



HLA and Pharmacogenomics The Abacavir Story

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**EFI-ASHI-APHIA Summer School
2013 Stintino**

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Rx + ☹️ = 😊

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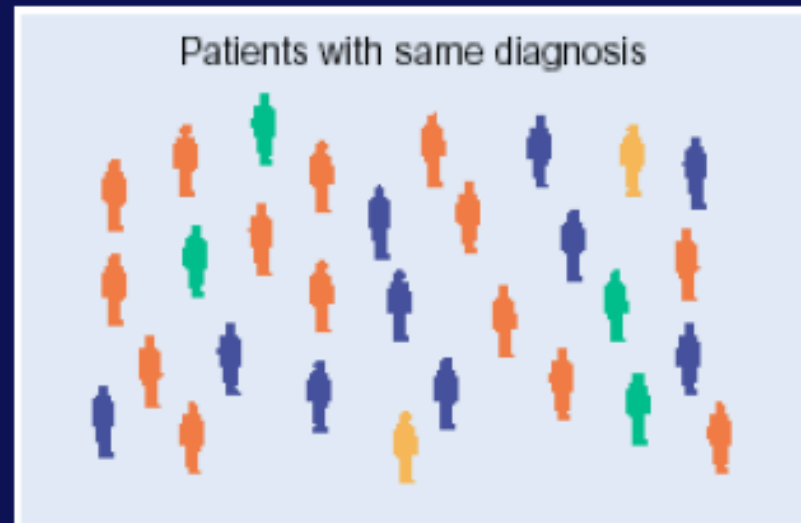
Differences in genetic constitution



PHARMACOGENETICS

The study of genetically
controlled variations in drug
response

Clinical Potential of Pharmacogenomics



1.



Predicted good
response to
tested drug

2.



Predicted poor or
nonresponse
Use different drug

3.



Predicted increased
toxicity risk
*Decrease dose or
use different drug*

GENETIC POLYMORPHISMS

Pharmacokinetic

- Transporters
- Plasma protein binding
- Metabolism

Pharmacodynamic

- Receptors
- Ion channels
- Enzymes
- Immune molecules

Table 1. Pharmacogenomic Biomarkers as Predictors of Adverse Drug Reactions.

Gene or Allele	Relevant Drug	Specificity of Biomarker	Percent of Patients with an Adverse Reaction to Drug [*]
<i>TPMT</i> (mutant)	6-Mercaptopurines	Very good	1–10
<i>UGT1A1</i> *28	Irinotecan	Good	30–40
<i>CYP2C9</i> and <i>VKORC1</i>	Warfarin [†]	Good	5–40
<i>CYP2D6</i> (mutant)	Tricyclic anti-depressants	Relatively good	5–7
HLA-B*5701	Abacavir	Very good	5–8
HLA-B*1502	Carbamazepine	Very good	10
HLA-DRB1*07 and DQA1*02	Ximelagatran	Good	5–7

* Percentages are of affected whites except that for HLA-B*1502, which is the percentage of affected Asians.

