Phylogenetic Clusters of HIV-1 Reveal Potential Viral Genetic Impact on Comorbidities

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Summary

• We systematically studied the clustering of comorbidities on the HIV transmission network.

• Some coinfections in HIV-infected individuals spread via the same transmission routes as HIV.

• Certain comorbidities might be influenced by viral genetics.

Why was this study done?

- Managing comorbidities in people living with HIV remains one of the major challenges in the era of highly active antiretroviral therapy.
- Can viral genetic data be sufficiently informative to discern differences in the occurrence of comorbidities based on viral genome similarities?

What methods were used?

- The Swiss HIV cohort study (SHCS) contains extensive demographic, clinical, laboratory and behavioral data of ~20’000 HIV-infected patients in Switzerland.
- A maximum-likelihood phylogenetic tree was build using the genotypic resistance test (GRT) database of the SHCS (sequences of 8’793 patients) and 11’390 Los Alamos background sequences.

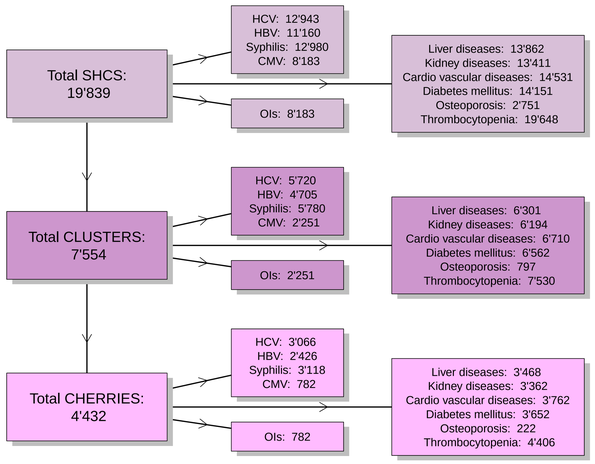


Figure 1: Size of the study population in each analysis. Coinfection: Hepatitis C (HCV), Hepatitis B (HBV), syphilis and cytomegalovirus (CMV); Non-communicable diseases: Liver diseases, kidney diseases, Cardio vascular diseases, Diabetes mellitus, Osteoporosis and thrombocytopenia; Opportunistic infections (OIs)

- Clusters with at least 90% SHCS sequences and maximal pairwise genetic distance of 5% were extracted.
- Cherries of SHCS patients with maximal genetic distance of 3% were extracted.
- Detecting the cluster effect: Comparison of the model *Disease ~ 1* with the mixed effects logistic regression model *Disease ~ 1 + 1| Cluster*.
- Quantifying the cluster effect: Parent-offspring regression on the cherries to calculate the odds of having a certain disease depending on the neighbor in the cherry.
- Correction for confounding: For those clinical endpoints which revealed a cluster pattern, we continued with a multivariate analysis.



Figure 2: Schematic tree for parent-offspring analysis. Is a patient (tips) more likely to have a disease (“yes”) if the neighbor in the cherry (purple) has the disease as well?

What was found?

Coinfections

- Hepatitis C: 1’582 of 12’943 (12%)
- Hepatitis B: 3’803 of 11’160 (34%)
- Syphilis: 2’811 of 12’980 (22%)
- Cytomegalovirus: 14’747 of 17’349 (85%)

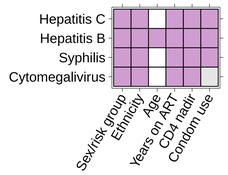


Figure 3: Confounder selection for coinfections (the purple confounders are included).

Hepatitis C, Hepatitis B, syphilis and cytomegalovirus all clustered on the phylogenetic tree. This suggests shared transmission routes for these infectious conditions.

