The use of computational models to predict response to HIV therapy and support optimal treatment selection

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hiv resistance response database initiative

State of the ART

- Combination antiretroviral therapy (ART): long-term suppression of HIV and prevents disease progression
- Despite 25 drugs / 6 classes, viral breakthrough often with resistance remains a significant challenge
- Sustained re-suppression of HIV requires optimal drug selection
- Selecting the optimum drug combination after failure is a major challenge:
  - Complexities of resistance
  - Archived mutations (undetectable)
  - Multiple drug combinations

State of the ART-2

- In well-resourced settings genotypic resistance tests are in common use but interpretation is challenging:
  - Rules based interpretation: point mutations – susceptibility to individual drugs
  - How do you predict response to combinations
  - Different interpretation systems give different answers
  - Genotypic sensitivity scores (GSS) only moderately predictive of virological response
- Computational modelling to predict response to combination therapy from many variables may be an advantage?
- Requires large amounts of data for training

The RDI at-a-glance

- Set up in 2002 as not-for-profit to collect data from clinical practice and develop computational models
- 2011: data from 85,000 patients, 850,000 viral loads, 80,000 genotypes
- Data used to train models to predict response to ART from up to 100 different variables
- Models typically 80% accurate vs 60-70% for GSS (genotyping + rules)
- Models now available as an aid to treatment selection through the on-line tool '**HIV-TRePS**'

Variables used by the models for their predictions

Models use the following information (up to approx 100 variables) to make their predictions:

- Baseline plasma viral load (copies HIV RNA/ml)
- Baseline CD4 count (cells/ml)
- Baseline genotype (e.g. 62 mutations)
- Treatment history (e.g. 18 drugs)
- Drugs in the new regimen (18 drugs covered by current system)
- Time to follow-up viral load (days)

The models make a prediction of the probability of virological response, e.g. <50 copies or <400 copies HIV RNA/ml