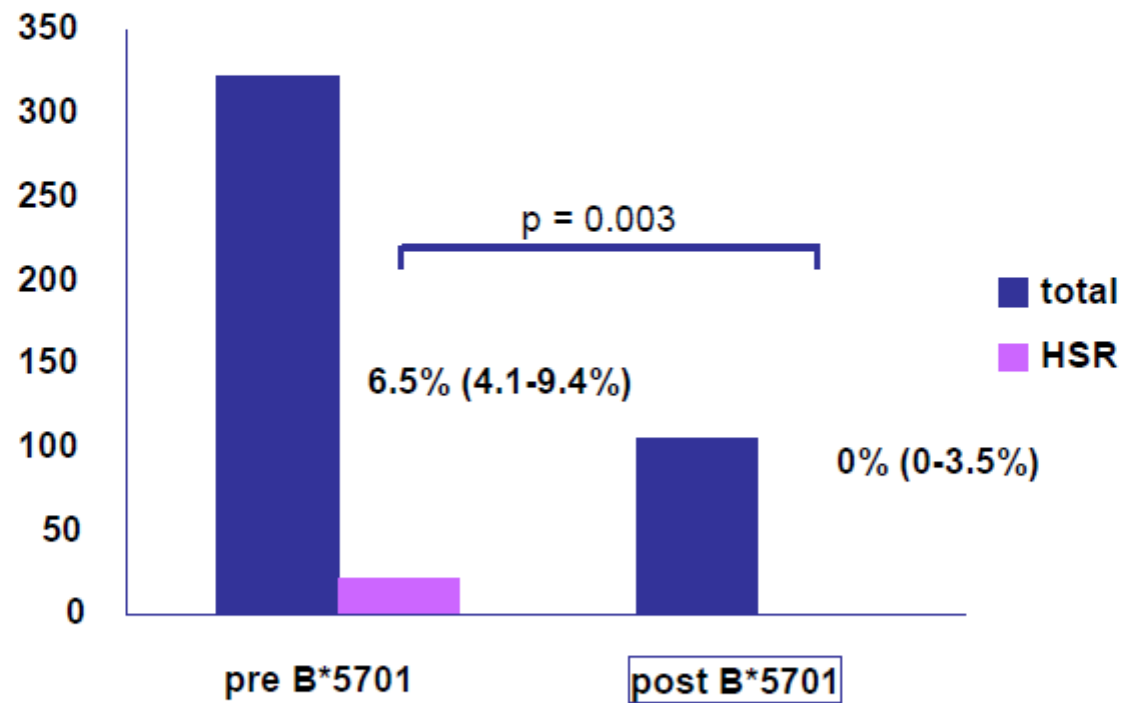
† Carriage of the *CYP2C9* and *VKORC1* alleles affects warfarin dosing.

Abacavir is a nucleoside reverse transcriptase inhibitor used in conjunction with other antiretroviral agents in the treatment of HIV infection.

Abacavir is generally well tolerated but can cause hypersensitivity in 5% to 8% of patients during the first 6 weeks of treatment

Hypersensitivity to abacavir is immunologically mediated, driven by conventional MHC-I antigen presentation and activation of HLA-B*5701. Activation of HLA-B*5701 restricted CD8+ T cells results in the secretion of the inflammatory mediators TNF-alpha and IFN-gamma and induces the delayed-type hypersensitivity reaction

Pharmacogenetics of Abacavir Hypersensitivity: Translation into Clinical Practice (Brighton Clinic)



