Human and Viral Genetic Factors
Influencing HIV Infection and Therapy

Division of Infectious Diseases and Hospital Epidemiology

roberto.speck@usz.ch
Search results
Items: 12

   PMID: 26096900

2. Epigenetic regulation of HIV, AIDS, and AIDS-related malignancies.
   PMID: 25421572

3. The contribution of viral genotype to plasma viral set-point in HIV infection.
   PMID: 24789308

4. Effect of natural and ARV-induced viral suppression and viral breakthrough on anti-HIV antibody proportion and avidity in patients with HIV-1 subtype B infection.
   PMID: 23437058

5. Determinants of sustained viral suppression in HIV-infected patients with self-reported poor adherence to antiretroviral therapy.
   PMID: 22235271
THE IMPACT OF HUMAN AND VIRAL GENETIC FACTORS ON

HIV Transmission Risk

HIV Progression Rate

Response to cART
Hallmark of HIV Infection is the Progressive CD4+ T-Cell Loss

Ping An and Cheryl A. Winkler, Trends in Genetics, 2010
HIV Viral Load Determines Mother-to-Child-Transmission Risk

Percentage of in utero transmission in term delivery (based on positive HIV1 PCR within 3 days after birth available for 40 of 52 term births)

Warszawski et al, AIDS 2008
MATERNAL HLA HOMOZYGOSITY AND MOTHER-CHILD HLA CONCORDANCE INCREASE THE RISK OF VERTICAL TRANSMISSION OF HIV-1

(J INFECT DIS, 2008)
The Good News are....


266 mother-child pairs included in the period 2003-2008:

**NO TRANSMISSION OCCURRED IN HIV+ MOTHERS UNDER CART (COMBINED ANTIRETROVIRAL TREATMENT)**
HIV Viral Load is the Chief Predictor of the Risk of Heterosexual Transmission of HIV-1

Quinn TC et al., NEJM 2000
Analysis of Social and Genetic Factors Influencing Heterosexual Transmission of HIV within Serodiscordant Couples in the Henan Cohort

HIV Viral Load in the Index Partner

Condom Use

- Education level
- cART

Transmission Risk in Serodiscordant Couples

Qian Zhu et al., PLOS|ONE 2015
Transmission Risk Defined...

- **Sexual**: HIV load of the index partner / chemokine receptor polymorphisms of the exposed one

- **MTCT**: HIV load / HLA homozygosity of the mother and/or concordance with the child
WHAT FACTOR(S) DETERMINE(S) HIV INFECTION RATE?
Hallmark of HIV Infection is the Progressive CD4+ T-Cell Loss
Hallmark of HIV Infection is the Progressive CD4+ T-Cell Loss

Ping An and Cheryl A. Winkler, Trends in Genetics, 2010
Hallmark of HIV infection is the Progressive CD4+ T-Cell Loss

+ exposed uninfected individuals

Kaur G and Mehra N, Tissue Antigens, 2009
HIV Viral Load Determines HIV Progression Rate

Mellors JW et al., Science 1996
What determines the HIV Viral Load?

- Social Factors / Comorbidities
- Host Genetic Factors
- Viral Factors

HIV Progression Rate
The Viral Setpoint Defines the HIV Progression Rate
Viral Factors Play a Minor Role for HIV’s Distinct Progression Rate

~9 Kb
Viral Factors Play a Minor Role for HIV’s Distinct Progression Rate

A nef/LTR defective strain of HIV-1 results in slow progression rate

Birch MR et al., J Clin Virol, 2001
Viral Factors Play a Minor Role for HIV's Distinct Progression Rate

A nef/LTR defective strain of HIV-1 results in slow progression rate

Birch MR et al., J Clin Virol, 2001
Viral Factors Play a Minor Role for HIV’s Distinct Progression Rate

The transmitted/founder virus is shaped by multiple genetic bottlenecks.

