ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ ΤΗΣ ΣΗΨΗΣ
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

# ΓΕΝΕΤΙΚΟΙ ΠΟΛΥΜΟΡΦΙΣΜΟΙ ΚΑΙ HIV ΛΟΙΜΩΞΗ

***Kotsaki Antigoni, MD, PhD***
***4th Department of Internal Medicine***
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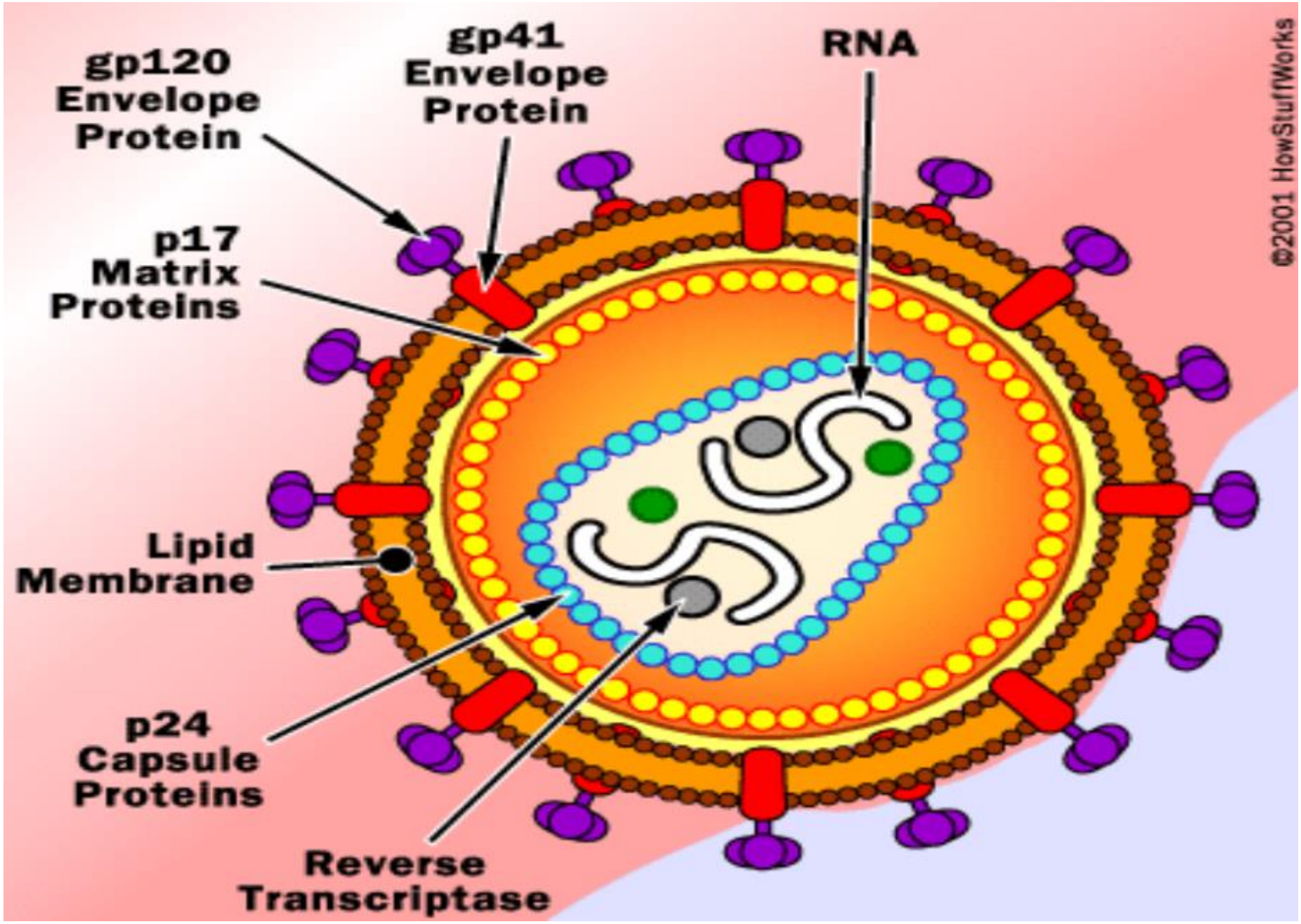
***Member, Hellenic Institute for the Study of Sepsis***

# ΓΕΝΕΤΙΚΟΙ ΠΟΛΥΜΟΡΦΙΣΜΟΙ

- Με τον όρο SNPs (single nucleotide polymorphism ) εννοούμε παραλλαγές στα αντίστοιχα αλληλόμορφα γονίδια που αφορούν ένα ζεύγος βάσεων
- Οφείλει να είναι τουλάχιστον 1%
- Εισαγωγή, διαγραφή, αντικατάσταση και δύναται να αφορά εσώνια, εξώνια ή περιοχές προαγωγής γονιδίου
- GWAS: genome-wide association study (GWAS) is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease. Once such genetic markers are identified, they can be used to understand how genes contribute to the disease and develop better prevention and treatment strategies