Reeves *et al.* HIV Medicine 2006

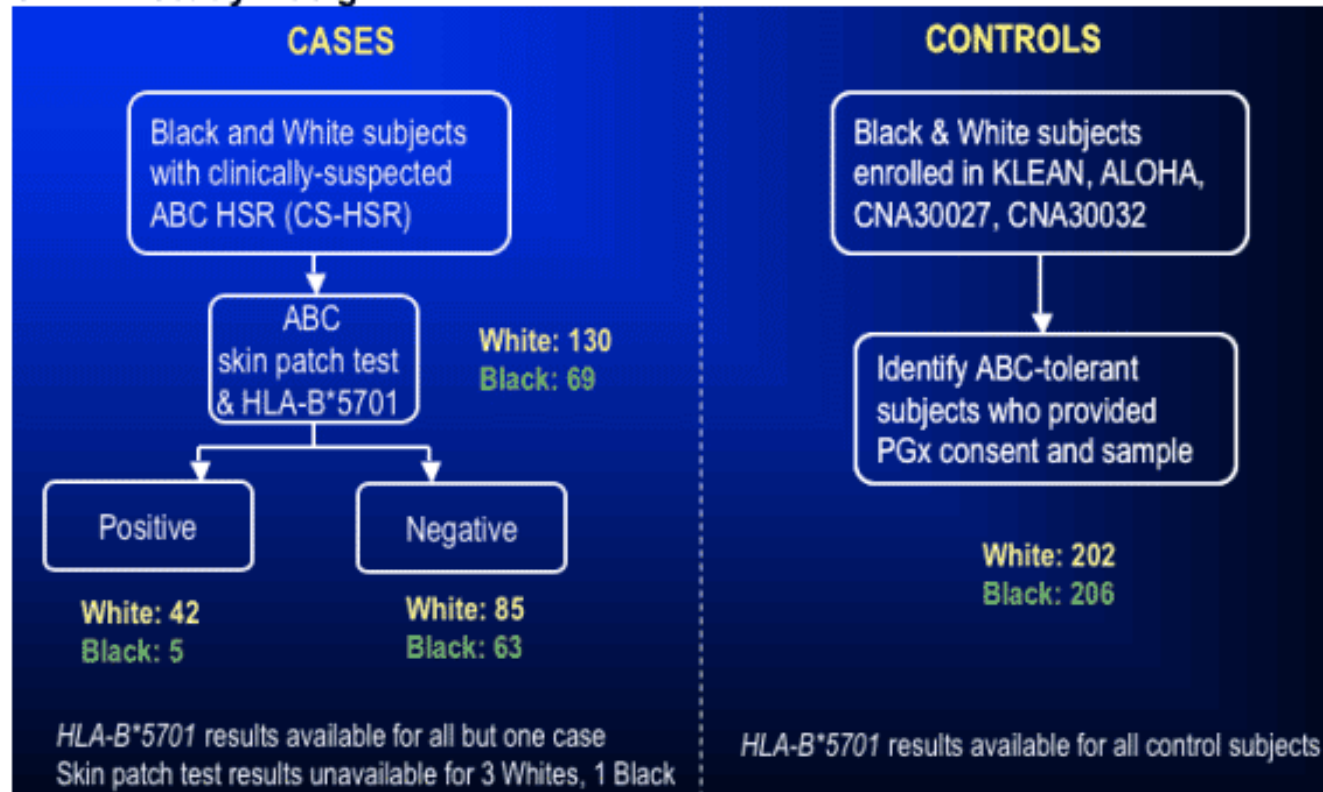
Abacavir Hypersensitivity and HLA Polymorphisms

	Abacavir Hypersensitive	Abacavir Tolerant	OR
HLA-B 5701	14 (78%)	4 (2%)	117
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73
HLA-B 5701, HLA-DR7, HLA-DQ3	13 (72%)	0 (0%)	822

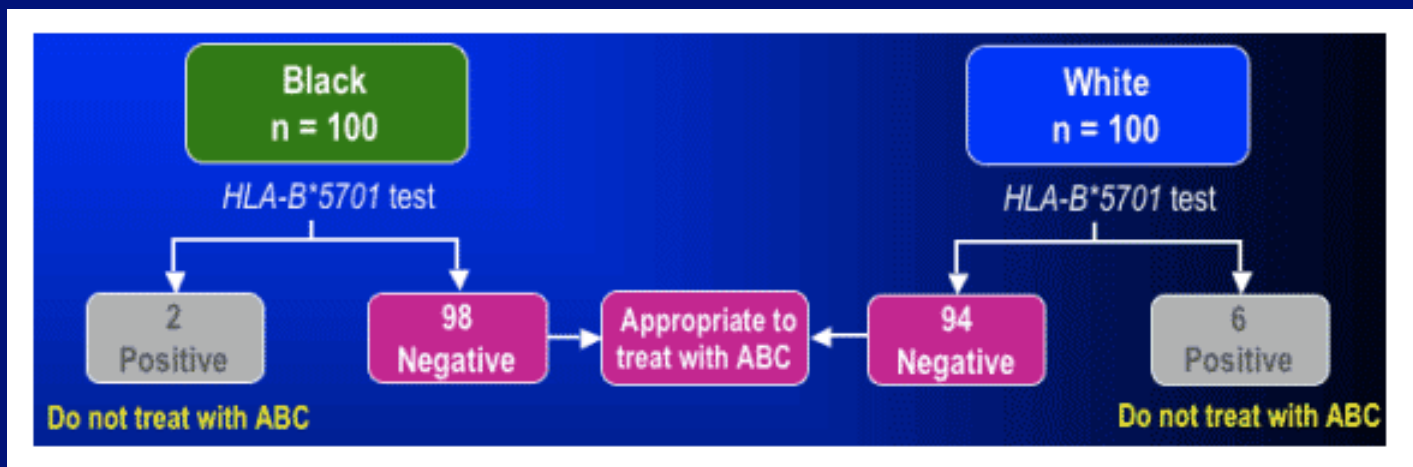
HLA = human leukocyte antigen; OR = odds ratio.

