



# **COMPUTATIONAL METHODS FOR THE ANALYSIS OF HIV DRUG RESISTANCE DYNAMICS**

*A thesis submitted in fulfillment of the requirements for the degree of*

**DOCTOR OF PHILOSOPHY**

In

The Faculty of Science

School of Information Technologies

**THE UNIVERSITY OF SYDNEY**

**MARCH 2007**

**ALI AL MAZARI**

## **CERTIFICATION BY THE SUPERVISORS**

We certify that the thesis entitled: “Computational Methods for the Analysis of HIV Drug Resistance Dynamics” submitted by Ali Al Mazari, for the Degree of Doctor of Philosophy, Biomedical Informatics Sciences, is ready for examination.

Supervisor:

Prof. Albert Y. Zomaya, Head of School  
CISCO Systems Chair Professor of Internetworking  
School of Information Technologies  
The University of Sydney  
Sydney, NSW, Australia

Co-supervisors:

Dr. Michael Charleston, Senior Lecturer in Bioinformatics  
School of Information Technologies  
The University of Sydney  
Sydney, NSW, Australia

Dr. Roger J. Garsia, Clinical Senior Lecturer  
Department of Medicine  
The University of Sydney  
Clinical Immunologist at RPAH  
Clinical Director HIV/AIDS  
Sydney South West Area Health Service

## **DECLARATION**

I, the author of the thesis, declare that none of the material in this thesis has been previously submitted by me or any other candidate for any degree to this or any other university.

Ali A Al Mazari

## ACKNOWLEDGEMENT

This thesis is dedicated to my family. I wish to thank my parents, Adnan and Farha and my wife, Om Kazem, for their encouragement and cheerful feeling during this quest, and my dear children, Kazem and Adnan. I thank my brothers, sisters and friends, who surround my heart.

Special thanks go to my supervisor, Professor Albert Zomaya, Head of the School of Information Technologies, for his skilled and supportive supervision and guidance, and to my cosupervisors, Dr Michael Charleston, School of Information Technologies, and Dr Roger Garsia, Department of Medicine. Thanks to Dr Tony Souter for his editorial assistance. Many thanks to Hanan Salem and Annamarie Maher, Molecular Biology Laboratory, Departments of Biochemistry and Clinical Immunology of Royal Prince Alfred Hospital, Sydney.

## **ETHICS REVIEW COMMITTEE APPROVAL**

Ethics approval from the Sydney South West Area Health Service Ethics Review Committee (SSWAHS ERC X05-0205) was obtained for this project.

## ABSTRACT

Despite the extensive quantitative and qualitative knowledge about therapeutic regimens and the molecular biology of HIV/AIDS, the eradication of HIV infection cannot be achieved with available antiretroviral regimens. HIV drug resistance remains the most challenging factor in the application of approved antiretroviral agents. Previous investigations and existing HIV/AIDS models and algorithms have not enabled the development of long-lasting and preventive drug agents. Therefore, the analysis of the dynamics of drug resistance and the development of sophisticated HIV/AIDS analytical algorithms and models are critical for the development of new, potent antiviral agents, and for the greater understanding of the evolutionary behaviours of HIV.

This study presents novel computational methods for the analysis of drug-resistance dynamics, including: viral sequences, phenotypic resistance, immunological and virological responses and key clinical data, from HIV-infected patients at Royal Prince Alfred Hospital in Sydney. The lability of immunological and virological responses is analysed in the context of the evolution of antiretroviral drug-resistance mutations. A novel Bayesian algorithm is developed for the detection and classification of neutral and adaptive mutational patterns associated with HIV drug resistance. To simplify and provide insights into the multifactorial interactions between viral populations, immune-system cells, drug resistance and treatment parameters, a Bayesian graphical model of drug-resistance dynamics is developed; the model supports the exploration of the interdependent associations among these dynamics.

# TABLE OF CONTENTS

Certification by the supervisors .....	i
Declaration .....	ii
Acknowledgement .....	iii
Ethics Review Committee Approval .....	iv
Abstract .....	v
Table of contents .....	vi
List of figures .....	xiii
List of tables .....	xvi
Abbreviations .....	xvii
Publications from thesis .....	xx
<b><u>1 INTRODUCTION.....</u></b>	<b>1</b>
1.1 The key issue: HIV drug resistance dynamics .....	2
1.2 Research objectives .....	3
1.3 Significance of the study .....	4
1.4 Structure of the dissertation .....	5
<b><u>2 HIV BIOLOGY, THERAPY, DRUG RESISTANCE AND MODELLING.....</u></b>	<b>7</b>
2.1 Molecular biology of HIV/AIDS .....	8
2.1.1 HIV as a retrovirus .....	8
2.1.2 Target cells of HIV .....	9
2.1.3 Genetic structure of HIV .....	9
2.1.4 Life cycle .....	13
2.1.5 Associated diseases .....	16

