EDCTP

EuResist
Integration of viral genomics with clinical data to predict response to anti-HIV treatment
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Prediction Of Antiretroviral Therapy Outcomes In Poor Resource Countries: Comparison Between Genotype Resistance Testing Based vs. Treatment History Models

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Summary

- In high-income countries, guidelines recommend genotypic resistance testing (GRT) both before starting antiretroviral therapy (ART) and at ART failure
- Appropriate funding and/or facilities to perform GRTs may be not available in low-middle income countries, leaving physicians to switch therapy based solely on the clinical/immunological conditions (sometimes even without virological monitoring)
- Treatment history is one of the most crucial factors to play a role in the response to a new treatment.
  - Other important factors are virologic and immunologic monitoring
- We investigated a set of statistical learning models to optimise ART sequencing in the absence of GRT

The Eu*Resist* GEIE data base

- Eu*Resist* is a no-profit foundation
- It is the largest data base in the world comprising clinical, demographic and genomic data of HIV+ patients from national cohorts of Western Europe (Italy, Germany, Sweden, Luxembourg)
  - ≈34'000 patients
  - ≈500'000 CD_4 and ≈400'000 HIV-RNA measurements
  - ≈100'000 antiretroviral therapies
  - ≈31'000 HIV sequences (polymerase)
- It is open to any kind of collaboration and data exchange
- We already set up collaboration with other European HIV cohorts (Virolab, comprising data from Spain, Netherlands, Belgium, and France) and with Russia

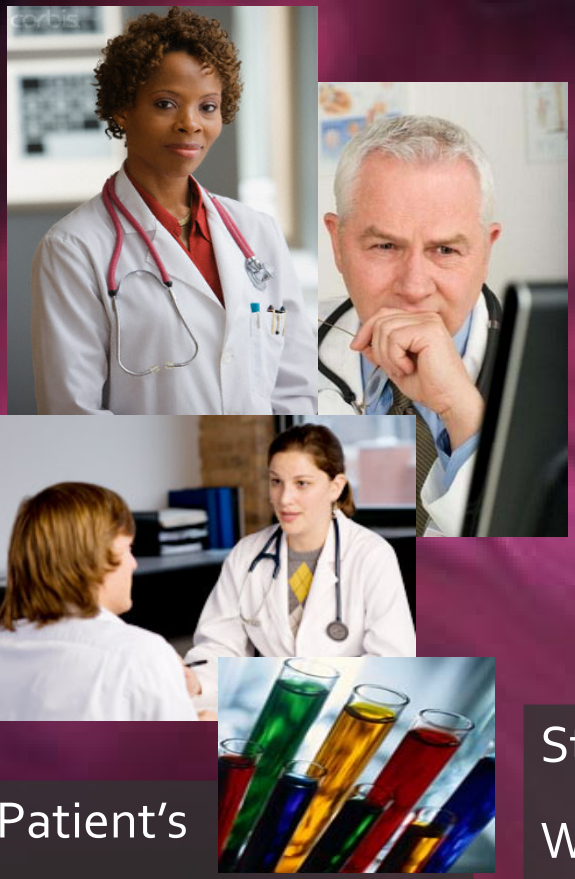
Eu*Resist* current model

- The EuResist GEIE in previous years developed a statistical learning methodology for optimal ART sequencing
  - http://engine.euresist.org
- The doctor inserts in a public website patient's GRT, HIV-RNA, CD_4 and other information
- The doctor gets a list of suitable therapies with an estimation of the probability to reach undetectable viral load after 8-weeks

Our ongoing research

- In low-middle income countries often the GRT is not available, and sometimes HIV-RNA testing
- We are developing a free model that provides optimal ART sequencing WITHOUT the need of a GRT, using only information of patient's therapy history and clinical markers

EuResist Model



Patient's

Age, gender

HIV RNA

CD_4

Experienced drugs

HIV GRT

Statistical model

Web-service

Customised ART sequencing

EuResist | Integration of viral genomics with clinical data to predict response to anti-HIV therapy

Results

Ranking of drug combinations

Top 10 best regimens for the patient described by your input data, ranked according to probability of success at 8 weeks after treatment change. The average accuracy of the system with a complete set of data in input is 76%.