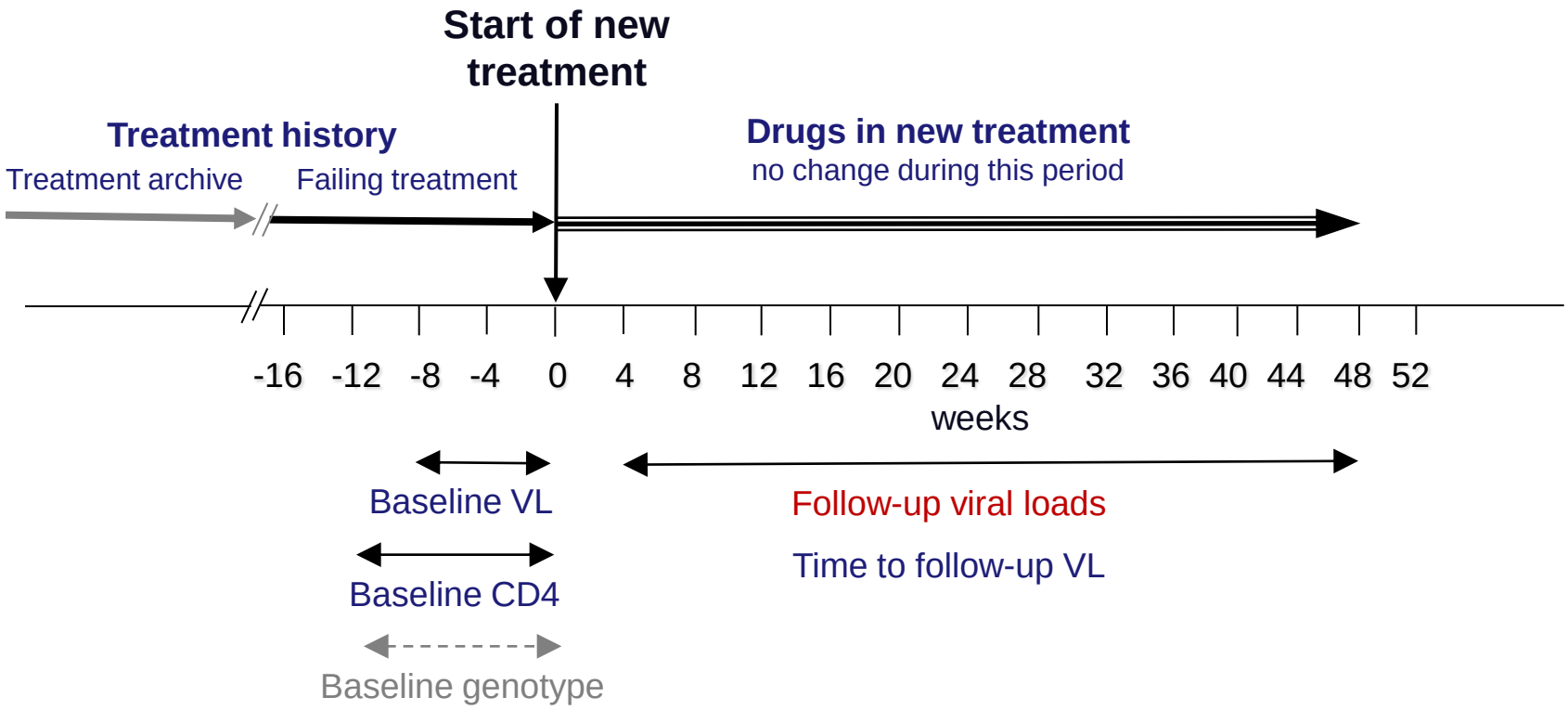
Resource-limited settings

- If resources are limited treatment selection can be even more challenging:
  - Genotyping may not not available
  - Newer drugs/classes may not be available
- Could computational modelling help in these situations?