Brookes AJ. Gene 1999;234:177
www.genome.gov/genetics-glossary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Capsule
Proteins
Reverse
Transcriptase
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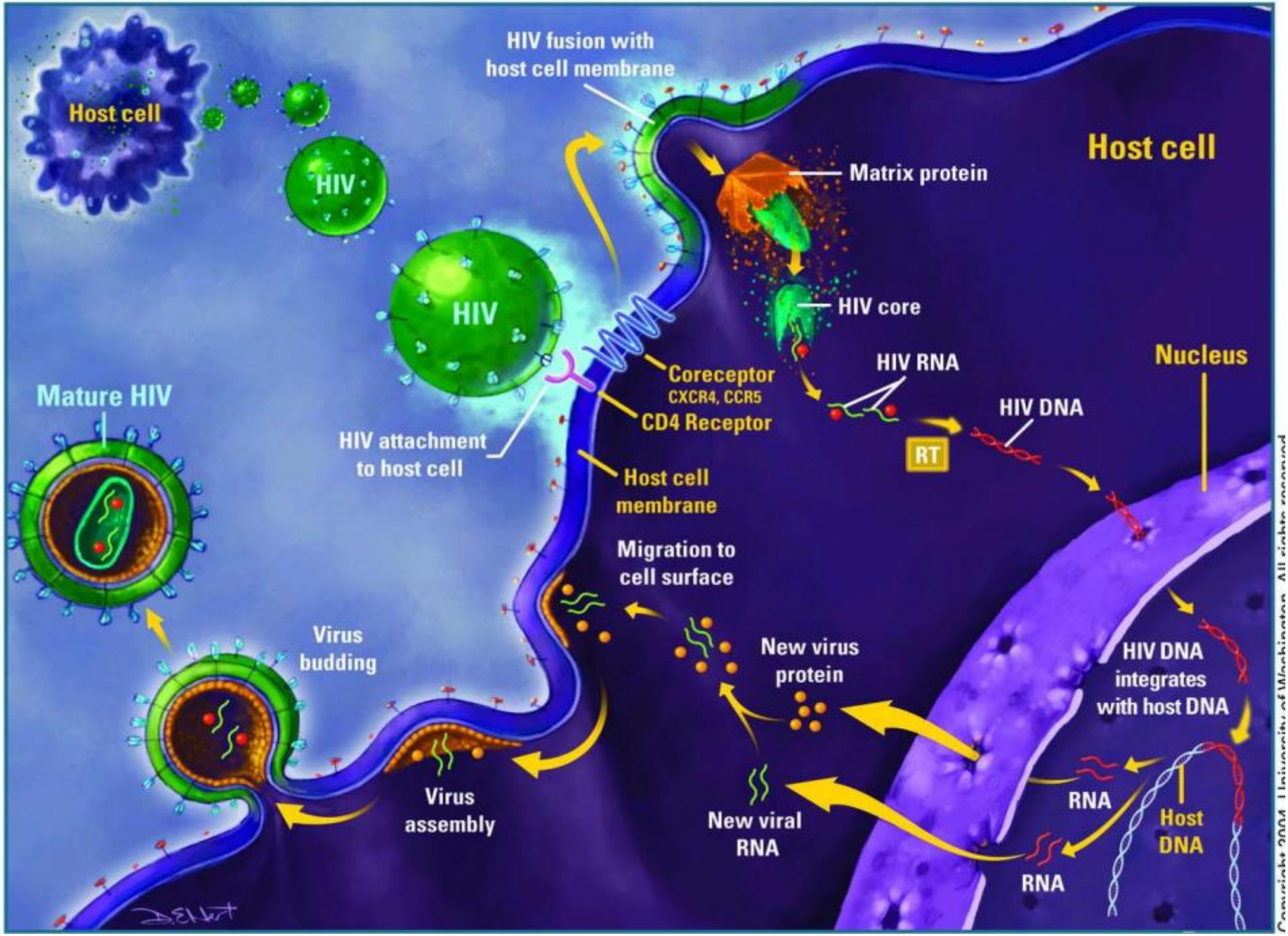
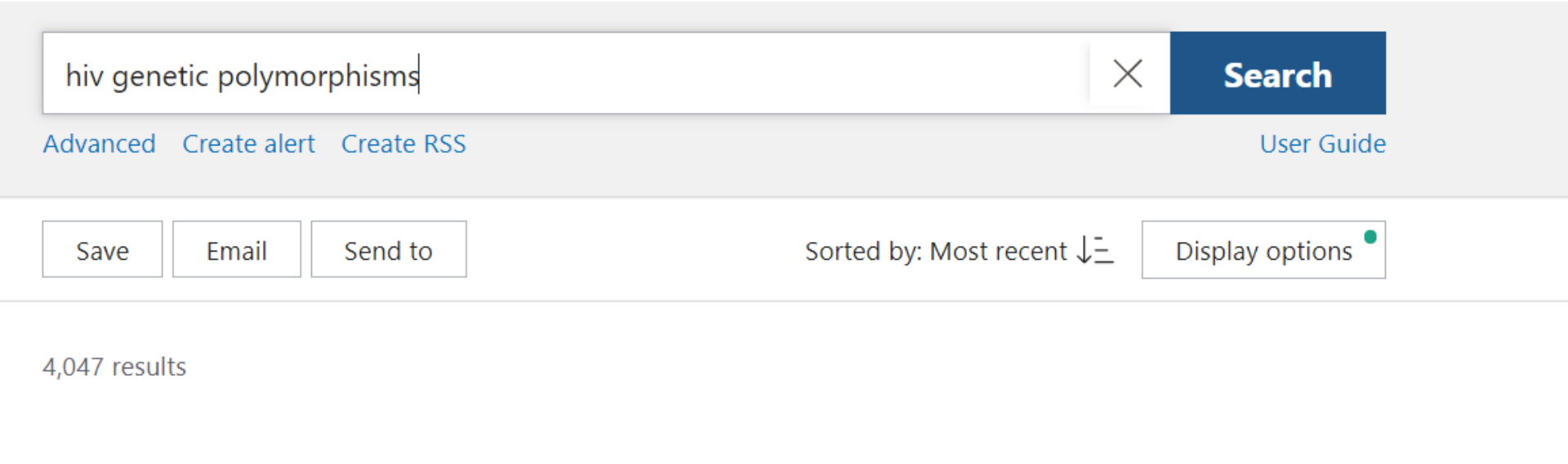


# HIV και γενετικοι πολυμορφισμοί

- Ευπάθεια σε HIV/εξέλιξη σε AIDS;
- Ευπάθεια σε ευκαιριακές λοιμώξεις;
- Φαρμακογενετικη;



Gingras, Shanelle N et al. “Minding the gap in HIV host genetics: opportunities and challenges.” *Human genetics* vol. 139,6-7 (2020): 865-875.