Mallal S, et al. *Lancet*. 2002;359:727-732.

SHAPE Study Design

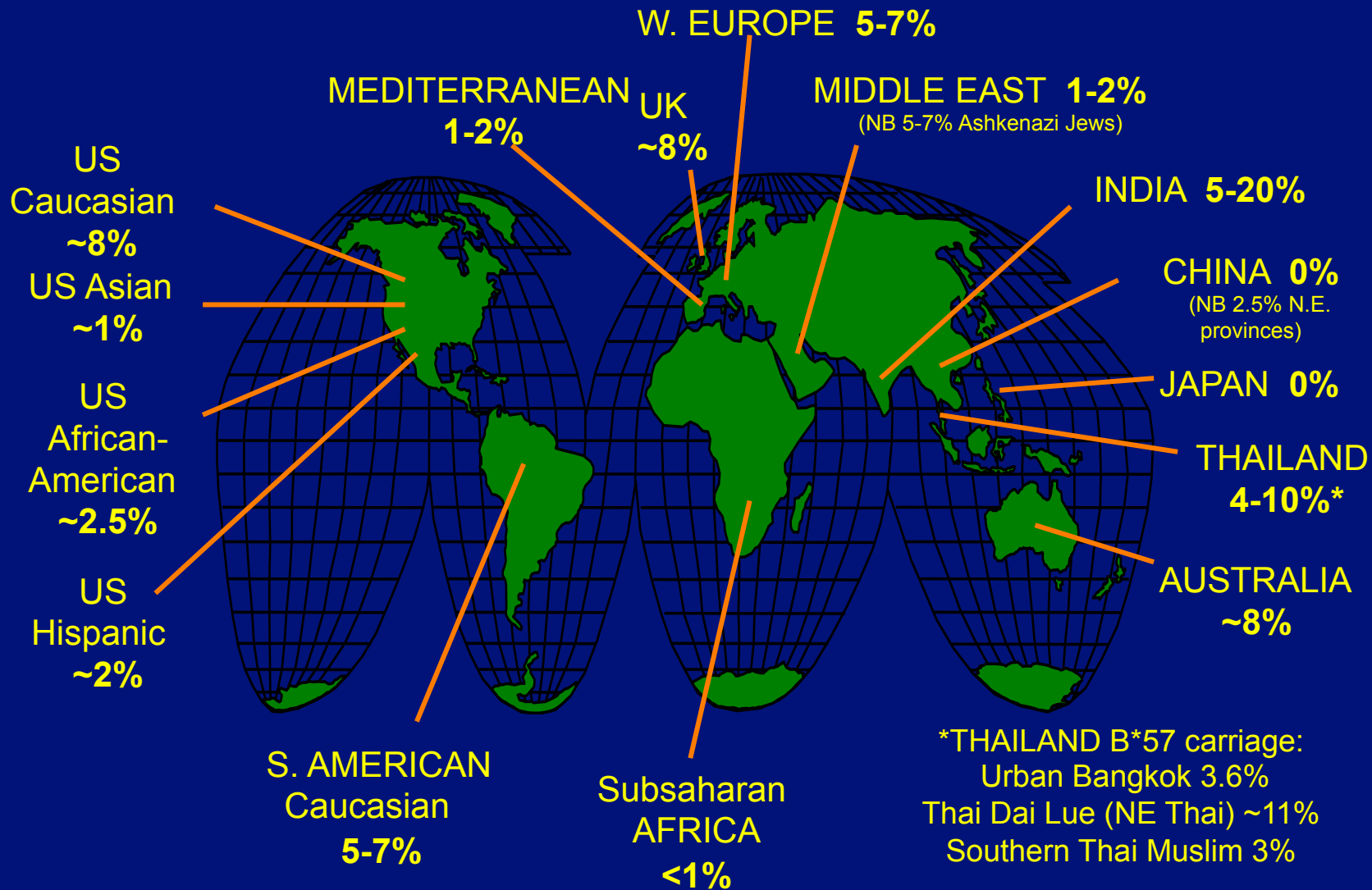


Clin Infect Dis. (2008) 46 (7): 1111-1118.



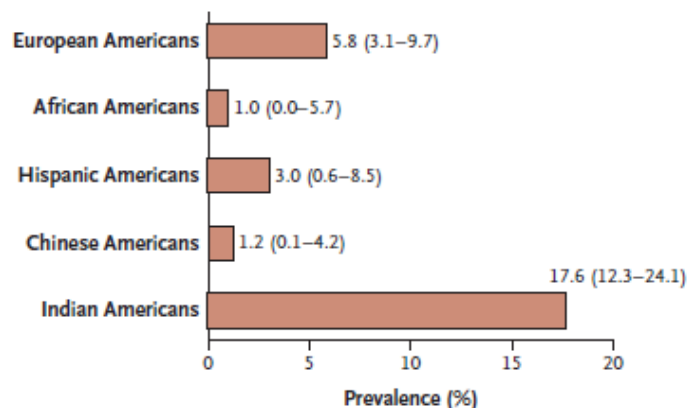
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HLA-B*5701 carriage frequency



To recommend screening for HLA-