10 BEST DRUG COMBINATIONS REGARDLESS OF YOUR SELECTION [*]

Rank	Regimen	Success probability	Range	Graphic bar
1	3TC TDF LPV	57.36%	50.43% - 69.84%	
2	3TC TDF FPV/rtv	57.68%	49.06% - 69.16%	
3	AZT TDF FPV/rtv	57.60%	49.06% - 69.41%	
4	D4T TDF FPV/rtv	56.44%	49.06% - 70.61%	
5	AZT TDF EFV	53.61%	45.57% - 63.61%	
6	AZT TDF LPV	56.45%	47.93% - 70.10%	
7	3TC TDF ATV/rtv	59.08%	49.06% - 74.92%	
8	3TC TDF EFV	59.61%	50.06% - 76.63%	
9	AZT TDF ATV/rtv	59.00%	49.06% - 75.14%	
10	D4T TDF ATV/rtv	58.59%	49.06% - 76.19%	

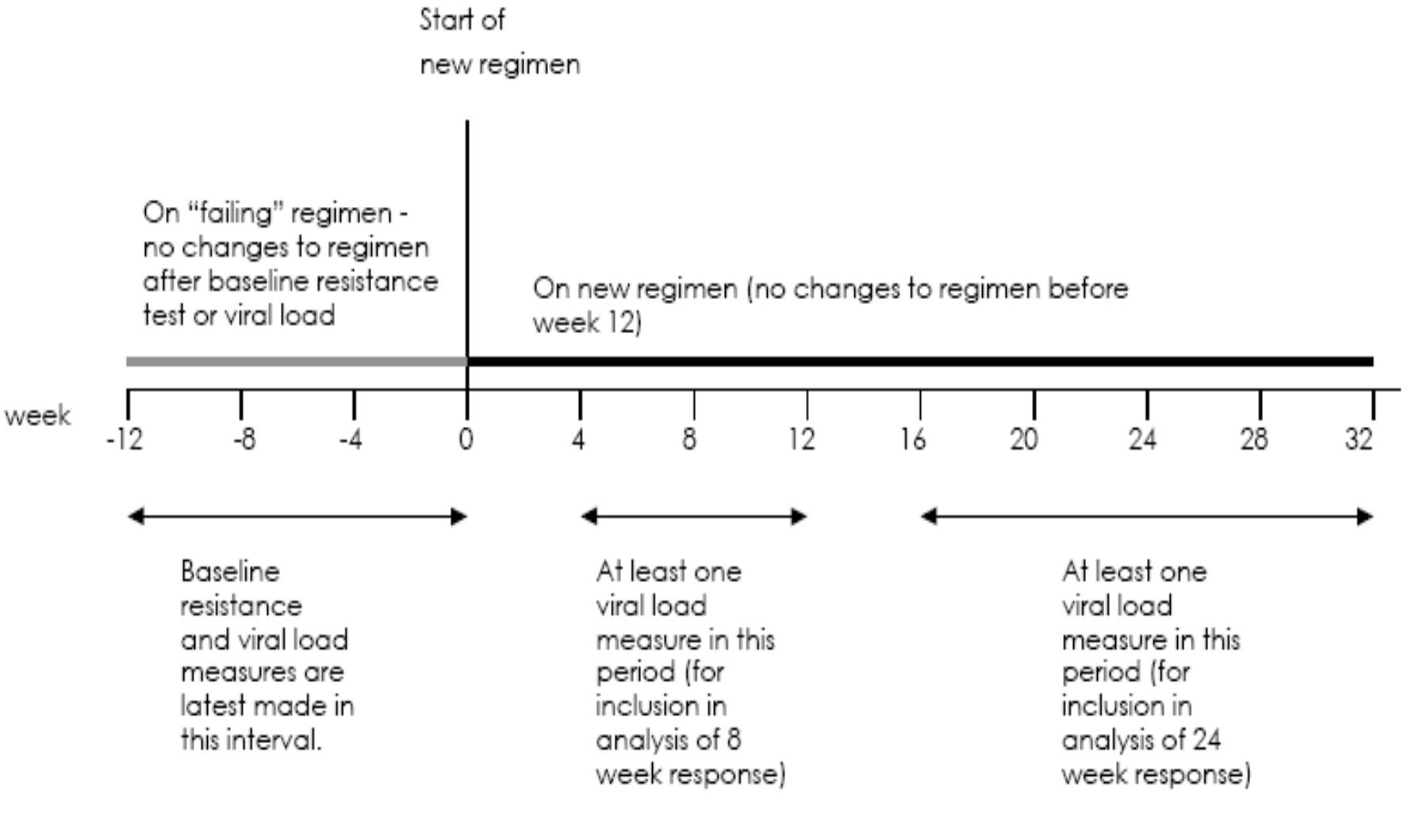
How can we create a prediction model from the data?