- Phenotypes explored in HIV GWAS; susceptibility to infection; spVL ;disease progression
- spVL; HLA-B*57:01,B*27:05,B*14:01
- CCR5 Δ32
- Precision Medicine;

**Conclusion**

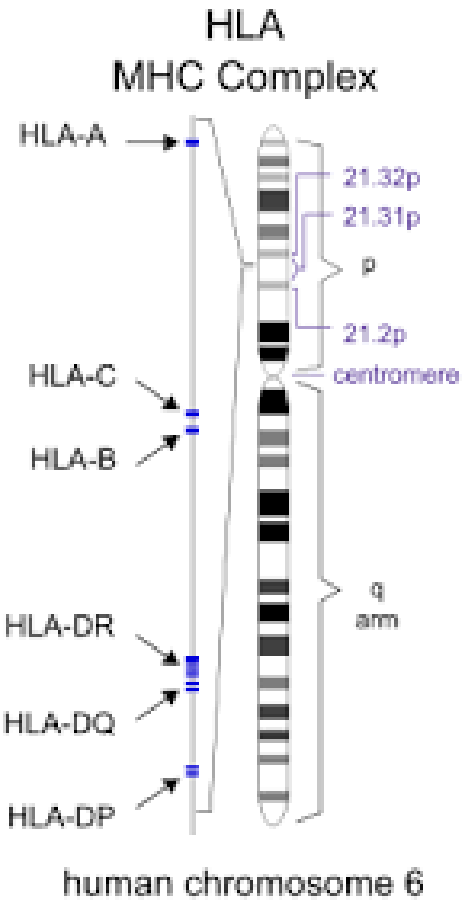
GWAS have been failing to accurately reflect the genetic diversity seen worldwide due to the extensive research in predominantly European populations. In recent years, there has been a concerted effort to address the gap in genomics between European and non-European cohorts, however, the discrepancy is still pronounced. Underrepresented populations have a greater risk for poorer health outcomes due to subpar prevention, diagnosis, and treatment options for their population. Through inclusivity, genomics has the opportunity to address these health disparities and improve health globally.

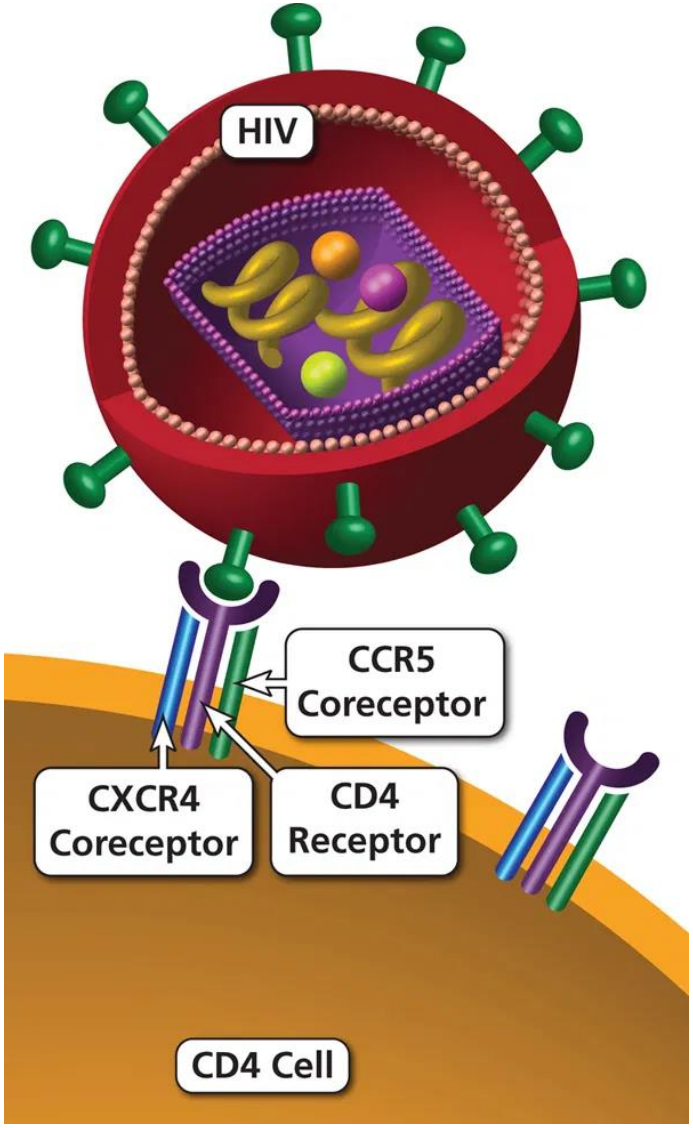
# Γενετικοί πολυμορφισμοί και ευπάθεια σε HIV

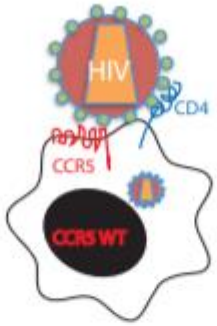
- Πολυμορφισμοί IL-10 p( -592, -1082, -819)
- «AA genotype of IL-10 -592 may confer increased susceptibility to HIV-1 infection, and that the AA genotype of -1082 may confer increased susceptibility in Caucasians. In contrast, the -819 polymorphism may not be associated with HIV-1 infection risk»

Fu DH, Deng WJ, Yang Z, et al. Medicine (Baltimore). 2020 Nov 25;99(48):e23069.

- Πρόσφατη εκτεταμένη μετα-ανάλυση κατλήγει ότι οι πολυμορφισμοί στις θέσεις CCR-5 και HLA

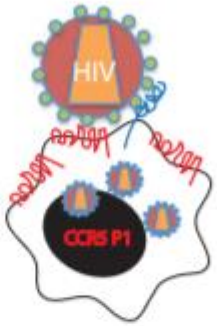





HIV gp120 interacts with CD4 and the co-receptor CCR5 on the surface of target cells