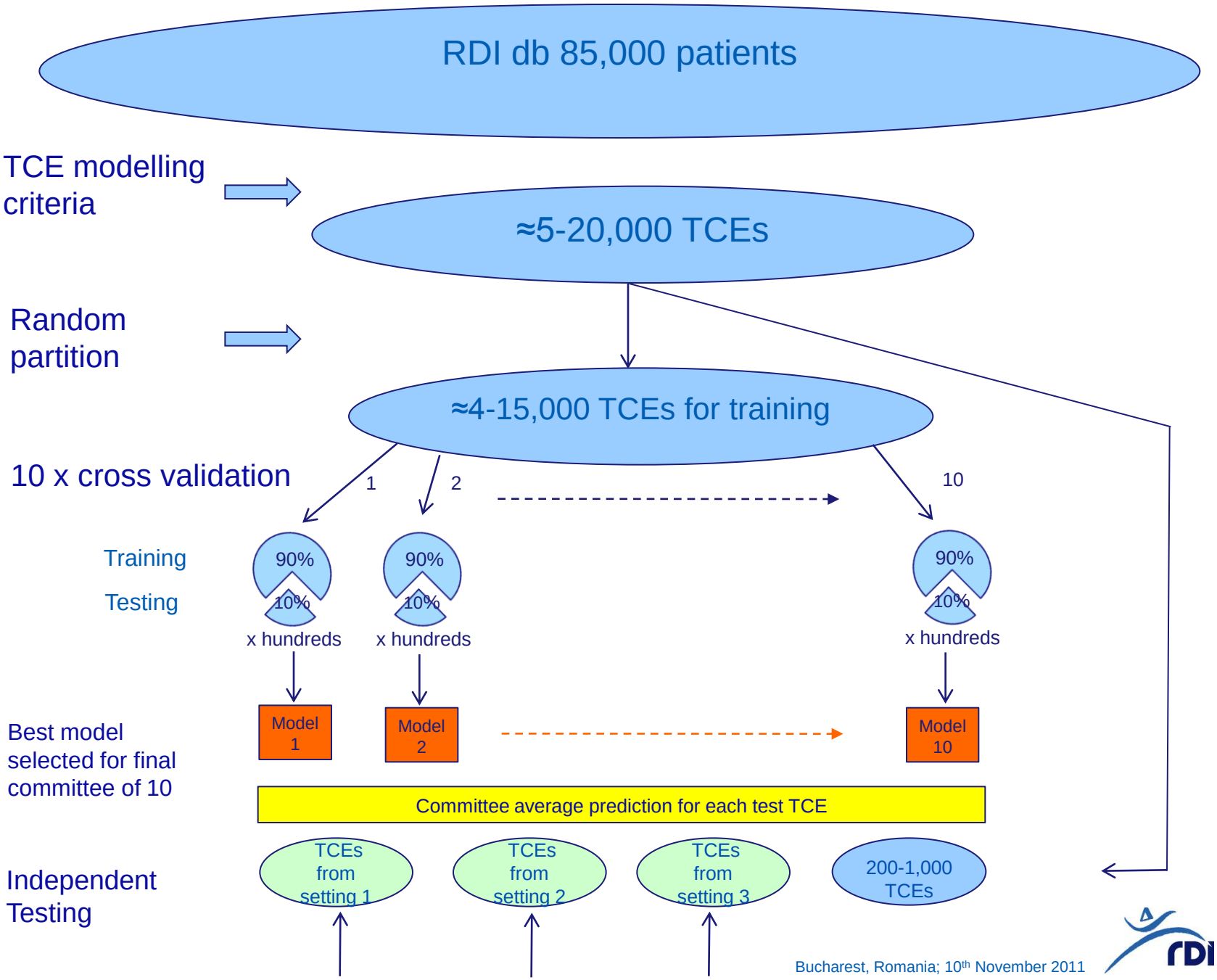
Resource-limited settings

- If resources are limited treatment selection is even more challenging:
  - Genotyping may not not available
  - Newer drugs/classes may not be available
- Could computational modelling help in these situations?
- Three studies modelling treatment response without the genotype
- Variables used: viral load, CD4 count, treatment history, drugs in new regimen, time to follow-up
- Results indicate a small loss of accuracy of approximately 5%
- ‘No-genotype’ models now also available online as part of HIV-TRePS