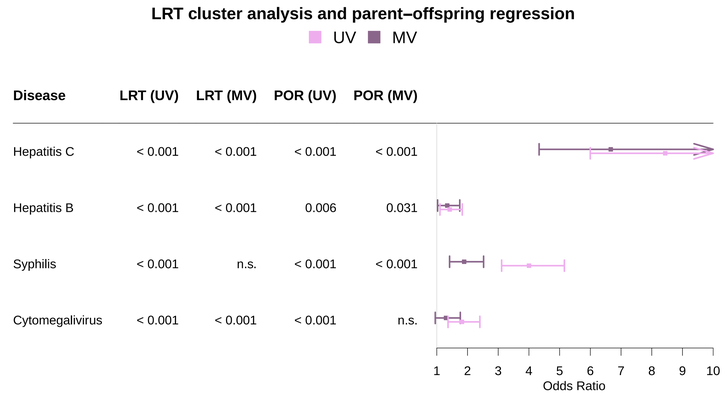


Figure 4: P-values of the likelihood ratio test (LRT) on the clusters, univariate (UV) and multivariate (MV); P-values of the parent-offspring regression (POR) on the cherries, univariate (UV) and multivariate (MV);

Non-communicable diseases:

Disease	Information used	Cases (%)	LRT (UV)	LRT (MV)
Liver diseases	Liver-related clinical events, >500’000 AST/ALT measurements, Fibro scans (1’815 patients)	4’187 (30.2%)	p < 0.001	p = 0.005
Kidney diseases	Kidney-related clinical events, eGFR (>300’000 serum creatinine measurements)	1’973 (14.7%)	p < 0.001	n.s.
Cardio vascular diseases	Cardio vascular clinical events (myocardial infarction, stenting,…)	1’011 (6.9%)	0.004	n.s.
Diabetes mellitus	Glucose measurements, intake of anti-diabetes drugs	855 (6.0%)	p < 0.001	n.s.
Osteoporosis	DEXA scans (2’751 patients)	393 (14.3%)	n.s.	n.s.
Thrombocytopenia	>500’000 platelet measurements	1’172 (6.0%)	p < 0.001	p < 0.001

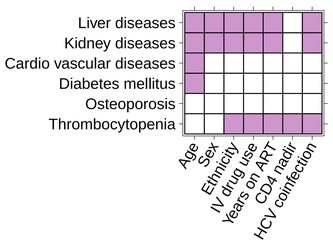


Figure 5: Confounder selection for non-communicable diseases (the purple confounders are included).

Some non-communicable diseases are clustered on the HIV-transmission tree. The clustering can in many cases be explained by confounding, e.g. by age.

Opportunistic infections:

Some AIDS-defining illnesses are clustered on the HIV-transmission tree, e.g. Kaposi’s sarcoma or HIV-related encephalopathy. Even after correcting for the risk group, the cluster pattern remained significant for HIV-related encephalopathy, CMV retinitis and pulmonary Mycobacterium tuberculosis.

Understanding confounding and finding suitable multivariate models are the main challenges to understanding why certain opportunistic infections cluster on the HIV transmission tree.

Opportunistic infection	Cases	LRT (UV)	LRT (correction for risk group)
Candida stomatitis	3’676 (44.9%)	p = 0.011	n.s.
Oral hairy leukoplakia	2’004 (24.5%)	n.s.	n.s.
Esophageal candidiasis	1’568 (19.2%)	n.s.	n.s.
Multidermatomal Herpes zoster	1’318 (16.1%)	n.s.	n.s.
Pneumocystis pneumonia	1’205 (14.7%)	n.s.	n.s.
HIV-related encephalopathy	758 (9.2%)	p = 0.0045	p = 0.007
Kaposi’s sarcoma	708 (8.6%)	< 0.001	n.s.
Toxoplasmosis of the brain	632 (7.7%)	n.s.	n.s.
Bacterial pneumonia	630 (7.7%)	p = 0.0012	n.s.
CMV retinitis	441 (5.4%)	p < 0.001	p < 0.001
Non-Hodgkin’s lymphoma	398 (4.9%)	n.s.	n.s.
Disseminated MAC disease	392 (4.8%)	n.s.	n.s.
Pulmonary M. tuberculosis	260 (3.2%)	p < 0.001	p < 0.001

n.s.: not significant (p < 0.05)