

The HIV Treatment Response Prediction System: using the experience of treating tens of thousands of patients to guide optimal drug selection

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HIV Resistance Response Database Initiative (RDI)

RDI launched in 2002 as a not-for-profit organisation with the following mission:

To develop & make freely available a system to predict response to combination antiretroviral therapy (ART) as an aid to optimising & individualising HIV treatment

RDI overview

- RDI global database: currently >150,000 patients, >1 million viral loads from >50 countries
- Data are used to train computer models to predict the probability of virological response to ART
- Models validated with independent test sets
- Models used to power the online HIV Treatment Response Prediction System (HIV-TRePS)

RDI key performance indicators

Ideally the system should be:

- Significantly more accurate predictor of response to ART than genotyping with rules-based interpretation
- At least as accurate as genotyping for patients without a genotype
- Able to identify alternative drug combinations with increased chance of success than those selected without the system

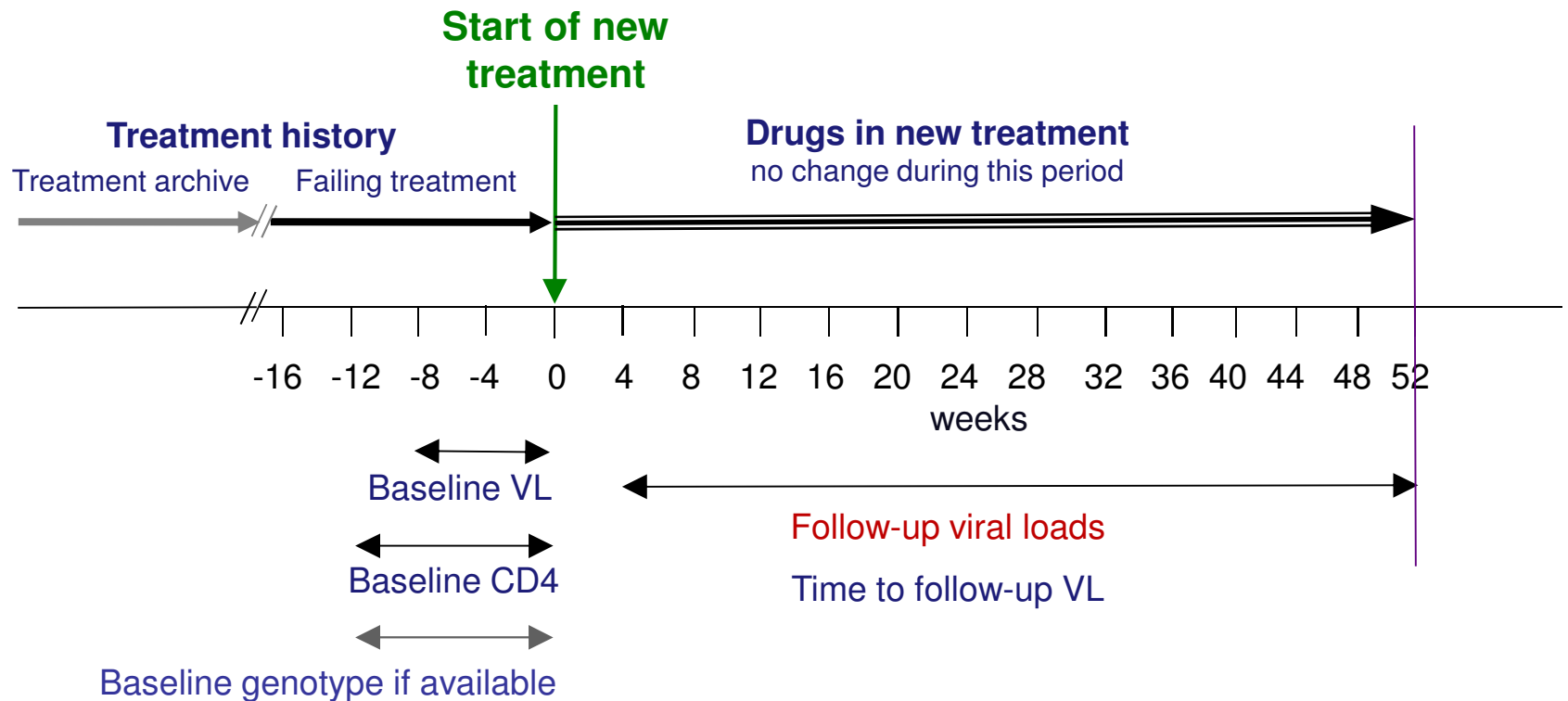
The advantage of computer modelling

- Models ‘learn’ by example
 - From extensive, real clinical data (thousands of cases)
- Work well for complex interactions between multiple variables
- Used successfully in other clinical areas
 - e.g. oncology, cardiology
- The models can give *quantitative* predictions of viral load response to drug *combinations*

What do RDI models use to make their predictions?

- Baseline viral load, CD4 count, (genotype)
- Antiretroviral drugs in treatment history
- Antiretroviral drugs in the new regimen
- Time to follow-up

The Treatment Change Episode (TCE)