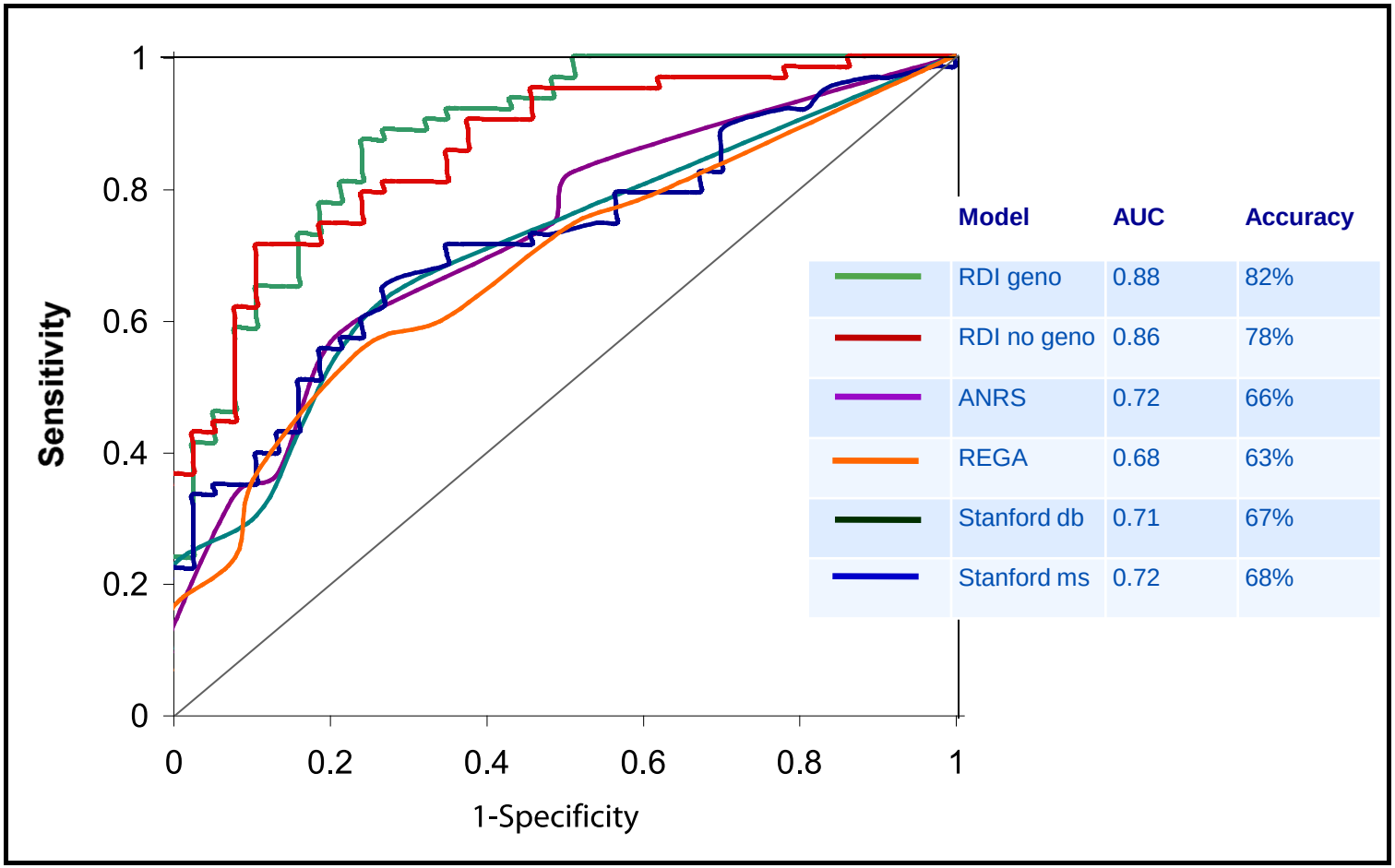
Unit of data used for training models: the Treatment Change Episode (TCE)



Model output: Probability of virological response


RDI db 85,000 patients
TCE modelling criteria
≈5-20,000 TCEs
Random partition
≈4-15,000 TCEs for training
10 x cross validation
1
2
10
Training
Testing
90%
10%
x hundreds
Model 1
Model 2
Model 10
Best model selected for final committee of 10
Committee average prediction for each test TCE
Independent Testing
TCEs from setting 1
TCEs from setting 2
TCEs from setting 3
200-1,000 TCEs