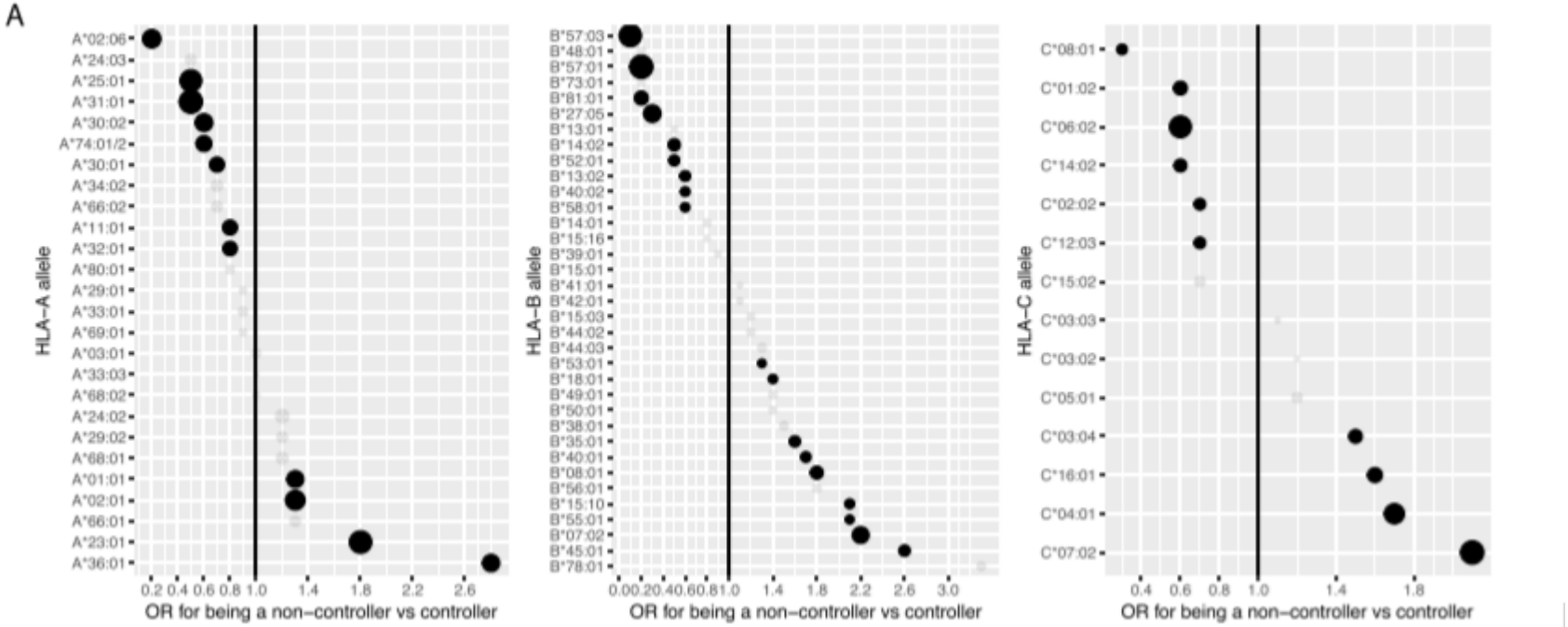

A truncation variant of CCR5 (CCR5Δ32) ablates co-receptor function and is associated with reduced acquisition risk and slower disease progression




The CCR5 P1 haplotype leads to elevated CCR5 expression and is associated with accelerated HIV disease progression

therapeutic translation


CCR5 blocking drugs are approved for the treatment of HIV



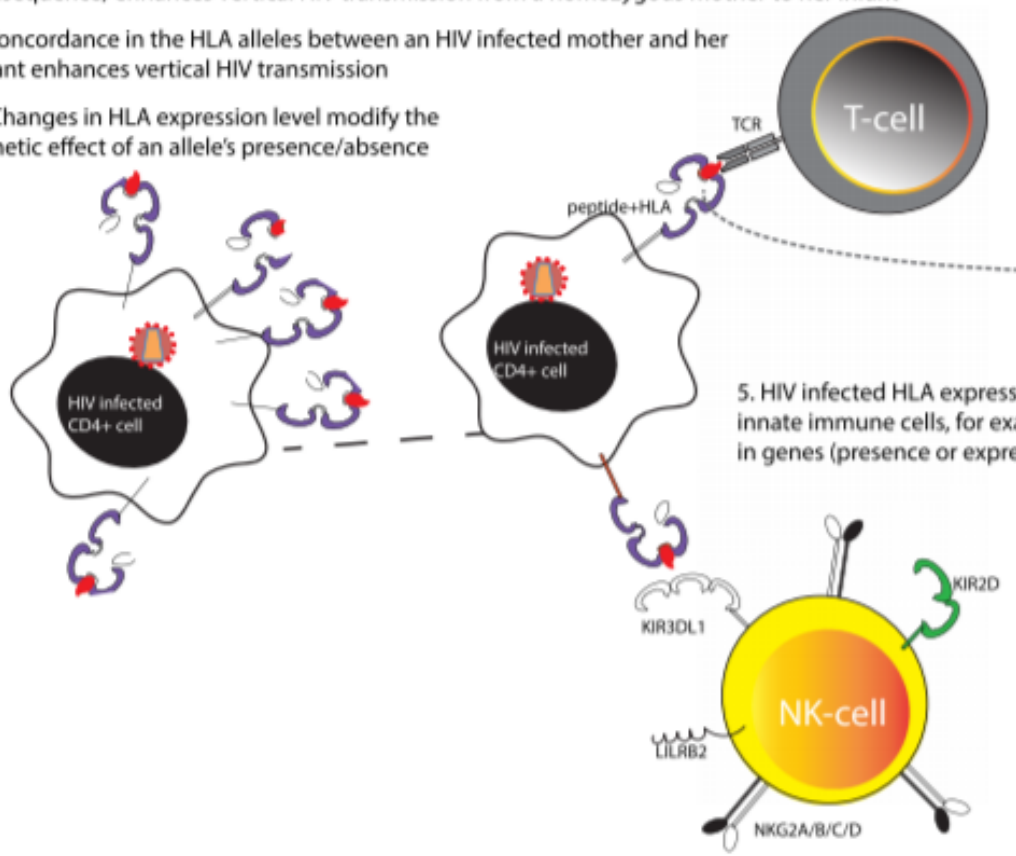

HLA-B*57,B*27, B*58:01, B*51, B*13, and B*81:01 are amongst the mostreproducibly protective correlates of HIV. In contrast, HLAB*58:02 and HLA-B*35Px alleles are associated with accelerated
HIV disease progression. I

1. HLA class I alleles show both protective and harmful effects in HIV (shown in A)

2. Homozygosity in the HLA region diminishes HIV control and (likely as a consequence) enhances vertical HIV transmission from a homozygous mother to her infant

3.Concordance in the HLA alleles between an HIV infected mother and her infant enhances vertical HIV transmission

4. Changes in HLA expression level modify the genetic effect of an allele's presence/absence




6. Viral variants with mutations that confer 'escape' from immune pressure evolve in an infected host. A greater degree of pre-adaptation to the host HLA, confers advantage to the virus in escaping HLA effects but can affect viral replication fitness.