2.1.6	Diagnosis and stages .....	16
2.1.7	Genetic variability of HIV .....	20
2.1.8	Epidemiology .....	22
2.1.9	Clinical laboratory tests .....	24
2.1.9.1	CD4 T-Cell count test .....	24
2.1.9.2	Viral load test .....	24
2.1.9.3	Drug resistance tests .....	25
2.1.10	Course of HIV and CD4 interaction .....	25
2.2	Drug resistance .....	28
2.2.1	Conceptual basis .....	28
2.2.2	Drug resistance levels .....	29
2.2.3	Resistance emergence and evolution of resistance .....	29
2.2.4	Drug resistance assays .....	30
2.2.4.1	Genotypic assays .....	30
2.2.4.2	Phenotypic assays .....	31
2.2.4.3	Virtual phenotypic assays .....	32
2.2.5	Genotypic sequence interpretation systems .....	33
2.2.5.1	Rule-based interpretation systems .....	33
2.2.5.2	Machine-learning interpretation systems .....	33
2.2.5.3	Inter-algorithm comparisons and algorithm validation systems .....	34
2.2.6	CREST Trial algorithm .....	34
2.2.7	Drug resistance databases .....	37
2.2.8	Database analysis methods .....	37
2.3	Antiretroviral therapy and associated resistance mutations and mechanisms .....	38
2.3.1	Antiretroviral agents and combinations .....	38
2.3.1.1	Protease inhibitors (PIs) .....	39
2.3.1.2	Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) .....	39
2.3.1.3	Non-nucleoside reverse transcriptase inhibitors (NNRTIs).....	40
2.3.1.4	Fusion inhibitors (FIs) .....	40
2.3.1.5	Combination antiretroviral therapy .....	43
2.3.2	Mechanisms of resistance to ARV agents .....	46
2.3.2.1	Mechanisms of resistance to PIs .....	46
2.3.2.2	Mechanisms of resistance to NRTIs .....	46



2.3.2.3 Mechanisms of resistance to NNRTIs .....	47
2.3.2.4 Mechanisms of resistance to FIs .....	47
2.3.3 Mutations associated with antiretroviral agents .....	50
2.3.3.1 Mutations associated with PIs .....	51
2.3.3.2 Mutations associated with NRTIs .....	53
2.3.3.3 Mutations associated with NNRTIs .....	55
2.3.4 Treatment considerations .....	57
2.3.4.1 Cross-resistance .....	57
2.3.4.2 Adherence .....	57
2.3.4.3 Toxicity .....	57
2.3.4.4 Initiation .....	58
2.3.4.5 Supporting Treatment strategies .....	58
2.4 Modelling of HIV/AIDS .....	60
2.4.1 HIV/AIDS modelling .....	60
2.4.2 The basic model of HIV .....	60
2.4.3 Modelling HIV/AIDS from an epidemiological and pathological perspective .....	62
2.4.3.1 Epidemiology models .....	62
2.4.3.2 Pathogenetic models .....	62
2.4.4 Modelling HIV/AIDS dynamics .....	62
2.4.4.1 Virology and immunology models .....	62
2.4.4.2 Drug resistance models .....	63
2.4.4.3 Treatment models .....	63
2.4.5 Modelling based on analytical methods .....	63
2.4.5.1 Mathematical modelling .....	63
2.4.5.2 Graphical modelling .....	64
2.4.5.3 Pharmacokinetic modelling .....	65
2.4.6 Modelling approaches .....	65
2.4.6.1 Stochastic modelling .....	65
2.4.6.2 Deterministic modelling .....	66
2.4.7 Significance and limitations of model types .....	66
2.4.7.1 Significance of graphical models .....	66
2.4.7.2 Limitations of mathematical models .....	67
<b><u>3 HIV GENOTYPING DATABASES.....</u></b>	<b>69</b>
3.1 Introduction .....	70

3.2 Data sources and analysis .....	71
3.2.1 Data on drug resistance mutations .....	71
3.2.2 The systematic analysis of genotypic databases .....	74
3.3 Related drug-resistance databases .....	75
3.3.1 Stanford University HIV Drug Resistance Database (HIVdb) .....	75
3.3.2 Arevir Database .....	76
3.3.3 UK Drug Resistance Database .....	76
3.3.4 Los Alamos HIV Databases .....	77
3.4 HIV-1 Genotyping Database .....	78
3.4.1 Tests .....	78
3.4.2 Database model .....	79
3.4.3 Database Dictionary .....	83
3.4.4 Database Schema .....	86