- Statistical learning (or data mining) is the process of mining knowledge from raw data, i.e. to build a decision system based on data evidences
- There are several modeling techniques that have been invented (some with strange names), such as Neural Networks, Linear or Logistic Regression, Decision Trees, Random Forests, Bayesian Networks, Support Vector Machines
- Every model is supported by statistical validation, i.e. we test how the model behaves with unseen examples

How to Predict virological response for a given ART: data needed

- Treatment Change Episodes (TCE) with ART or cART
- Baseline HIV RNA load, CD4+ T cell counts
- Baseline HIV *polymerase* genotype and subtype
- Patient's demographics (age, sex, ethnicity, mode of HIV transmission…)
- Previous drug usages (>1 year usage) for each drug class and each single drug
- 8-weeks and 24-weeks HIV RNA response
  - Success defined as the achievement of <500 cp/ml (or >2 Log decrease from baseline at 8-weeks)

A treatment change episode



The challenge: predicting optimal ART without GRT

- Current Eu*Resist* model, that uses GRT, predicts the correct virological outcome for a given ART - on average - with 76% accuracy
- We will test some statistical learning models that DO NOT USE GRT, but only information of patient's drug history (DH)
- We will compare GRT-based vs DH-based models and we will see if there are sensible loss in performance
- We will investigate the performance of the model in extra-EU scenarios

Statistical models and validation procedures

- Random Forest (RF) classifier
  - Nested modelling on subsets of input covariates
    - Genotype based (GRT)
    - Drug history based (DH)
  - Non-linear, high-performing model
- Goodness-of-fit functions
  - Accuracy (% of correct classifications)
  - Area Under the Receiver Operating Characteristic (AUC), true positive vs. false negative rates
- Multiple Cross Validation (MCV)
  - Model comparison via adjusted t-test

Results on the Eu*Resist* data subset used for training and validation

Descriptive Statistics

- 2,831 and 2,579 instances for 8- and 24-weeks response data subsets
- 68.2% and 69.8% of patients reached virological success at 8- and 24-weeks