5. HIV infected HLA expressing cells are recognised by T-cells (adaptive immune system) and innate immune cells, for example NK cells, through multiple different receptors. Genetic variation in genes (presence or expression modifiers) for some receptors modify HLA effects eg. KIR3DL1.

Naranbhai V, Carrington M. Immunogenetics. 2017 Aug;69(8-9):489-498. doi: 10.1007/s00251-017-1000-z. Epub 2017 Jul 10.

# Association of Toll-Like Receptor 4 Asp299Gly and Thr399Ile Polymorphisms with Increased Infection Risk in Patients with Advanced HIV-1 Infection

**Antonios I. Papadopoulos,[1] Bart Ferwerda,[2] Anastasia Antoniadou,[1] Vissaria Sakka,[1] Lambrini Galani,[1] Dimitra Kavatha,[1] Periklis Panagopoulos,[1] Garyphalia Poulakou,[1] Kyriaki Kanellakopoulou,[1] Jos W. M. van der Meer,[2] Evangelos J. Giamarellos-Bourboulis,[1] and Mihai G. Netea[2]**

[1]4th Department of Internal Medicine, University of Athens Medical School, Athens, Greece; and [2]Department of Internal Medicine and Center for Infectious Diseases, University St Radboud, Nijmegen Medical Center, Nijmegen, the Netherlands

***Background.*** The Toll-like receptor 4 (TLR4) is an essential component of the innate immune response to various microorganisms. We investigated the association between TLR4 polymorphism and the risk of acquiring severe infections, in patients with human immunodeficiency virus (HIV)–1 infection.

***Methods.*** The presence of TLR4 Asp299Gly and Thr399Ile single nucleotide polymorphisms (SNPs) was determined in a cohort of 199 HIV-1 infected patients and evaluated in relation to the occurrence of various infections.

***Results.*** One hundred seventy-two patients were homozygous for the wild-type genotype; 22 patients (11%) were heterozygous for both SNPs; 4 were heterozygous for 1 polymorphism; 1 patient was heterozygous for the Asp299Gly SNP and homozygous for the Thr399Ile SNP. Of individuals with a nadir CD4 cell count of <100 cells/mm$^3$, those who carried both SNPs, compared with those who carried the wild-type genotype, demonstrated a >3-fold increase in the odds ratio (OR) of any serious infection (OR, 6.33 vs OR, 1.83, $P = .043$).

***Conclusions.*** This study suggests an association between the presence of TLR4 Asp299Gly and Thr399Ile polymorphisms and the occurrence of serious infections in HIV-1 infected patients with a history of nadir CD4 cell count of <100 cells/mm$^3$.

# Effects of TLR7 Polymorphisms on the Susceptibility and Progression of HIV-1 Infection in Chinese MSM Population

*Tong Zhang[1†], Junping Zhu[2†], Bin Su[1], Lina Cao[2], Zhen Li[1], Huanhuan Wei[2], Xiaojie Huang[1], Kai Zheng[2], Aixin Li[1], Ning Chen[2], Lifeng Liu[1], Wei Xia[1], Hao Wu[1*] and Qiushui He[2,3*]*

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Toll-like receptor (TLR) 7 plays a key role in innate and adaptive immunity for HIV-1 infection. We evaluated the effect of TLR7 polymorphisms on disease susceptibility and progression of HIV-1 infection in Chinese MSM (men who have sex with men). Blood samples were taken from 270 patients with laboratory confirmed HIV infection, 196 male controls were tested, and three TLR7 intronic polymorphisms (rs179010-C > T, X:12884766; rs2074109-T > C, X:12885330; and rs179009-A > G, X:12885361) were analyzed by PCR-based sequencing. The frequency of TLR7 rs179010 T allele was significantly lower in MSM patients than in controls (P = 0.039). The haplotype TTA was associated with a decreased susceptibility to HIV-1 infection (P = 0.013), especially to acute HIV-1 infection (AHI) (P = 0.002), but not to chronic HIV-1 infection (CHI). Furthermore, the haplotype TTA is linked to slow disease progression in AHI patients (P = 0.002) and a lower viral load (P = 0.042). In contrast, TLR7 rs179009 allele A contributed to a higher set point in AHI patients with rapid progression, and the frequency of rs179009 minor allele G was over-presented in CHI patients. This finding supports a role for genetic variations of TLR7 in susceptibility and disease progression of an HIV-1 infection in Chinese Han population and warrants further studies on the effect of TLR7 polymorphisms on HIV-1 infection in different populations.

**Keywords: toll-like receptor 7, polymorphism, HIV-1, progression, viral load, set point**

# Γενετικοι πολυμορφισμοι και ευκαιριακες λοιμώξεις

- Λοιμώξεις από κρυπτόκοκκο
- Πολυμορφισμοί στον υποδοχέα TLR-9 (θέση 1935) σχετίζονται με ευπάθεια σε EBV και CMV (Beima-Sofie K, et al. AIDS. 2018 Jan 14;32(2):267)
- Πολυμορφισμός IFNL ¾ αμφιβληστροειδοπάθεια

Wojtowicz A, et al. AIDS. 2014 Aug 24;28(13):1885-9.

- Πολυμορφισμός στην προγωγό περιοχή τυ γονιδίου CCR5 σχετίστηκε επίσης με CMV αμφιβληστροειδοπάθεια (Sezgin E, et al. Am J Ophthalmol. 2011 Jun;151(6):999-1006.e4).