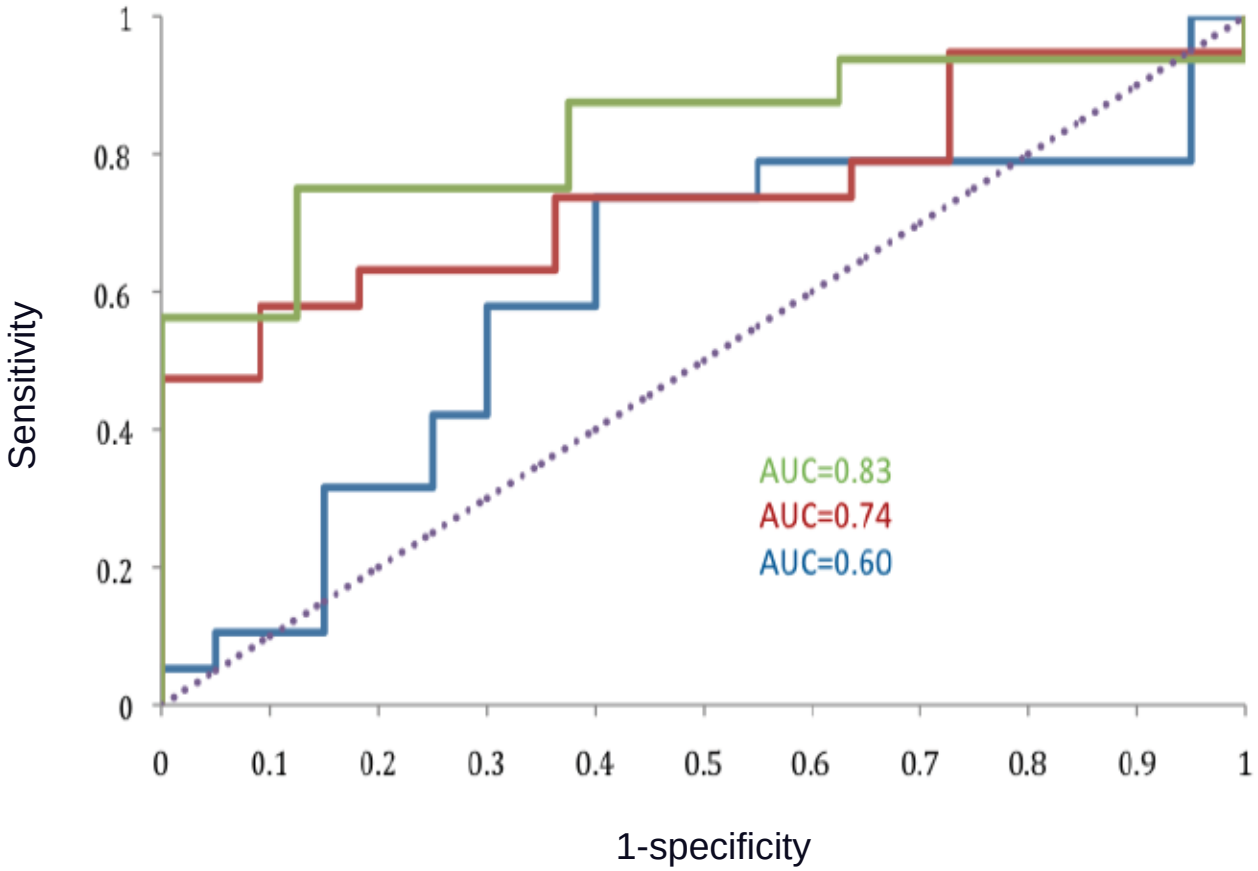
ROC curves for RDI models with and without genotype and GSS from common rules systems



Model	AUC	Accuracy
RDI geno	0.88	82%
RDI no geno	0.86	78%
ANRS	0.72	66%
REGA	0.68	63%
Stanford db	0.71	67%
Stanford ms	0.72	68%

Larder BA *et al*. 49th ICAAC, 2009; H-894

ROC curves for analyses of Romanian data



Ene L *et al*. 18th CROI, 2011; L-208

Clinical pilot studies in USA, Canada and Italy

- 23 HIV physicians entered genotype, treatment history, viral loads, CD4 counts for 114 patients on failing ART via RDI website
- Also made treatment decisions based on these data
- Models made predictions of virological response for their selections and hundreds of alternatives
- Physicians received report with predictions for their selections plus the best alternatives ranked in order of predicted response
- Physicians made final treatment selection

Larder BA *et al*. AIDS Patient Care & STDs, 2011; 25(1):29-36

Main findings of clinical pilot studies

- HIV physicians changed 33% of their treatment decisions after using RDI system
- Changed decisions were predicted to result in greater virological response
- Changed decisions involved fewer drugs overall
- System rated as a useful clinical tool that was easy to use

Larder BA *et al*. AIDS Patient Care & STDs, 2011; 25(1):29-36

Predictions of virological response in the clinical pilot studies

Cases where the treatment decision was changed (n=38)	Physician's original decision	Physician's final decision	Best RDI alternative
Mean	-1.92	-1.99	-2.12
Median	-1.91	-1.99	-2.06
Proportion with >2 log reduction	39%	50%	58%
Statistical significance (vs physician's initial selection)		p<0.05	p<0.0001