Results

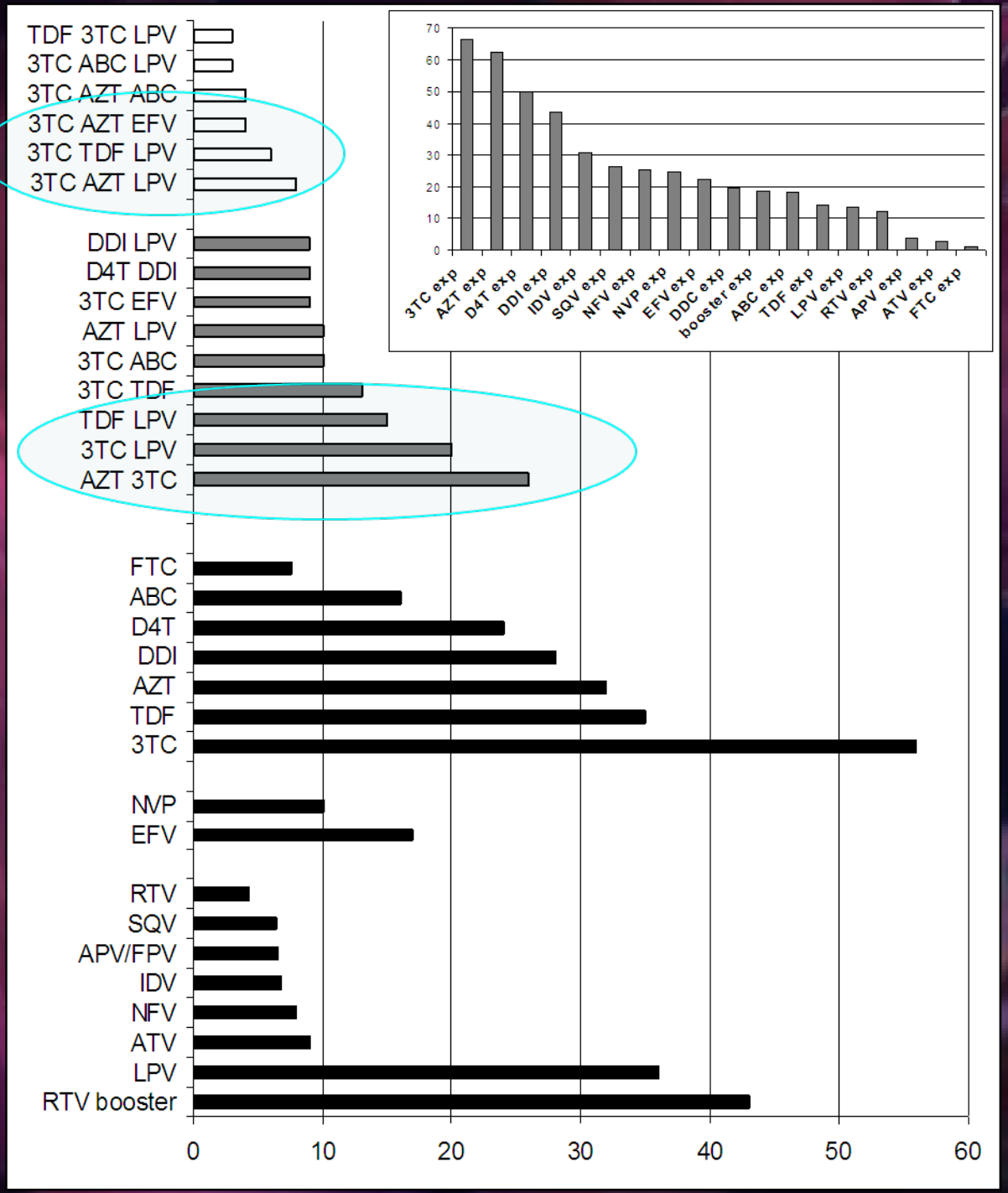
Descriptive statistics

Patients' baseline characteristics (n=2831)	Value
Mean (SD) patient age	42 (13)
Percentage of cases from male patients	70
Percentage of cases from drug users	27
Percentage of cases from homosexual men	32
Percentage of cases from heterosexual patients	38
Percentage of cases from Caucasian patients	72
Percentage of cases from African patients	22
Percentage of cases with previous exposure to NRTI	74
Percentage of cases with previous exposure to NNRTI	41
Percentage of cases with previous exposure to PI	58
Median (IQR) log baseline HIV RNA load	4.4 (3.8-5.0)
Median (IQR) baseline CD4+ percentage	16.5 (11-20)
Median (IQR) baseline CD4+ count	255 (137-397)
Median (IQR) number of previous treatment lines	3 (1-6)
Median (IQR) number of drugs included in the cART	3 (1-4)
Percentage of subtype B sequences	83
Percentage of subtype C sequences	3
Percentage of subtype 02_AG sequences	2.5
Percentage of subtype F1 sequences	2.3
Median (IQR) baseline IAS NRTI mutations	1 (0-3)
Median (IQR) baseline IAS NNRTI mutations	0 (0-1)
Median (IQR) baseline IAS PI mutations	3 (2-5)