# Genome-Wide Association Study Identifies Novel Colony Stimulating Factor 1 Locus Conferring Susceptibility to Cryptococcosis in Human Immunodeficiency Virus-Infected South Africans

**Shichina Kannambath,[1,2] Joseph N. Jarvis,[3,4] Rachel M. Wake,[1,5] Nicky Longley,[1] Angela Loyse,[1] Vicky Matzaraki,[6] Raúl Aguirre-Gamboa,[6] Cisca Wijmenga,[6] Ronan Doyle,[3] Maria Paximadis,[7] Caroline T. Tiemessen,[7] Vinod Kumar,[6,9] Alan Pittman,[1] Graeme Meintjes,[8] Thomas S. Harrison,[1,5,8] Mihai G. Netea,[9,10] and Tihana Bicanic[1,5]**

[1]Institute of Infection and Immunity, St George's University of London, London, United Kingdom, [2]National Institute of Health Research Biomedical Research Centre at Guy's and St Thomas' Hospital and King's College London, London, United Kingdom, [3]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom, [4]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, [5]Clinical Academic Group in Infection, St George's Hospital NHS Trust, London, United Kingdom, [6]University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, the Netherlands, [7]Centre for HIV and STIs, National Institute for Communicable Diseases and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [8]Department of Medicine and Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa, [9]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University, Nijmegen, the Netherlands, [10]Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany

***Background.*** *Cryptococcus* is the most common cause of meningitis in human immunodeficiency virus (HIV)-infected Africans. Despite universal exposure, only 5%–10% of patients with HIV/acquired immune deficiency syndrome and profound $CD4^+$ T-cell depletion develop disseminated cryptococcosis: host genetic factors may play a role. Prior targeted immunogenetic studies in cryptococcosis have comprised few Africans.

***Methods.*** We analyzed genome-wide single-nucleotide polymorphism (SNP) genotype data from 524 patients of African descent: 243 cases (advanced HIV with cryptococcal antigenemia and/or cryptococcal meningitis) and 281 controls (advanced HIV, no history of cryptococcosis, negative serum cryptococcal antigen).

***Results.*** Six loci upstream of the colony-stimulating factor 1 (*CSF1*) gene, encoding macrophage colony-stimulating factor (M-CSF) were associated with susceptibility to cryptococcosis at $P < 10^{-6}$ and remained significantly associated in a second South African cohort (83 cases; 128 controls). Meta-analysis of the genotyped *CSF1* SNP rs1999713 showed an odds ratio for cryptococcosis susceptibility of 0.53 (95% confidence interval, 0.42–0.66; $P = 5.96 \times 10^{-8}$). Ex vivo functional validation and transcriptomic studies confirmed the importance of macrophage activation by M-CSF in host defence against *Cryptococcus* in HIV-infected patients and healthy, ethnically matched controls.

***Conclusions.*** This first genome-wide association study of susceptibility to cryptococcosis has identified novel and immunologically relevant susceptibility loci, which may help define novel strategies for prevention or immunotherapy of HIV-associated cryptococcal meningitis.

**Keywords.** Africa; Cryptococcal meningitis; genome-wide association study (GWAS); HIV; macrophage colony-stimulating factor (M-CSF).

- Επίδραση πολυμορφισμών CYP-3A5 στα επίπεδα λουμεφαντρίνης σε HIV γυναίκες υπό αγωγή για ελονοσία (Adegbola AJ, et al/Pharmacogenomics. 2020)
- HIV πολυμορφισμοί και TB; Υπάρχουν γενετικοί δείκτες ως προς τη φαρμακοκινητική αντι-TB φαρμάκων

› Clin Pharmacol Ther. 2019 Aug;106(2):450-457. doi: 10.1002/cpt.1403. Epub 2019 Mar 29.

# The Influence of Pharmacogenetic Variants in HIV/Tuberculosis Coinfected Patients in Uganda in the SOUTH Study

Andrea Calcagno [1], Jessica Cusato [1], Christine Sekaggya-Wiltshire [2], Amrei von Braun [3], Ilaria Motta [1], Grace Turyasingura [2], Barbara Castelnuovo [2], Jan Fehr [4 5], Giovanni Di Perri [1], Mohammed Lamorde [2]

Affiliations + expand

PMID: 30779340 DOI: 10.1002/cpt.1403

Free article

# Effects of genetic variability on rifampicin and isoniazid pharmacokinetics in South African patients with recurrent tuberculosis

Anushka Naidoo [1], Maxwell Chirehwa [2], Veron Ramsuran [1 3], Helen McIlleron [2], Kogieleum Naidoo [1 4], Nonhlanhla Yende-Zuma [1], Ravesh Singh [5], Sinaye Ncgapu [1], John Adamson [6], Katya Govender [6], Paolo Denti [2], Nesri Padayatchi [1 4]

Affiliations + expand

J Pharm Biomed Anal. 2019 Feb 5;164:698-705. doi: 10.1016/j.jpba.2018.11.026. Epub 2018 Nov 16

# In vivo phenotyping of cytochrome 450 isoforms involved in the metabolism of anti-HIV and anti-tubercular drugs in human using cocktail approach: An LC-MS/MS analysis

Ekta Varshney [1], Monika Tandon [2], Nilanjan Saha [2], Shakir Ali [3]

