIV Infection

To be confirmed
Further studies in this field are needed

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---

**SYSTEMIC CIRCULATION**

- **OCT2**
- **OAT1**
- **OAT2**
- **OAT3**
- **ABCC1**

**URINE**

- **Proximal tubule Cell**

**Glomerular filtration**

And

**Active tubular secretion**

- **OAT4**
- **ABCB1**
- **ABCC2**
- **ABCC4**

---

**To be confirmed**

Further studies in this field are needed

NRTI associated PERIPHERAL NEUROPATHY

ACTG 384 Study

509 Patients

Didanosine (ddl) + Stavudine (d4T) → 108 (73%) PERIPHERAL NEUROPATHY

Zidovudine (AZT) + Lamivudine (3TC) → 3 years later 147 (29%)

39 (27%)

First generation NRTIs

Didanosine (Videx®)

Stavudine (Zérit®)

Overactivation of Intracellular Phosphorylation

And/or

Cellular energy production

Oxidative phosphorylation

MITOCHONDRIAL DEPLETION or DYSFUNCTION

NRTI Inhibition

Mitochondrial DNA polymerase γ

POLγ gene mutation

845G>A (R964C)

Mitochondrial DNA Haplotpy T ND5 region

7028C>T + 10398G>A + 13368G>A

MitND2(*)LHON 4917G

(OR: 5.4)

Alteration of iron adsorption and transport

HFE gene mutation

845G>A (C282Y)

Protective (OR: 0.3)

Various effects

PERIPHERAL NEUROPATHY and lactic acidosis

Accumulation of pyruvic and lactic acid

To be confirmed

Further studies in this field are needed

Canter et al. The mitochondrial pharmacogenetic of haplotopy T and antiretroiral therapy-associated peripheral neuropathy. 2008 Pharmacogenom J 8: 71-7

Kallanpur A et al. Hemochromatosis gene mutation and peripheral neuropathy during antiretroiral therapy; AIDS 2006 20 1503-13