Results

Descriptive statistics

% of drugs and drug combinations in TCE

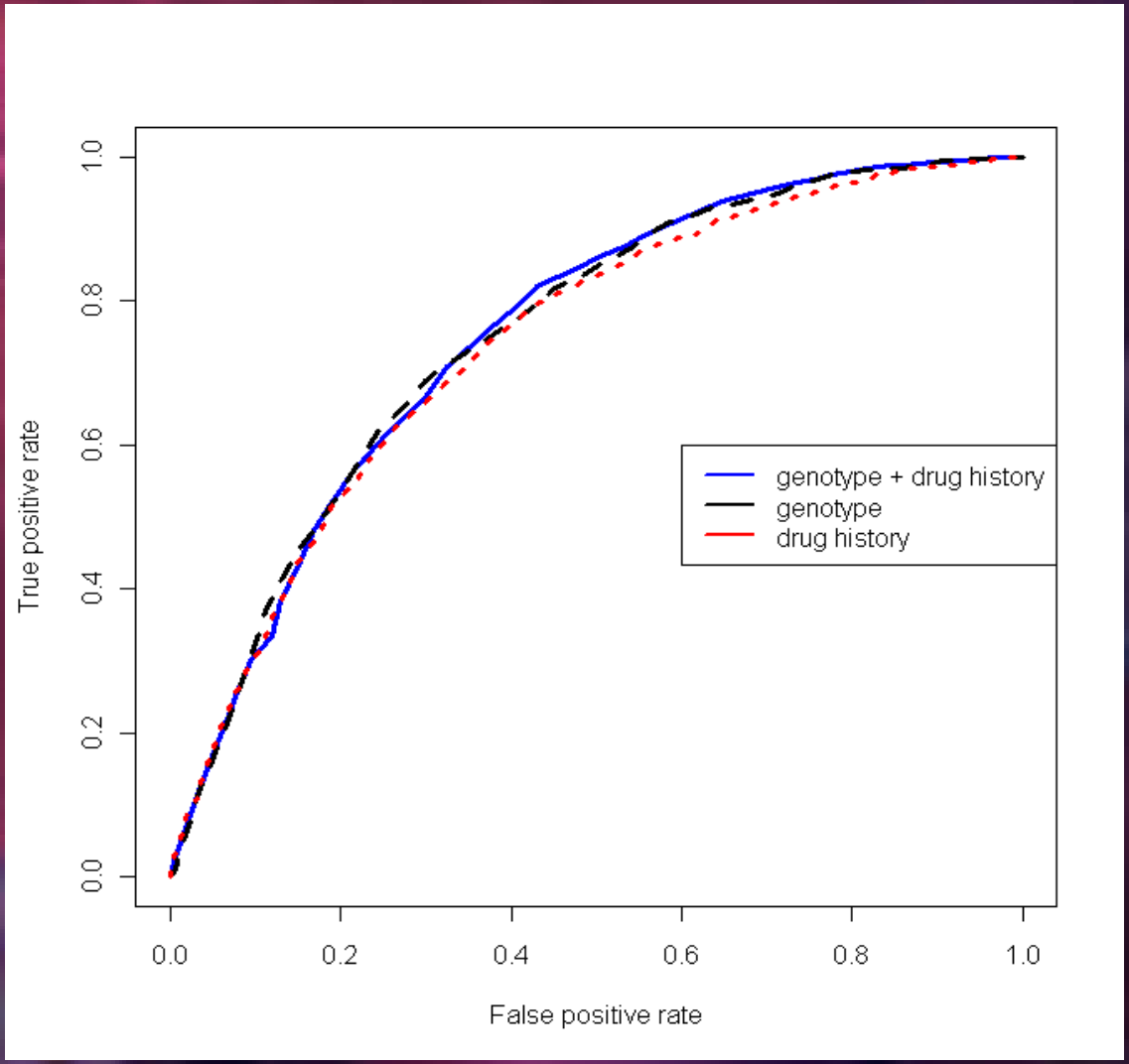


Results: GRT vs. DH

model	*8-weeks outcome*		*24-weeks outcome*	
	Accuracy (sd)	*AUC (sd)*	*Accuracy (sd)*	*AUC (sd)*
DH	74.78% (1.97)	0.76 (0.03)	78.64% (2.19)	0.83 (0.02)
GRT + DH	76.25% (1.93)	0.77 (0.03)	79.75% (2.14)	0.84 (0.03)