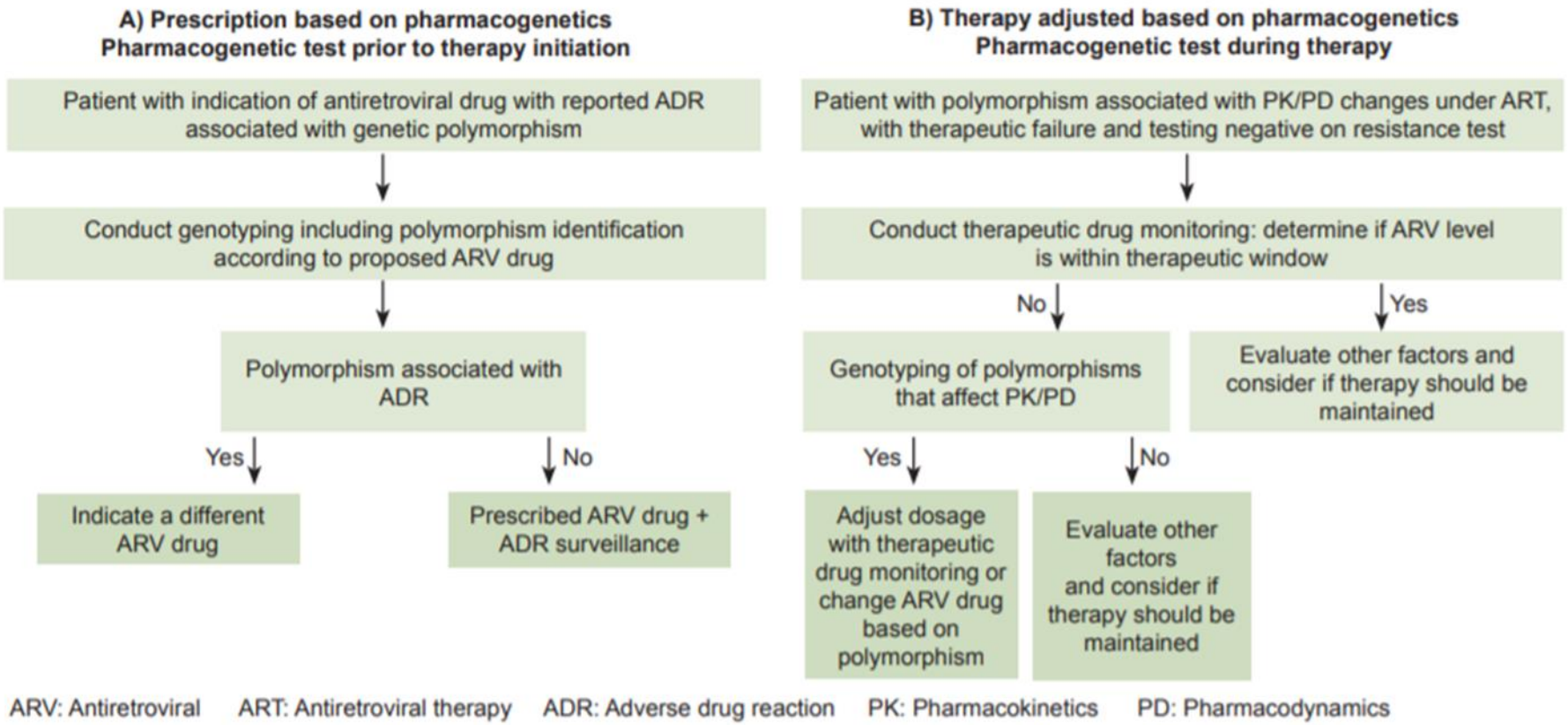
| Nucleoside reverse transcriptase inhibitors | | | |
|---|---|---|---|
| **ARV** | **Gene (Protein)** | **Variation** | **Effect** |
| Abacavir (ABC) | HLA-B | HLA-B*5701[a,b] | HSR |
| | HLA complex P5 (HCP5) | 335T>G (rs2395029)[a] | Alternative marker to determine risk of HSR to ABC |
| Tenofovir (TDF) | ABCC4 (MRP4) | 3463A>G (rs1751034) | Affects TDF pharmacokinetics leading to renal toxicity |
| | | 669C>T (rs899494)[a] | |
| | | 4131 T>G o G>G | Associated with increased TDF levels |
| | ABCC2 (MRP2) | "CATC" haplotype<br>24C>T, (rs717620)<br>1249G>A[a] (rs2273697)<br>3563T>A (rs8187694)<br>3972C>T (rs3740066)<br>24C (rs717620) | Higher risk of renal tubular disorders |
| Lamivudine (3TC) | ABCC4 (MRP4) | 4131T>G | Increased plasma levels |
| Zidovudine (AZT) | ABCC4 (MRP4) | 3724G>A | |

| Non-nucleoside reverse transcriptase inhibitors | | | |
|---|---|---|---|
| Efavirenz (EFV) | CYP2B6 (CYP2B6) | 516 G>T[b] (rs3745274) | Neurotoxicity of CNS<br>Associated with extremely high plasma levels |
| | | CYP2B6 *6/*6[b] | Prolonged QTc interval |
| | CYP2A9 | *9B T>G (rs28399433) | Lower EFV metabolism |
| | ABCC1 | 3435 C>T[a]<br>2677 G>T/A[a] | Associated with increased plasma levels.<br>Significant association with decreased probability of virologic failure |
| Nevirapine (NVP) | CYP2B6 | 516 G>T (rs3745274) | Presence of polymorphism associated with varying degrees of neuropsychological toxicity |
| | | 983 T>C (rs28399499) | Associated with decrease in NPV clearance |
| | HLA-DR | HLADRB1* 0101 | Risk of HSR and hepatotoxicity |
| | HLA-C | HLA-Cw*8 | Higher risk of HSR |
| | HLA-B | HLA-B*14 | |
| | ABCB1 (MDR1/P-gp) | 3435 C>T[a] (rs1045642) | Associated with lower risk of hepatotoxicity |

García-Blanco D, et al. MEDICC Rev. 2019 Apr-Jul;21(2-3):59

| | | | |
|---|---|---|---|
| **Protease inhibitors** | | | |
| Atazanavir (ATV) | UGT1A1 (UGT1A1) | UGT1A1 *28 (rs887829) | Hyperbilirubinemia Gilbert's syndrome |
| | ABCB1 (P-gp) | 3435 C>T[a] (rs1045642) | C/C carriers have higher ATV plasma levels than patients with C/T or T/T genotypes |
| Indinavir (IDV) | UGT1A1 (UGT1A1) | UGT1A1*28[a] (rs8175347) | Associated with increased risk of hyperbilirubinemia |
| | | UGT1A1*6[a] | Increased risk of hyperbilirubinemia. Diagnosed only in Asian patients |
| | CYP3A5 | CYP3A5*3 (A6986G) | Affects pharmacokinetics of IDV |
| Nelfinavir (NFV) | CYP2C19 | 681G>A | Possible effect on plasma levels |
| | ABCB1 (P-gp) | 3435C>T | Elevated plasma levels |
| Lopinavir (LPV) | SLCO1B1 (OATP1B1) | 521 T>C (rs4149056) | Higher plasma levels of LPV |
| Ritonavir (RTV) | APOE | APOE, APOC3, APOA5, CETP, y ABCA1 | Increased risk of severe hypertriglyceridemia |
| | APOC3 | 482 C>T, 455 T>C | Toxicity – hyperlipidemia |
| **Integrase inhibitors** | | | |
| Dolutegravir (DTG) | ABCG2 | 421 C>A (rs2231142) | Variations in plasma levels |