Larder BA *et al*. AIDS Patient Care & STDs, 2011; 25(1):29-36

The issue of generalisability

- Most RDI data is from western Europe, USA, Canada, Australia and Japan
- Our previous studies have shown that models are most accurate for patients from the settings that provided the training data
- Our models are therefore evaluated not only during cross validation but with independent test sets and data from other settings
- ***How accurate are the RDI's 'no-genotype' models be for real cases from resource-limited settings (RLS)?***

Recent study objectives

1. To develop random forest (RF) models to predict virological response to cART without the use of genotype
2. To test these models with data from RLS
3. To use the models to identify potentially effective alternative regimens for cases of actual virological failure in RLS

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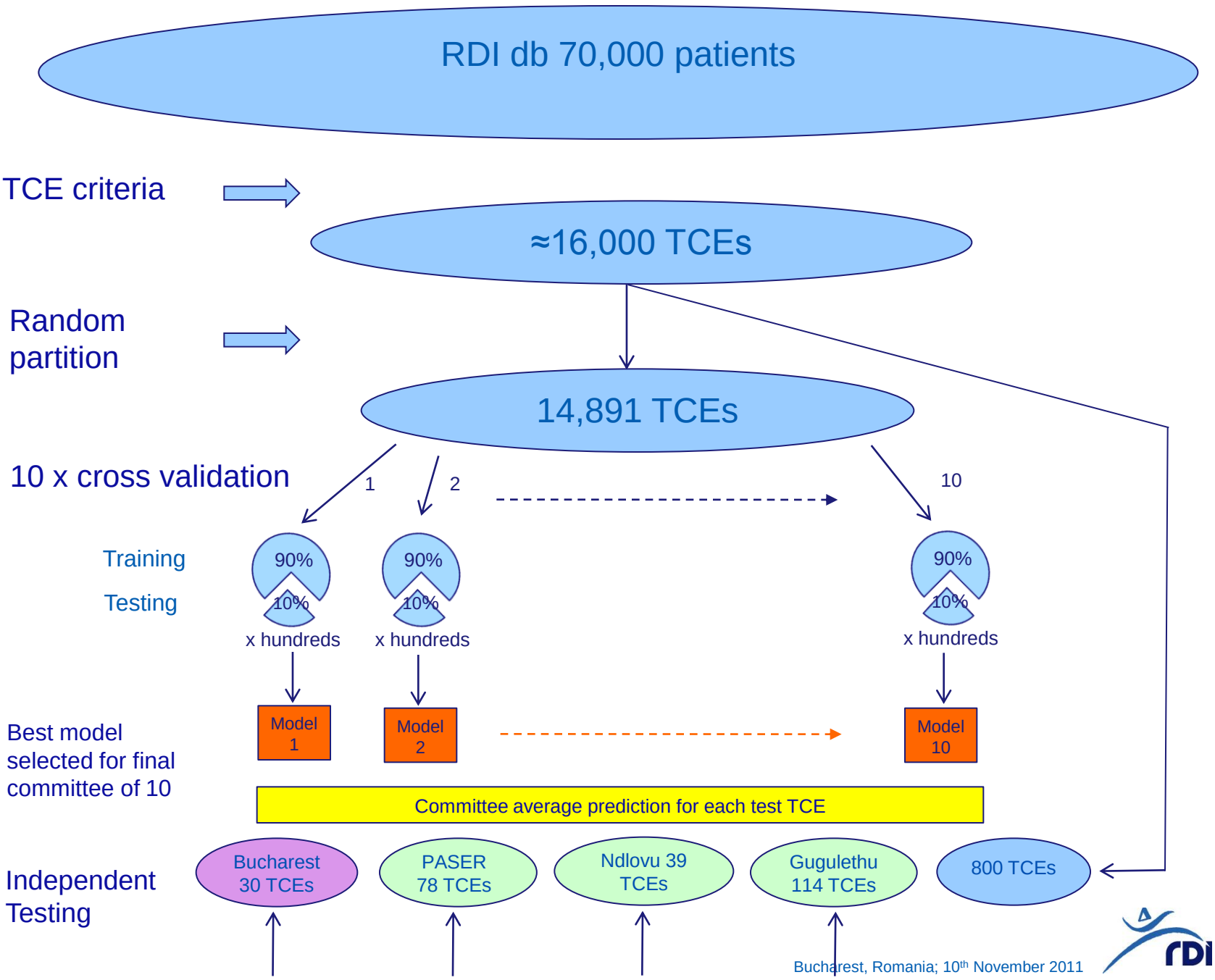
RDI db 70,000 patients
TCE criteria
≈16,000 TCEs
Random partition
14,891 TCEs
10 x cross validation
1
2
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Training
Testing
90%
10%
x hundreds
Model 1
Model 2
Model 10
Best model selected for final committee of 10
Committee average prediction for each test TCE
Independent Testing
Bucharest 30 TCEs
PASER 78 TCEs
Ndlovu 39 TCEs
Gugulethu 114 TCEs
800 TCEs