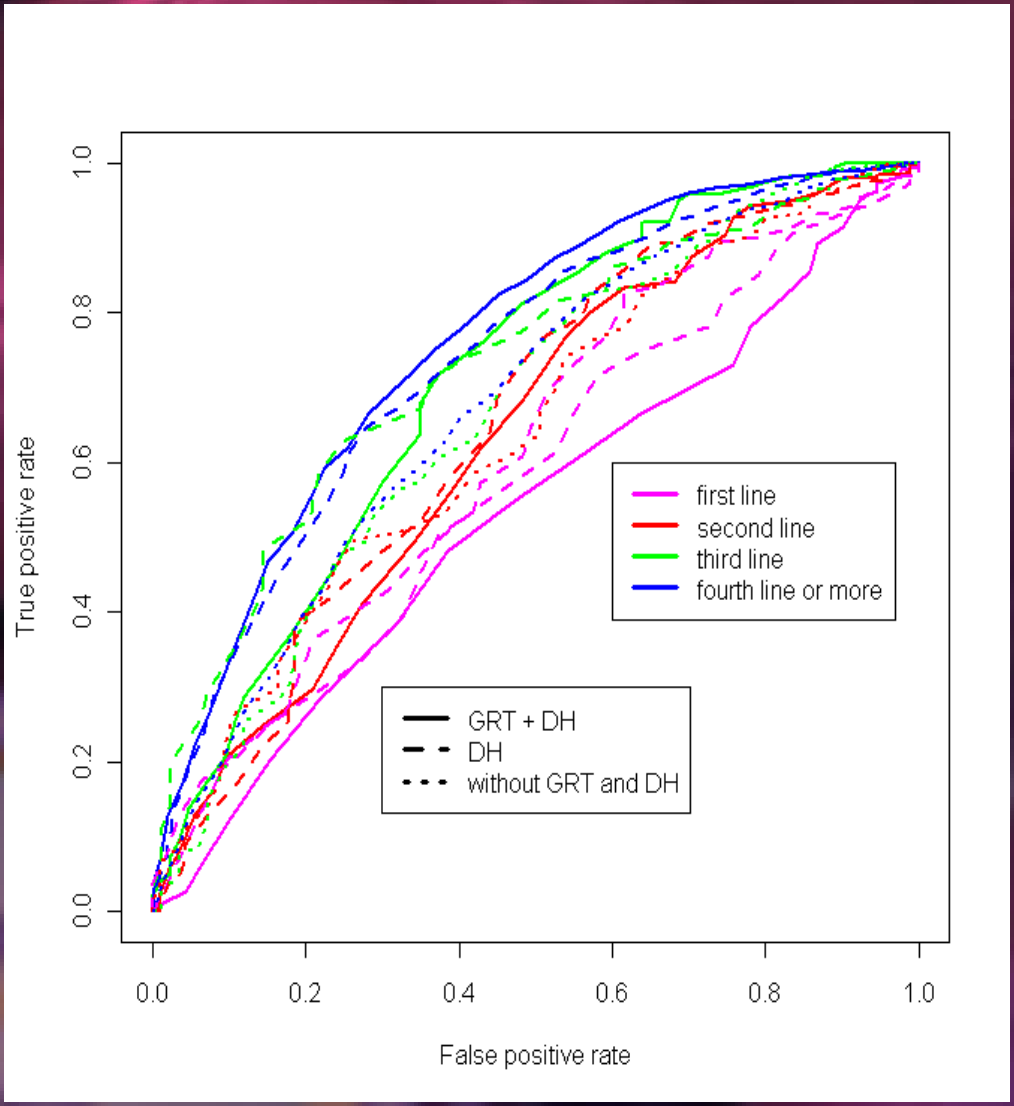
- All models adjusted for baseline markers, current ART, and demographic indicators
- No statistically significant differences found between GRT and DH after adjusted t-test