B*5701 in European populations or of
European origin but not in some Asian
or African populations could be
problematic?

A U.S. Populations



B Other World Populations

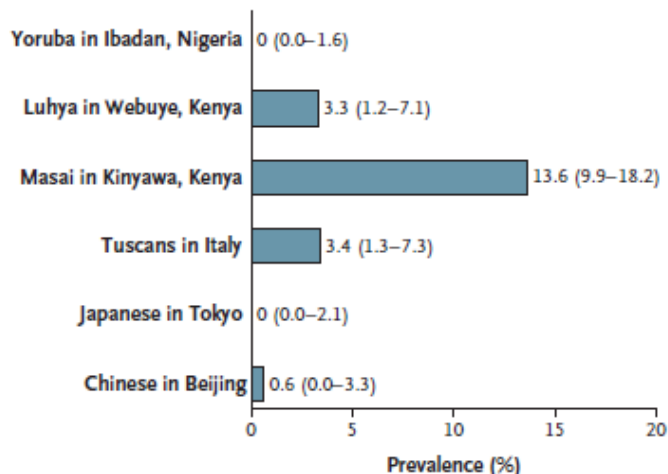


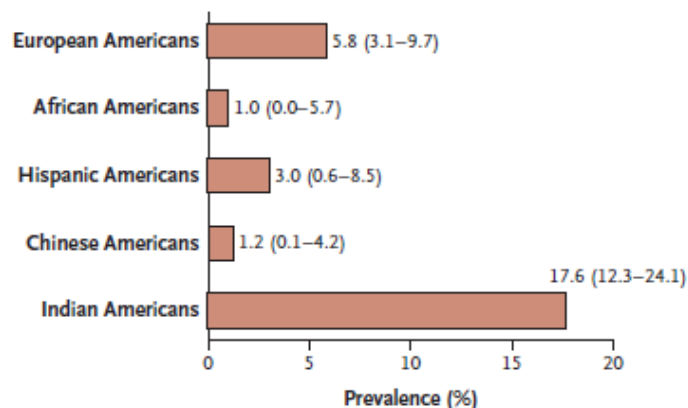
Figure 1. Variation in the HLA-B*5701 Locus in 11 HapMap Samples.