Results

	Cross validation (n=14,891)	Test (n=800)	Gugulethu (n=114)	Ndlovu (n=39)	PASER-M (n=78)	South Africa (n= 164)	"Dr Victor Babes" Bucharest(n =30)
ROC AUC (95% CI)	0.77 (0.76, 0.78)	0.77 (0.73, 0.80)	0.65 (0.55, 0.76)	0.61 (0.40, 0.73)	0.58* (0.38, 0.77)	0.62* (0.53, 0.71)	0.60* (0.36,0.84)
Overall accuracy (95% CI)	72% (71%, 73%)	71% (68%, 74%)	67% (57%, 75%)	72% (55%, 85%)	71% (59%, 80%)	65% (57%, 72%)	67% (47%, 83%)

Statistical comparison vs 800 test set using Delong's test for comparing ROC curves:
* Significant ($p<0.05$)

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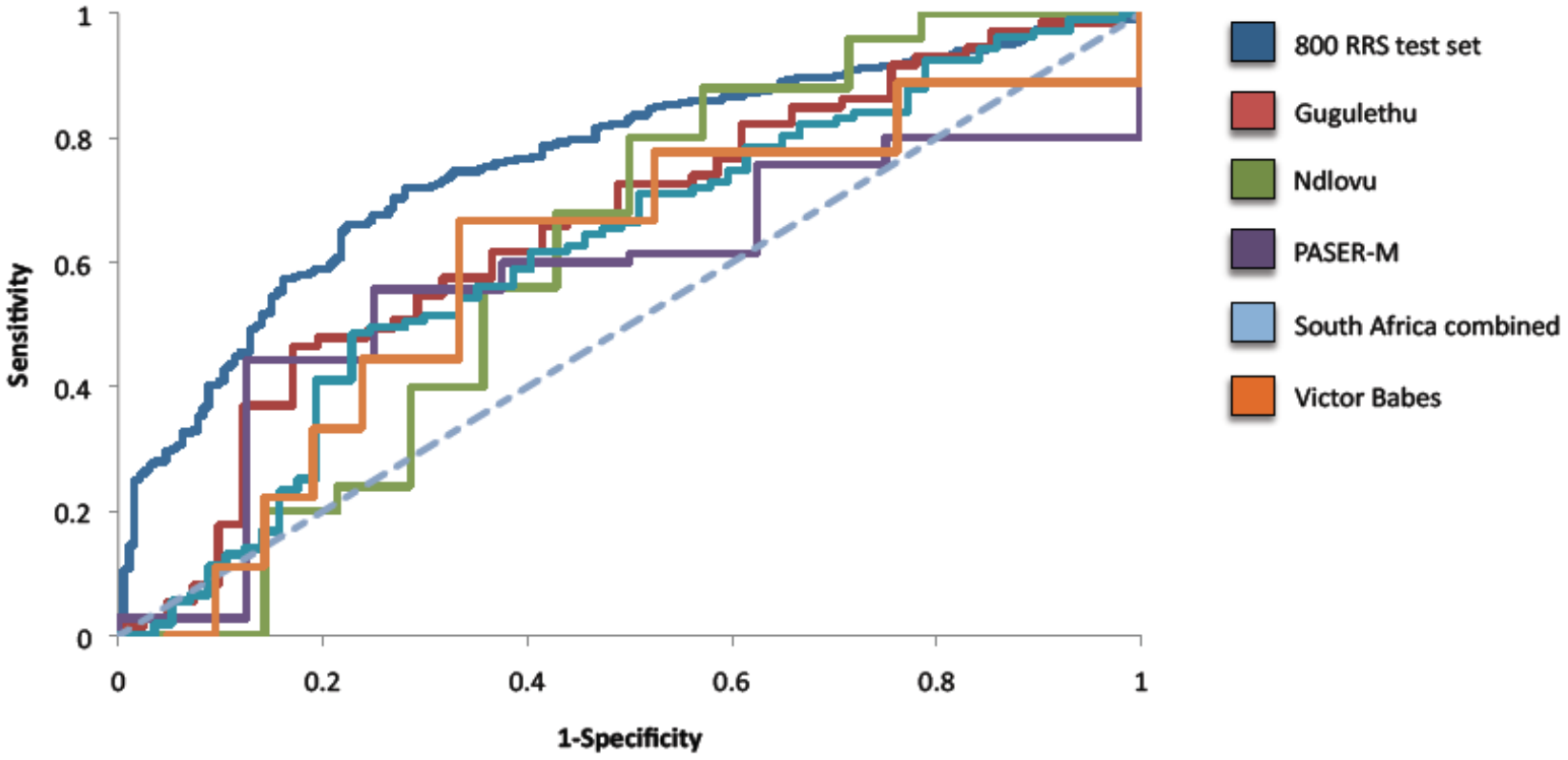
ROC curves