**Figure 1: Intervention proposals based on pharmacogenetic tests for Cuban HIV patients**




ARV: Antiretroviral ART: Antiretroviral therapy ADR: Adverse drug reaction PK: Pharmacokinetics PD: Pharmacodynamics

# Genetic variation near CXCL12 is associated with susceptibility to HIV-related non-Hodgkin lymphoma

Christian W. Thorball, Tiphaine Oudot-Mellakh, Nava Ehsan, Christian Hammer, Federico A. Santoni, Jonathan Niay, Dominique Costagliola, Cécile Goujard, Laurence Meyer, Sophia S. Wang, Shehnaz K. Hussain, Ioannis Theodorou, Matthias Cavassini, Andri Rauch, Manuel Battegay, Matthias Hoffmann, Patrick Schmid, Enos Bernasconi, Huldrych F. Gü Pejman Mohammadi, Paul J. McLaren, Charles S. Rabkin, Caroline Besson, Jacques Fellay

Haematologica Early view Jul 16, 2020 https://doi.org/10.3324/haematol.2020.247023



## Abstract

Human immunodeficiency virus (HIV) infection is associated with an increased risk of non-Hodgkin lymphoma (NHL). Even in the era of suppressive antiretroviral treatment, HIV-infected individuals remain at higher risk of developing NHL compared to the general population. To identify potential genetic risk loci, we performed case-control genome-wide association studies and a meta-analysis across three cohorts of HIV+ patients of European ancestry, including a total of 278 cases and 1924 matched controls. We observed a significant association with NHL susceptibility in the C-X-C motif chemokine ligand 12 (CXCL12) region on chromosome 10. A fine mapping analysis identified rs7919208 as the most likely causal variant (P = 4.77e-11), with the G>A polymorphism creating a new transcription factor binding site for BATF and JUND. These results suggest a modulatory

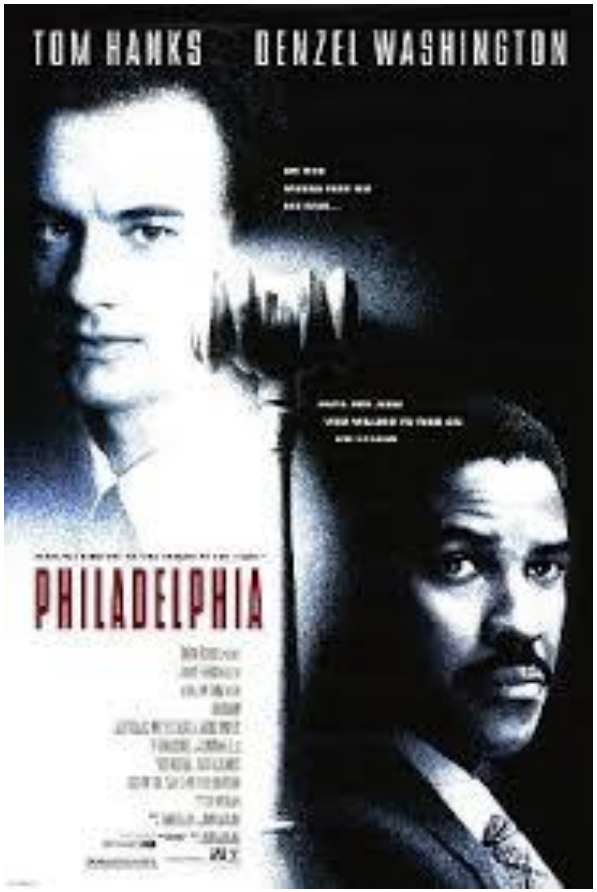
**Results:** In the 204,000 SNP screenings, we scrutinized the SNPs that differ in the case of Kaposi's Sarcoma [KS (+) and HIV (+)] on the basis of Control [KS(-) and HIV(-)] and HIV+ [KS(-)], and two SNPs of the ENDRA gene, three SNPs of the ADRA1A gene, six SNPs of the STIM1 gene, four SNPs of the EFNB2 gene, and one SNP of the CD209 gene were found to be different. However, when it comes to all SNPs (all the 204.000 SNPs) screened in terms of allele, it was observed that the AA and BB alleles were lower in the patient with Kaposi's Sarcoma [KS (+) and HIV (+)] compared to other groups and AB alleles were found to be higher than others in the patient with Kaposi's sarcoma [KS] (+) and HIV (+)].

**Conclusion:** In the microarray study we have conducted, 204,000 SNPs were screened for Control (HIV-) HIV (+) and HIV (+) patient with Kaposi's Sarcoma. It was found that 32,362 of those SNPs had different alleles in the Kaposi's Sarcoma [KS + HIV (+)] patient, while they had the same ones in the control [KS (-) and HIV (-)] and HIV + [KS (-)] group. 16 of the 32,362 SNPs took place among the genes related to Kaposi's Sarcoma. In the cases of Kaposi's Sarcoma with suspected diagnosis, it can be used as a beneficial laboratory test.

**Keywords:** HIV; Kaposi's sarcoma; SNP analyzes; genome; microarray; single nucleotide polymorphism..



Koyuncu I, et al. Curr HIV Res. 2020;18(3):154-164.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MATTHEW McCONAUGHEY
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JENNIFER GARNER AND JARED LETO
"HUGELY ENTERTAINING."
"MATTHEW McCONAUGHEY IS ASTOUNDING."
"EXHILARATING. IMPOSSIBLE TO FORGET."
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