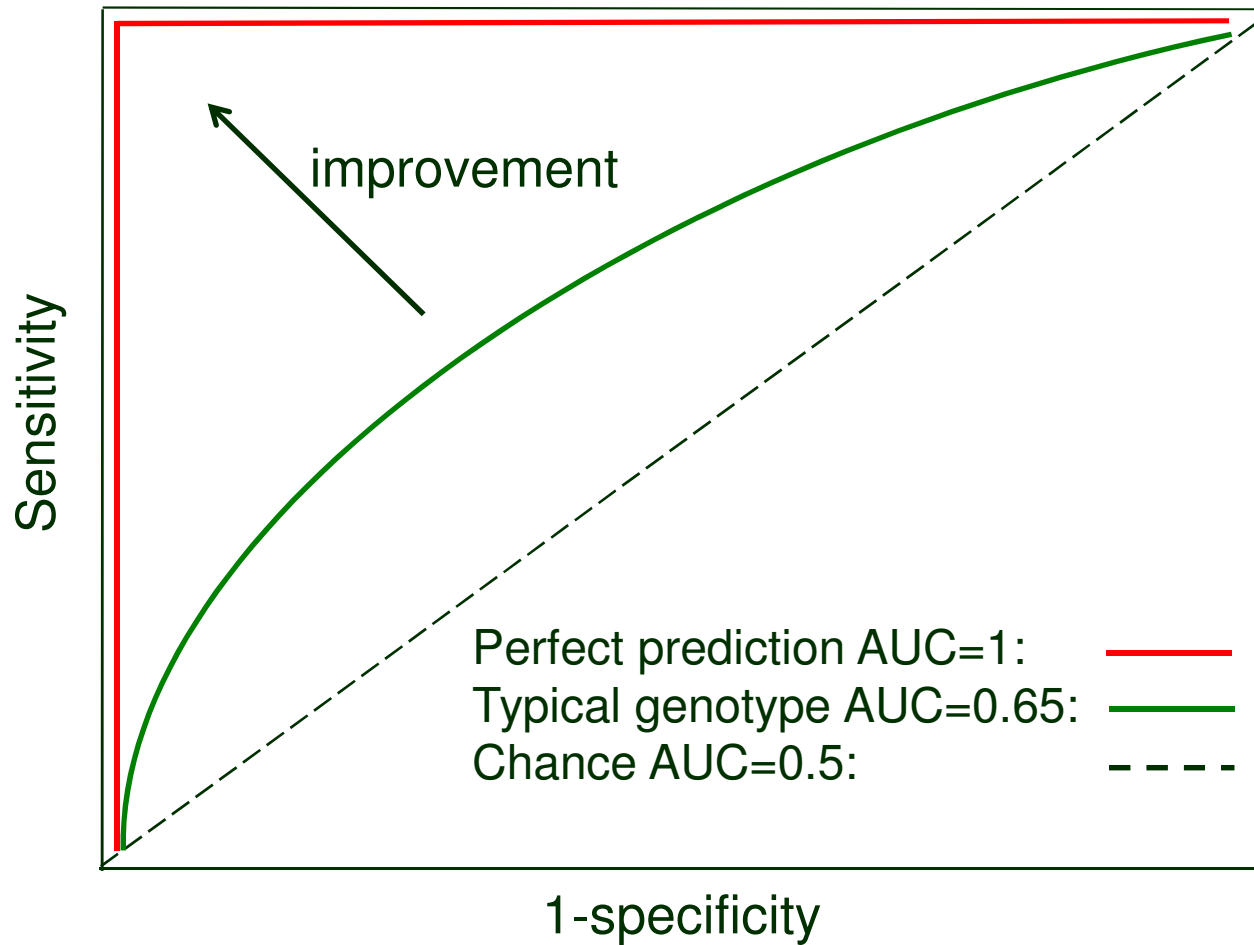


Model output: Probability of the follow-up viral load <50 copies/ml

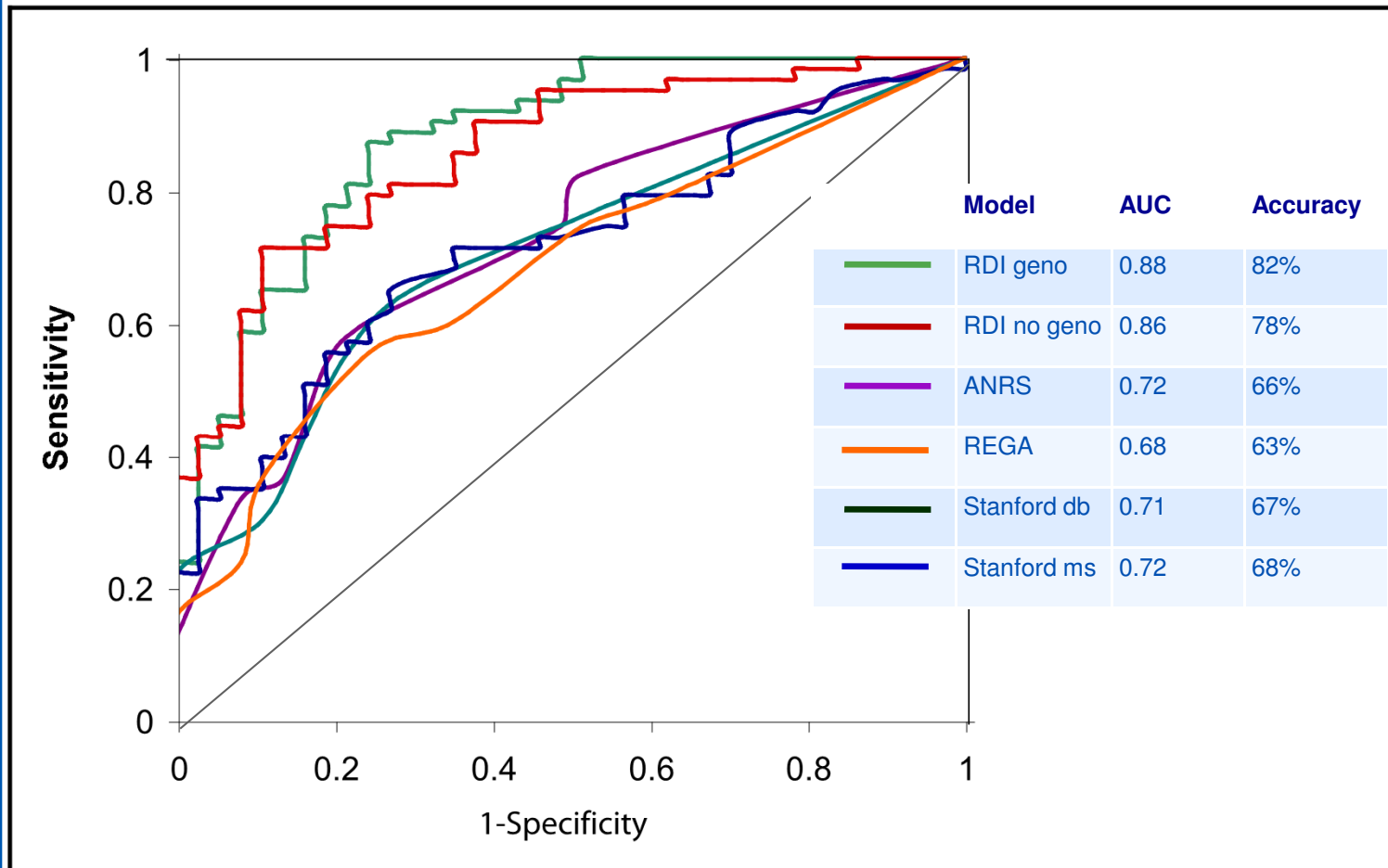
Model development and testing

- TCEs extracted from database that meet the modelling criteria (no missing data)