Joseph SB et al. Nature Reviews|Microbiology, 2015
CGA, Unbiased GWA and Genome-Wide RNAi Screen Identified a Number of Host Factors Crucial for HIV Infection

(CGA: candidate gene approach; GWA: genome-wide association studies)
Host Genes Associated with HIV are Found at Different Levels

Immune response

Intrinsic HIV-1 restriction factors
RFs are anti-viral proteins that are produced in the host and counteract or «restrict» viral replication (1st line of defence)

Host cellular factors important for HIV replication
Key Steps in the HIV Replication Cycle
HIV Enters Cells using CD4 and CCR5
Protective Effect of the CCR5 Gene Variant Δ32 against HIV
Early Protective Effect of CCR5-Δ32 Heterozygosity on HIV-1 Disease Progression: Relationship with Viral Load

Meyer L et al. AIDS 1997

Fig. 1. Comparison of serum viral load between heterozygous and wild-type homozygous HIV-infected patients during the first 7 years after infection (SEROCO cohort).
Cure of HIV by a Stem Cell Transplant from a CCR5Δ32+/+ Donor

Hütter et al, NEJM 2009
Loss of HIV-specific T-cells and antibodies in the HIV+ patient transplanted with CCR5Δ32+/+
Gene Engineering Human Cells in Hu Mice using a microRNA against CCR5
Hu Mice Transplanted with a rather Pure Population of Gene-Engineered Cells show Drastic Reduction in Viral Load

Myburgh R et al., J Virol 2015
Allelic Variations of the Genes Encoding Chemokines Binding to the HIV-Co-Receptors may Impact HIV Infection and Pathogenesis

Sharma G et al., Indian J Med Res 2011
Other Check Points Controlled by Cellular Factors

**Cyclophilin A**  
(peptidylprolyl isomerase A)  
- No coding SNPs  
- SNP 1604G affects transcription factor binding
Innate and adaptive immune defence mechanisms contributing to spontaneous HIV-1 control

Bruce D. Walker and Xu G. Yu, Nature Reviews Immunology, 2013
Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotypes</th>
<th>RP (n = 65)</th>
<th>Others (n = 363)</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>P* value (full model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR9 +1237 T/C</td>
<td>TT</td>
<td>0.80</td>
<td>0.68</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>0.18</td>
<td>0.29</td>
<td>0.53 (0.26–1.04)</td>
<td>0.065</td>
<td></td>
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<tr>
<td></td>
<td>CC</td>
<td>0.015</td>
<td>0.03</td>
<td>0.52 (0.06–4.29)</td>
<td>0.545</td>
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<tr>
<td>TLR9 -1174 G/A</td>
<td>GG</td>
<td>0.12</td>
<td>0.34</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>0.57</td>
<td>0.45</td>
<td>3.64 (1.61–8.21)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>0.31</td>
<td>0.21</td>
<td>4.22 (1.74–10.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>TLR9 1635 A/G</td>
<td>AA</td>
<td>0.11</td>
<td>0.32</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>0.60</td>
<td>0.48</td>
<td>3.92 (1.67–9.18)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>0.29</td>
<td>0.20</td>
<td>4.73 (1.86–12.0)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Haplotypes^c</td>
<td>T-G-A</td>
<td>0.51</td>
<td>0.62</td>
<td>0.58 (0.34–1.01)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-G-A</td>
<td>0.20</td>
<td>0.32</td>
<td>0.54 (0.28–1.04)</td>
<td>0.07</td>
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</tr>
<tr>
<td></td>
<td>T-A-G</td>
<td>0.88</td>
<td>0.67</td>
<td>3.66 (1.67–8.04)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Bochud PY et al., AIDS 2007
HIV Infection Results in the Upregulation of a Large Number of IFN α Stimulated Genes (ISGs)

HIV Infection Results in the Upregulation of a Large Number of IFN α Stimulated Genes (ISGs)

- LY6E: 9.3
- BST2: 3.4
- MX2: 7.1
- IFI16*: 2.9

Immune defense / inflammatory response

Rather All Intrinsic Restriction Factors are IFN α Stimulated Genes (ISGs)