Results: GRT vs. DH overall



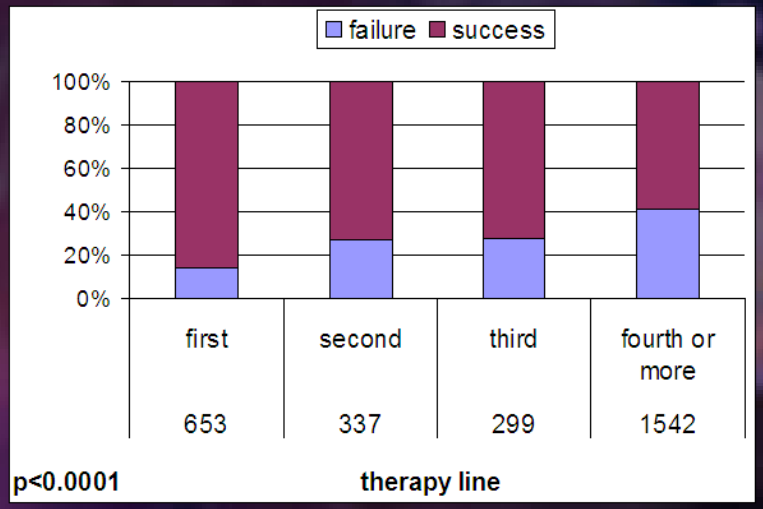
8-weeks response

Results: GRT vs. DH by therapy line

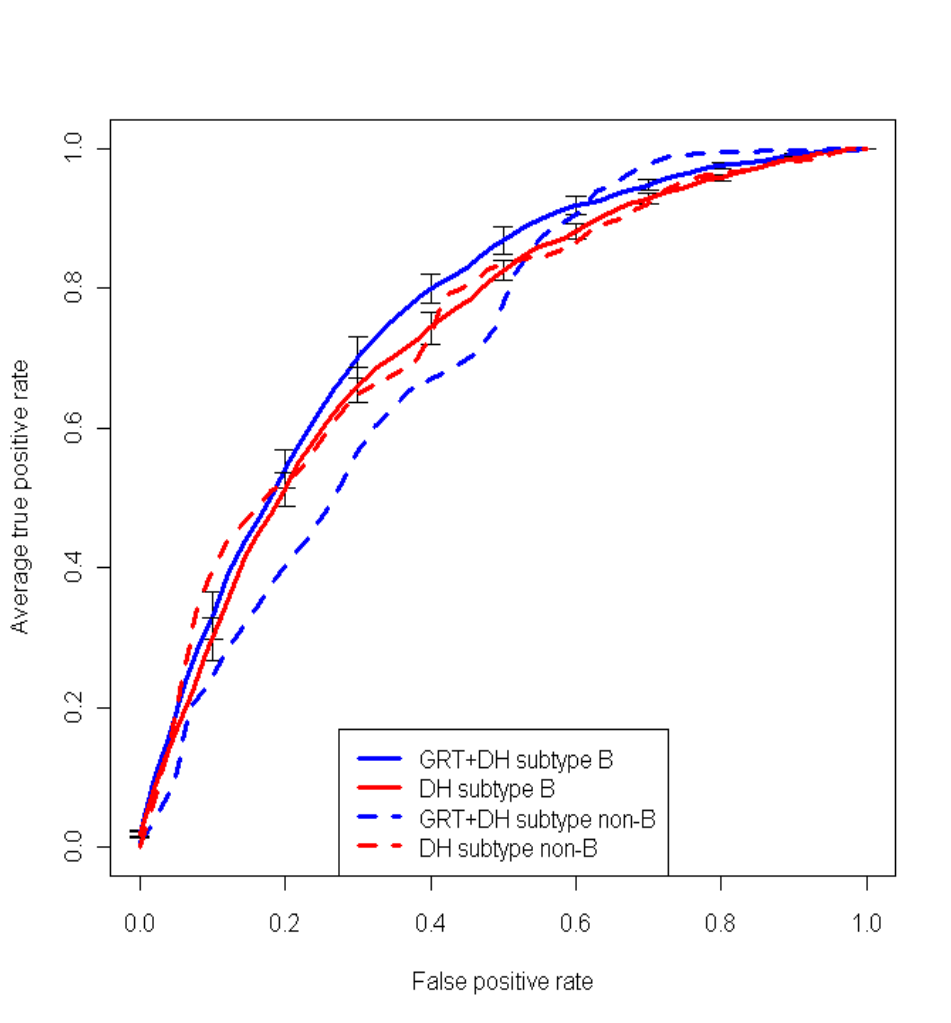


There is an increase in performance by increasing the therapy line: i.e. all models predict better when there is a long known therapy history

On the other hand, subsequent therapy lines are likely to be more unsuccessful



Results: GRT vs. DH by subtype



There is a drop in performance both for GRT and DH, but seems that the DH model is more robust to the subtype change

8-weeks response

Conclusions

- In our study population, GRT and DH RF models show equivalent performance, and the same holds when comparing against GRT+DH RF model
  - by increasing therapy line, there is a concomitant increase in performance, but a clear higher risk of virological failure
  - By training on B subtypes and testing on non-B, there is a drop in performance both for GRT and DH models; however, it seems that the DH based model is more robust to this loss
  - By an additional sensitivity analysis, we excluded GRT-guided TCE and our main findings were confirmed

Limitations and future perspectives

- We assumed that there is availability of baseline HIV RNA load tests and we considered virologic success as outcome
- We did not account for different ART switching policies driven by clinical/immunological criteria rather than by virologic criteria
- We did not restrict analysis on ART combination more commonly used in low-middle income countries

- Additional analyses to solve these issues above are advisable
- In addition we foresee:
  - In-depth analysis for non-B subtypes
    - *data contribution to EuResist is welcome*
  - Free web service implementation

Contacts

Eu*Resist* website

www.euresist.org

Eu*Resist* ART optimisation engine

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