- TCEs randomly partitioned by patient into 90% for training & 10% for validation
- ‘Committee’ of 10 models (‘random forest’) developed using a cross-validation scheme
- The baseline/historical data & drugs in new regimen for test cases used by models to estimate the probability of response (committee average prediction)
- Predictions compared with actual response data on file
- Further validation using new data sets

Receiver Operating Characteristic (ROC) curves



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



Latest 'no-genotype' model training

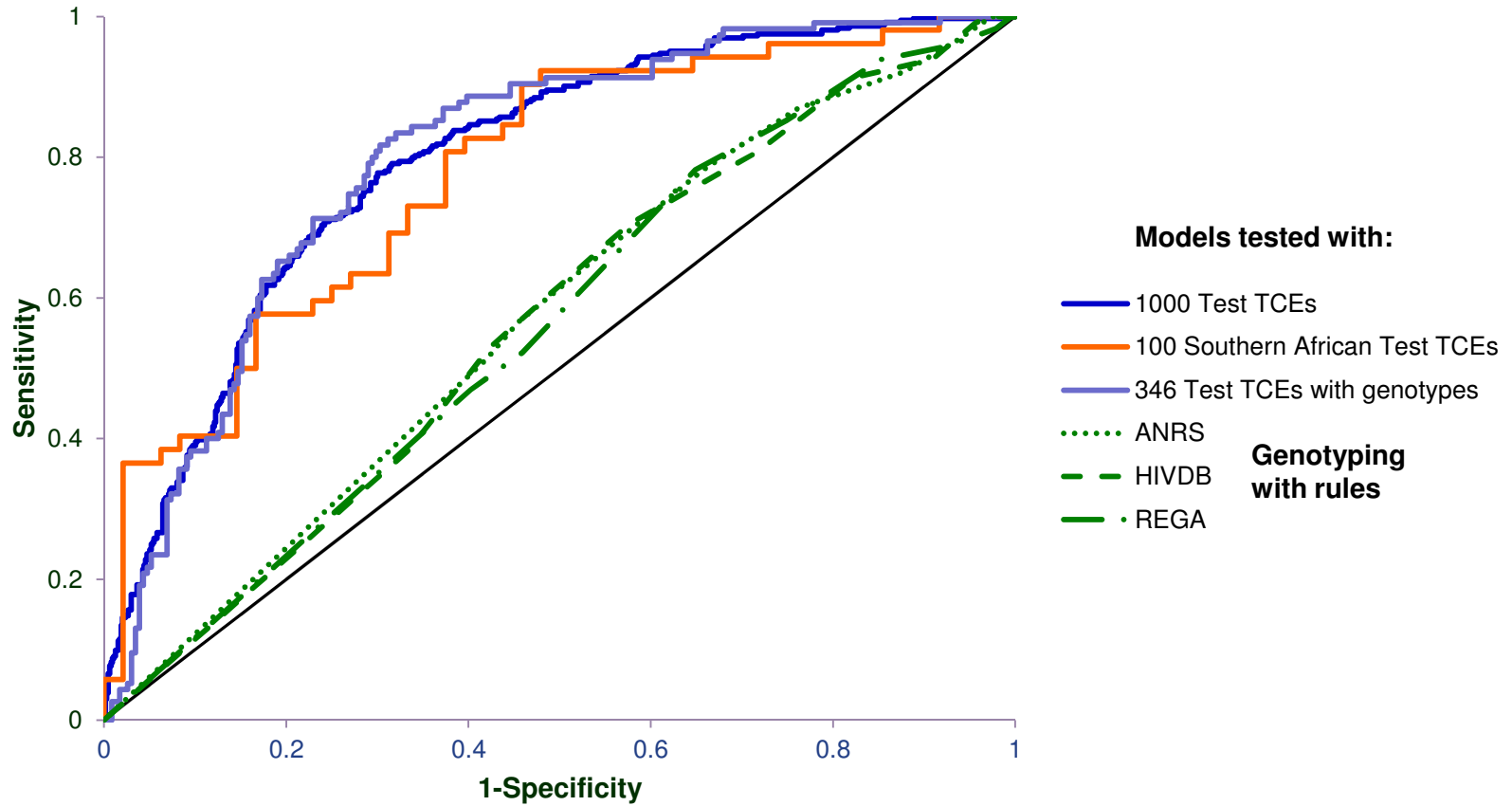
10 'random forest' models were developed:

- Data: around **24,000** cases of therapy change following virological failure (multiple sources, largely 'western' but including 1,090 from southern Africa)
- 22,567 training & 1,000 for validation
- 43 input variables: viral load & CD4 count before treatment change, treatment history, drugs in the new regimen, time to follow-up & follow-up viral load
- **Output: prediction of the probability of response to therapy (<50 copies HIV RNA/ml)**

Revell AD, Wang D, Wood R *et al.* An update to the HIV-TRePS system: The development of new computational models that do not require a genotype to predict HIV treatment outcomes. *J Antimicrob Chemother* 2014; 69:1104-1110.



ROC curves



RF models *versus* genotyping

(346 cases from global test set)

		Sensitivity	Specificity	Accuracy	
Prediction System	AUC	(%)	(%)	(%)	p (GSS vs RF)
ANRS	0.57	51	58	55	<0.0001
HIVdb	0.57	53	57	56	<0.0001
REGA	0.56	52	54	53	<0.0001
Ave:	0.57	52	56	55	
RF Models	0.80	65	80	75	

Modelling alternative regimens for southern Africa

- Baseline data from 100 southern African test cases input to the models
- Predictions of the probability of response obtained for alternative 3-drug regimens comprising only those drugs available in the clinic at the time of the treatment change
- Outcome measure - the number (%) of cases for which alternative regimens were identified that were predicted to be effective

Modelling alternative regimens for southern Africa

	All cases (100)	Failures (n=48)
Number (%) of cases for which alternatives were identified that were predicted to give a response	76 (76%)	31 (65%)

Summary of modelling study

- Models accurately predicted virological response to ART *without* a genotype (approx 80%)
- These were significantly more accurate predictors of response than genotyping with rules-based interpretation ($p < 0.001$)
- As accurate for cases from southern Africa as for other regions
- Identified alternative regimens predicted to be effective for the majority of cases where the new regimen in the clinic failed

Overview of two other recent studies

Clinical pilot study in Canada, US (NIH) & Italy

- HIV experts made salvage treatment decisions using genotype all other data & their expertise
- Then received predictions from the models
- *One-third of treatment decisions were changed*

Retrospective study of switching from 1st to 2nd line in Indian cohort (Bathalapalli)

- *Models identified cost-saving alternatives with greater probability of response for 88% of cases of actual failure*