<table>
<thead>
<tr>
<th>Host restriction factor</th>
<th>Restriction mechanism</th>
<th>IFN upregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOBEC3F/G</td>
<td>Hypermutation of the nascent cDNA, other mechanisms</td>
<td>IFN-α[22-24]</td>
</tr>
<tr>
<td>Bst-2/Tetherin</td>
<td>Tethering of viral particles to the cell surface for subsequent endocytosis and degradation</td>
<td>IFN-α[25, 26]</td>
</tr>
<tr>
<td>CNP</td>
<td>Binding to Gag, blocking viral particle assembly</td>
<td>IFN Type I[27, 28]</td>
</tr>
<tr>
<td>HERC5</td>
<td>Arresting Gag particles at the assembly site on the plasma membrane</td>
<td>IFN-β[29]</td>
</tr>
<tr>
<td>IFITM 1, 2, 3</td>
<td>Inhibition of viral entry: negative effect in Gag expression</td>
<td>IFN type I and II[28, 30]</td>
</tr>
<tr>
<td>ISG15</td>
<td>Inhibition of viral budding and release</td>
<td>IFN-α[31]</td>
</tr>
<tr>
<td>MX2</td>
<td>Inhibition of nuclear import</td>
<td>IFN-α[32, 33]</td>
</tr>
<tr>
<td>PKR</td>
<td>Inhibition of protein translation</td>
<td>IFN-α[34]</td>
</tr>
<tr>
<td>Rassie L/2-5A</td>
<td>Viral RNA degradation</td>
<td>IFN type I and II[35, 36]</td>
</tr>
<tr>
<td>SAMHD1</td>
<td>Depletion of dNTP pool during reverse transcription</td>
<td>IFN-α and IFN-γ[37, 38]</td>
</tr>
<tr>
<td>SLFN11</td>
<td>Inhibition of viral protein synthesis, codona-usage-dependent manner</td>
<td>IFN Type II[39, 40]</td>
</tr>
<tr>
<td>TRIM5a</td>
<td>Premature uncoating of the viral capsid or capsid degradation</td>
<td>IFN type I and II[41, 42]</td>
</tr>
<tr>
<td>TRIM22</td>
<td>Transcription inhibition, alteration of Gag trafficking</td>
<td>IFN type I and II[43]</td>
</tr>
</tbody>
</table>
Most (or all) RFs are neutralized by HIV’s accessory genes

HIV PROGRESSION RATE

INTRINSIC HIV-1 RESTRICTION FACTORS

U3 R U5 gag pol

vif rev tat

nef vpr env vpu

~9 Kb
Sequential strategies for the restriction of HIV-1 by virion-incorporated A3G
Sequential strategies for the restriction of HIV-1 by virion-incorporated A3G
Intrinsic HIV-1 Restriction Factors

Simon Viviana et al., Nature Immunology 2015
SERINC (Serin Incorporator) Proteins Impair Viral Delivery

Aiken C, Nature 2015

Innate and adaptive immune defense mechanisms contributing to spontaneous HIV-1 control

Bruce D. Walker and Xu G. Yu, Nature Reviews Immunology, 2013
The palace guard: HLA …→ HIV specific CTLs

- HLA homozygosity for 1, 2 or 3 class I loci → positively correlated with disease progression
  - Limited repertoire of HIV recognition
    - More rapid emergence of immune escape mutations

- HLA-B*27 and HLA-B*57 protective against HIV
  - HLA-B*27: nonselective in antigen presentation making it harder for HIV to lose binding affinity by mutation
  - HLA-B*57: escape mutants to HLA-B*57 goes along with decreased virus fitness.
PHARMACOGENETICS AS A TOOL TO TAILOR ANTIRETROVIRAL THERAPY: A REVIEW
WORLD JOURNAL OF VIROLOGY 2015
Aids in der Schweiz
Gemeldete Todesfälle seit 1983: Todesjahr (Daten nur bis 2011 verfügbar)

- Total
- Homosexuelle Kontakte
- Drogeninjektion
- Heterosexuelle Kontakte
- anderer

BAG, September 2016
2 Nucleoside Reverse Transcriptase Inhibitors + Integrase Inhibitor or Protease Inhibitor ➔ Standard of Care (combined anti-retroviral treatment cART)
# Guidelines EACS Version 8.0

## Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)* **

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Food requirement</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NRTIs + INSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/DTG (i, ii)</td>
<td>ABC/3TC/DTG 600/300/50 mg, 1 tablet qd</td>
<td>None</td>
<td>Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).</td>
</tr>
<tr>
<td>TDF/FTC (iii, iv) + DTG</td>
<td>TDF/FTC 300 (^{\text{oral}})/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd</td>
<td>None</td>
<td>Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).</td>
</tr>
<tr>
<td>TDF/FTC/EVG/c (iii, iv, v)</td>
<td>TDF/FTC/EVG/c 300 (^{\text{oral}})/200/150/150 mg, 1 tablet qd</td>
<td>With food</td>
<td>Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).</td>
</tr>
<tr>
<td>TDF/FTC (iii, iv) + RAL</td>
<td>TDF/FTC 300 (^{\text{oral}})/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid</td>
<td>None</td>
<td>Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).</td>
</tr>
</tbody>
</table>

| 2 NRTIs + NNRTI          |                                                                        |                  |                                                                        |
| TDF/FTC/RPV (iii)        | TDF/FTC/RPV 300 \(^{\text{oral}}\)/200/25 mg, 1 tablet qd            | With food (min 390 Kcal required) | Only if CD4 count >200 cells/µL and HIV VL <100,000 copies/mL. PPI contraindicated. H2 antagonists to be taken 12h before or 4h after RPV. |

| 2 NRTIs + PI/r           |                                                                        |                  |                                                                        |
| TDF/FTC (iii, iv) + DRV/r | TDF/FTC 300 \(^{\text{oral}}\)/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd | With food        | Monitor in persons with a known sulfonamide allergy. |
Hypersensitivity Reaction Syndrom (HRS) due to Abacavir

- Hypersensitivity in 5% to 8% of patients during the first 6 wk of treatment (fever, rash, gastrointestinal and respiratory tract symptoms)
- Continued use will worsen symptoms / rechallenge potentially life threatening
- HRS is driven by MHC-I antigen presentation. HLA-B*5701 activation restricted to CD8+ T-cells results in the secretion of TNF-α and IFN-γ.
- HLA-B*5701 allele occurs at approximately 5% frequency in European populations, 1% in Asian populations, and less than 1% in African populations.
- NPV of HLA-B*5701 nearly 100% and PPV of ~50%.

Genotyping prior to use of Abacavir widely and strictly recommended
<table>
<thead>
<tr>
<th>ARVs</th>
<th>Polymorphisms</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
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<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
<td>Hypersensitivity Reaction Syndrome</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>ABCC2-MRP2 1249G &gt; A</td>
<td>Increased risk of tubulopathy</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>MRP4 4131T &gt; G</td>
<td>Increased plasma concentrations</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>MRP4 3724G &gt; A</td>
<td>Increased plasma concentrations</td>
</tr>
<tr>
<td>Didanosine</td>
<td>CFTR 1717-1G &gt; A, IV585T,</td>
<td>Higher risk of pancreatitis</td>
</tr>
<tr>
<td>Didanosine(ddI), Zalcitabine(ddC), Stavudine(ddT)</td>
<td>SPINK-1 112C &gt; T, MTND1 LHON4216C, MTND2 LHON4917G</td>
<td>Leber’s Hereditary Optic Neuropathy, Peripheral Neuropathy</td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-B*58:01, *15:02, *35:05, ABCC10rs2125739, CYP2B6 516G &gt; T</td>
<td>Cutaneous rash, SJS/TEN, Increased plasma concentration, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced risk of hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher plasma concentrations, SNC side effects</td>
</tr>
<tr>
<td>EFV</td>
<td>MDR1 3435C &gt; T, CYP2B6 G516T, T983C</td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>SLC01B1 521T &gt; C (rs4149056)</td>
<td>Increased plasma concentrations</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>UGT1A1*28</td>
<td>Increased plasma concentrations</td>
</tr>
</tbody>
</table>
LONG-TERM MANAGEMENT OF HIV WILL BENEFIT FROM

- PHARMACOGENOMICS,

- TESTING FOR DRUG-DRUG INTERACTIONS

- AND TDM
Acknowledgment

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