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In silico analysis

- Cases from the RLS were identified where the new treatment failed and this failure was correctly predicted by the models
- Models used the baseline data to predict responses to multiple alternative 3-drug regimens involving only those drugs in use in the centre(s)

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In silico analysis

	Ndlovu	Gugulethu	PASER-M	South Africa	Victor Babes
No of actual treatment failures	14	41	8	57	21
No. (%)of these predicted to fail	8 (57%)	26 (63%)	5 (63%)	34 (60%)	14 (67%)
No. (%) for which alternative regimens were found that were predicted to be effective	4 (50%)	20 (77%)	2 (40%)	27 (79%)	14 (100%)
No. (%) for which alternative regimens were found with higher predictions of response	8 (100%)	26 (100%)	5 (100%)	34 (100%)	14 (100%)
Overall no. (%) of failures for which alternative regimens were found that were predicted to be effective	10 (71%)	35 (85%)	5 (63%)	50 (88%)	21 (100%)
No. (%) for which alternative regimens were found with higher predictions of response	14 (100%)	41 (100%)	8 (100%)	57 (100%)	21 (100%)

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Conclusions

- RF models, trained with large datasets from well-resourced settings, are highly accurate predictors of virological response for cases from those countries
- ‘No-genotype’ models are approximately 5% less accurate than models that use the a genotype in their predictions
- Models are less accurate for cases from unfamiliar settings but still comparable to genotyping with rules-based interpretation
- The models have the potential to predict and avoid treatment failure by identifying effective, alternative, practical regimens
- This approach has potential utility as an aid to the management of treatment failures, particularly in RLS.

Next steps

- To maximise the utility of this approach in any particular setting, models should be used that were developed including data from that setting
- RDI database currently lacks data from regions where the approach could have high utility, particularly RLS
- Aim is to collect sufficient data to develop regional models:
  - Sub-Saharan Africa
  - SE Asia
  - Eastern Europe

The RDI's Advisory Group

- Julio Montaner, Vancouver, Canada
- Jose Gatell, Barcelona, Spain
- Richard Harrigan, Vancouver, Canada
- Carlo Torti, Brescia, Italy
- Brian Gazzard, London, UK
- John Baxter, Camden, NJ, USA
- Sean Emery, Sydney, Australia
- Anna Maria Geretti, London, UK

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The RDI …

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HIV TReePS

HIV Treatment Response Prediction System