Larder, BA, Revell, AD, Mican J, et al. Clinical Evaluation of the Potential Utility of Computational Modeling as an HIV Treatment Selection Tool by Physicians with Considerable HIV Experience. *AIDS Patient Care and STDs* 2011; 25(1):29-36

Revell AD, Alvarez-Uria G, Wang D, Pozniak A, Montaner JSG, Lane HC, Larder BA. Potential Impact of a Free Online HIV Treatment Response Prediction System for Reducing Virological Failures and Drug Costs after Antiretroviral Therapy Failure in a Resource-Limited Setting. *BioMed Res Int* 2013; doi 10.1155/2013/579741

HIV Treatment Response Prediction System (HIV-TRePS)

1. Patient requires treatment change
2. Viral load, CD4, Tx history (*with or without genotype*) entered online
3. RF models predict VL responses to thousands of alternative combinations in real time
4. PDF report produced within a minute

HIV-TRePS sample report: No GT



Case summary for RDI case 1292, patient ID TestCase

Baseline Data Completed: 27/09/2013

Patient Details

DATE OF BIRTH	SEX	PREGNANT
22/01/1970	M	N

Viral Load

SAMPLE DATE	VIRAL LOAD VALUE
16/09/2013	25,400

CD4

SAMPLE DATE	CD4 VALUE
09/09/2013	342

Genotype

GENOTYPE SAMPLE DATE	PROTEASE MUTATIONS	RT NRTI MUTATIONS	RT NNRTI MUTATIONS
No genotype provided			

Treatment History and Drug Exclusions

PREVIOUS DRUG EXPOSURE	UNAVAILABLE DRUGS	EXCLUDED DRUGS
3TC,AZT,D4T,DDI,IDV/rtv LPV/rtv,NFV,NVP,SQV/rtv	ENF,MVC	D4T,ENF,MVC,TPV/rtv

Predictions*

HIV-TRePS (v5.3.2.0) was instructed to model responses at 24 weeks to user-defined antiretroviral regimens plus alternatives comprising no more than 4 drugs.

The table below lists the regimen(s) you selected plus the top five alternatives, ranked by the predicted probability of virological response (viral load <50 copies).

Those regimens that the system predicts will produce a response (using the cut-off value for the probability of response that produces optimal accuracy) are highlighted in green and those predicted to fail in red.

Predictions of responses at 24 weeks for the regimens you selected plus the top five alternatives (up to 4 drugs)

RANK	DRUGS USED TO TREAT PATIENT	NO. DRUGS	PROBABILITY VL <50	RANGE OF MODELS PREDICTION	RESPONSE CATEGORY
1	DRV/rtv, ETV, RAL	3	83%	75 - 96%	Response
2	3TC, DRV/rtv, ETV, RAL	4	82%	73 - 96%	Response
3	AZT, DRV/rtv, ETV, RAL	4	81%	76 - 93%	Response
4	3TC, DRV/rtv, RAL	3	80%	71 - 96%	Response
5	DRV/rtv, EFV, RAL	3	79%	71 - 96%	Response
User	ABC, ETV, RAL, TDF	4	55%	45 - 70%	Response
User	DRV/rtv, EFV, FTC, TDF	4	51%	43 - 63%	Response

These predictions were requested without genotype information being provided and were made by models specially developed for that purpose. Their predictions may be less accurate than those made by models that use the genotype.