Screening for the HLA-B*5701 (rs2395029) allele substantially reduces the incidence of abacavir hypersensitivity in patients being treated for human immunodeficiency virus infection. Shown are the prevalences (with 95% confidence intervals) of the HLA-B*5701 variant in five U.S. ethnic groups (Panel A) and in six global ethnic groups (Panel B). This variant has a prevalence of 13.6% among the Masai in Kenya but a prevalence of 0% among the Yoruba in Nigeria, which indicates that the use of racial or continental labels such as “black” or “African” can sometimes obscure important, biomedically relevant variation.



Ancestry and Disease in the Age
of Genomic Medicine
N Engl J Med 363;16 October 14, 2010

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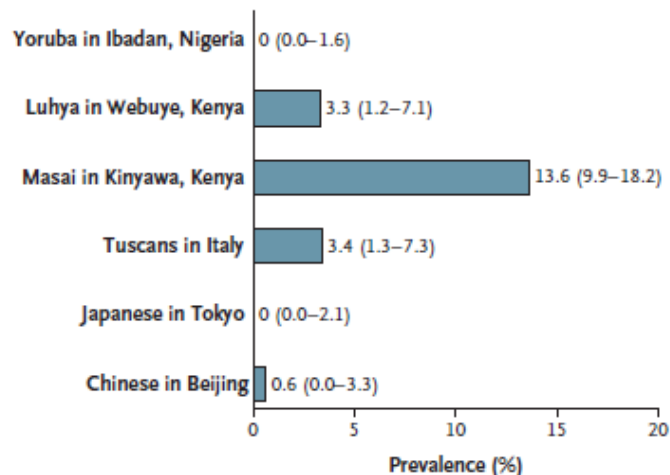
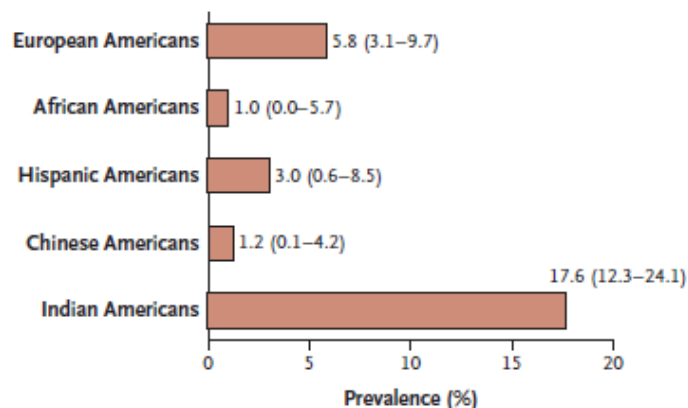


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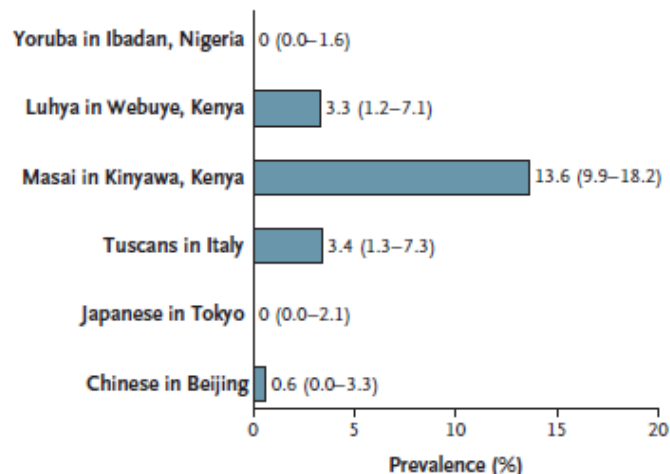


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Virgin of the Rocks (1495 - 1508)

Virgin of the Rocks (Madonna and child, San Giovannino and angel) is an oil painting on a panel of 189,5 x 120 cm, executed between 1495 and 1508 by Leonardo da Vinci.



National Gallery



Louvre