Bayesian Network Analysis of Resistance Pathways in HIV-2 Reverse Transcriptase

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HIV-2 world distribution

~1.000.000 / 2.000.000 people infected in West Africa  
(UNAIDS / WHO, 2006)

Highest prevalence: Guinea-Bissau  

Highest prevalence in Europe: Portugal (3,2% AIDS cases), followed by France  
(INSA, Portugal, 2008)
Background – HIV-2

- Not all antiretrovirals are active against HIV-2 (NNRTIs, T-20).
  

- HIV-2 drug resistance pathways are still poorly understood.

- Selection of drug resistance is much faster than in HIV-1.
  

- Most drugs lose their efficacy with fewer mutations than in HIV-1.
  

- Viral enzyme Reverse Transcriptase (RT) is one of the main therapeutic targets.
Aim of the study

To investigate associations of mutations in the HIV-2 reverse transcriptase (RT), and infer resistance pathways against nucleoside RT inhibitors (NRTIs).
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Bayesian Networks

Probabilistic model that describes graphically statistical independencies between drug resistance mutations, polymorphisms and exposure to treatment.


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Materials & Methods

- 176 HIV-2 group A infected patients: 76 naïve (controls) and 100 treatment experienced

- plasma sequencing of a 1280-bp HIV-2 pol gene fragment comprising RT using an in-house method

- nucleotide sequences edited and analyzed with SeqScape® v.2.5 using ROD HIV-2 strain as reference

- Fisher test, Bayesian Network analysis and the Jaccard index of association used to identify mutations selected during therapy and investigate direct dependencies between them

- robustness of network features assessed with non-parametric bootstrap — only interactions with bootstrap support ≥ 70% considered for analysis

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Results

Bayesian Network for HIV-2 RT

Legend:
- **treat** treatment node
- **M** drug associated amino acid (Met)
- **K** wild-type amino acid (Lys)
- **R** drug anti-associated wild-type amino acid (Arg)

Arc = direct dependency between variables

Arc thickness $\Rightarrow$ proportional to bootstrap support (70-100%, and < 70%)

Arc color
- black = influence of NRTI-associated mutations
- blue = influence of background polymorphisms

Further details: Poster 46

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Results

❖ **K65R, Q151M** and **M184V** are directly connected to treatment and considered primary RT mutations.

❖ **S215A/C/F/L/Y** substitutions are also directly connected to treatment, but with a bootstrap support < 70%.

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Results

Several secondary mutations were selected in the presence of primary mutations:

- **R22K, T53S, A62V** and **V111I** were independently selected in the presence of **K65R**, possibly representing distinct resistance pathways.

- Two resistance pathways were associated with **Q151M**: one through accessory mutation **F214L**, and another through **V111I**.

- Association between **K65R** and **Q151M** was not robust (< 70%).
Discussion

HIV-2 reverse transcriptase seems to select three main pathways towards drug resistance, through mutations K65R, Q151M and M184V, and, eventually a fourth one through S215A/C/F/L/Y.

These amino acid substitutions also emerged with high frequency (>10%) in the cross-sectional analysis of our data.

Cavaco Silva J. et al., CROI 2009, Poster M-205

K65R, Q151M and M184V often appear together in HIV-2 treated patients, causing classwide NRTI resistance.


S215F/Y confer reduced susceptibility to AZT and d4T in HIV-1. In HIV-2, they were selected in 15% of treated patients, along with A/C/L variants, but their true impact on HIV-2 drug resistance remains to be determined.
The association between K65R and Q151M remains unclear.

K65R and Q151M are significantly more common in HIV-2 than in HIV-1.


Several authors have reported the association between K65R and Q151M.


In our dataset, 59% of the genotypes that presented K65R (17/29) also displayed Q151M. However, there was no statistically significant association between them ($J = 0.32$, $p = 0.9$), as supported by the Bayesian Network.

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Several mutations were selected by HIV-2 as accessory mutations: R22K, T53S, A62V, V111I and F214L.

Although some of them also occur as natural polymorphisms, namely R22K, V111I and F214L, in our dataset they were significantly more common in treated patients.

In vitro mutagenesis studies are required to corroborate their true phenotypic impact in HIV-2.
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