* TRePS Predictions Disclaimer

Use of the HIV-TRePS is subject to the following conditions, to which you have agreed:



Registered TRePS users can:

- Obtain predictions of response for drug combinations they are considering
- Identify combinations most likely to work from alternatives in clinical use
- Rule out drugs for toxicity, unavailability, etc
- Input local drug costs & model alternatives within a certain budget
- Identify the least expensive regimens that are predicted to work
- Store their cases in their personal online archive

Conclusions

- Computational models can be accurate predictors of virological response, even without a genotype
- They are significantly more accurate than genotyping
- The models have the potential to avoid treatment failure by identifying effective, alternative, practical regimens
- The system has the potential to save money by identifying less costly but effective alternative ART
- The system supports but is NOT a substitute for clinical judgement
- This approach has potential utility as an aid to the management of treatment failures in resource-limited settings

Overall conclusion

This system has the potential to help optimise therapy in settings with limited resources where genotyping is less available or affordable but viral load testing is common

The RDI models are freely available via:

www.hivrDI.org/treps



Our data contributors

- AREVIR database, c/o the University of Cologne, Germany: *Rolf Kaiser*
- ATHENA database c/o Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands: *Peter Reiss and Ard van Sighem*
- BC Centre for Excellence in HIV/AIDS: *Richard Harrigan & Julio Montaner*
- Chelsea and Westminster Hospital, London: *Brian Gazzard, Anton Pozniak & Mark Nelson*
- CPCRA: *John Bartlett, Mike Kozal, Jody Lawrence*
- Desmond Tutu HIV Centre, Cape town, South Africa: *Carl Morrow and Robin Wood*
- “Dr. Victor Babes” Hospital for Infectious and Tropical Diseases, Bucharest, Romania: *Luminita Ene*
- Federal University of Sao Paulo, Sao Paulo, Brazil: *Ricardo Diaz & Cecilia Sucupira*
- Fundacion IrsiCaixa, Badelona: *Bonaventura Clotet & Lidia Ruiz*
- Gilead Sciences: *Michael Miller and Jim Rooney*
- Hôpital Timone, Marseilles, France: *Catherine Tamalet*
- Hospital Clinic Barcelona: *Jose Gatell & Elisa Lazzari*
- Hospital of the JW Goethe University, Frankfurt: *Schlomo Staszewski*
- ICONA: *Antonella Monforte & Alessandro Cozzi-Lepri*
- Istituto Superiore di Sanità, Rome, Italy: *Stefano Vella and Raffaella Bucciardini*
- Italian MASTER Cohort (c/o University of Brescia, Italy): *Carlo Torti*
- Italian ARCA database, University of Siena, Siena, Italy: *Maurizio Zazzi*
- The Kirby Institute, University of New South Wales, Sydney, Australia: *Sean Emery and Mark Boyd*
- National Institutes of Allergy and Infectious Diseases: *Cliff Lane, Julie Metcalf, Robin Dewar*
- National Institute of Infectious Diseases, Bucharest, Romania: *Adrian Streinu-Cercel and Oana Streinu-Cercel*
- National Institute of Infectious Diseases, Tokyo: *Wataru Sugiura*
- Ndlovu Medical Centre, Elandsdoorn, South Africa: *Roos Barth & Hugo Tempelman*
- PASER-M Cohort, Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe: *Raph Hamers*
- PhenGen study, Italy: *Laura Monno*
- PHIDISA study, c/o National Institutes of Allergy and Infectious Diseases, Bethesda, USA: *Julie Metcalf*
- Ramon y Cajal Hospital, Madrid, Spain: *Maria-Jesus Perez-Elias*
- Royal Free Hospital, London, UK: *Anna Maria Geretti*
- Rural Development Trust (RDT) Hospital, Bathalapalli, AP, India: *Gerardo Alvarez-Uria*
- Sapienza University, Rome, Italy: *Gabriella d’Ettorre*
- SATuRN Netowrk in Southern Africa: *Tulio de Oliveira*
- Tibotec Pharmaceuticals: *Gaston Picchio and Marie-Pierre deBethune*
- US Military HIV Research Program: *Scott Wegner & Brian Agan*
- University of Belgrade, Belgrade, Serbia: *Gordana Dragovic*

Acknowledgments

RDI



Andy Revell



Daniel Coe



Dechao Wang

NIAID

Cliff Lane and Julie Metcalf...
...for funding, data and encouragement

Funded by NCI Contract No. HHSN261200800001E. This research was supported [in part] by the National Institute of Allergy and Infectious Diseases