## **4 IMMUNOLOGICAL AND VIROLOGICAL RESPONSES IN THE EVOLUTION OF RESISTANCE..... 87**

4.1 Introduction .....	88
4.2 Classification of resistance and immunological and virological responses .....	89
4.2.1 Resistance classification .....	89
4.2.2 Immunological and virological responses classification .....	91
4.2.3 Tracking trends of CD4 T-cell counts and VL associated with EoR .....	92
4.3 Experimental materials and methods .....	95
4.3.1 Study population: sampling and baseline .....	95
4.3.2 Mutation genotyping and interpretation .....	95
4.3.3 Immunological and virological parameters .....	96
4.3.4 Data analysis and computations .....	97

4.3.5 LOESS Normalisation curves .....	97
4.4 Experimental results .....	98
4.4.1 Population and treatment baselines .....	98
4.4.2 Evolutionary mutational patterns associated with ARV .....	98
4.4.3 Immunological changes associated with EoR .....	103
4.4.4 Virological changes associated with EoR .....	108
4.5 Discussion .....	112
4.5.1 Patterns of EoR .....	112
4.5.2 Predictors of EoR .....	113
4.6 Conclusion .....	114

## **5 ADAPTIVE AND NEUTRAL EVOLUTIONARY PATTERNS ASSOCIATED WITH HIV DRUG RESISTANCE .....**

5.1 Introduction .....	117
5.2 Evolutionary patterns associated with HIV drug resistance .....	118
5.2.1 Emergence and evolution of drug resistance .....	118
5.2.2 Classes of the evolutionary patterns associated with drug resistance .....	119
5.2.3 Current evolutionary models and their limitations .....	122
5.3 An algorithm for HIV evolutionary patterns .....	123
5.3.1 The formalism of Bayes' theorem .....	123
5.3.2 Data parameters .....	125
5.3.3 Algorithm and procedure .....	125
5.4 Experimental data and methods .....	130
5.4.1 Study population .....	130
5.4.2 Mutational patterns associated with antiretroviral agents .....	131
5.4.3 Application of the algorithm .....	132

5.5 Results and discussion .....	137
5.5.1 Prevalence of neutral, positively and negatively selected patterns .....	137
5.5.2 Evolutionary patterns consisting of two mutations .....	139
5.5.3 Evolutionary patterns consisting of three mutations .....	140
5.5.4 Significance of the algorithm .....	141
5.5.5 Limitations .....	141
5.6 Further applications and conclusions .....	141
5.6.1 Applications based on mutation types .....	141
5.6.2 Applications based on the site of mutations .....	142
5.6.3 Applications based on the number and combination of mutations .....	142
5.6.4 Applications in relation to other HIV variables .....	142
5.6.5 Conclusion .....	143

## **6 A MULTIVARIATE BAYESIAN MODEL OF HIV DRUG RESISTANCE DYNAMICS.....** 144

6.1 Introduction .....	145
6.2 HIV drug resistance .....	146
6.3 HIV/AIDS modelling .....	148
6.3.1 The need for modelling .....	148
6.3.2 Mathematical modelling of HIV/AIDS .....	149
6.3.3 Limitations of mathematical modelling of HIV .....	150
6.3.4 Graphical modelling of HIV/AIDS .....	151
6.4 BNs and modelling .....	152
6.4.1 Bayesian belief networks .....	152
6.4.2 BN modelling .....	156
6.5 The model of HIV drug resistance dynamics .....	157
6.5.1 Methods of model construction .....	157
6.5.2 Learning model parameters and structure .....	158
6.5.3 Making inferences .....	167
6.5.4 Message-Passing Algorithm .....	169

6.6 Discussion .....	176
6.6.1 Significance of BNs .....	176
6.6.2 Limitations of BNs .....	176
6.7 Conclusion .....	176
<b><u>7 CONCLUSION.....</u></b>	<b>178</b>
7.1 Summary of the dissertation .....	178
7.2 Summary of results .....	179
7.3 Research limitations .....	180
7.4 Future directions .....	181
<b><u>APPENDICES.....</u></b>	<b>184</b>
Appendix A: Web resources for HIV drug resistance testing in clinical and research Settings .....	185
Appendix B: HIV-1 PR and RT Sequencing Kits .....	188
Appendix C: Sample reports used for clinical decision-making at RPAH .....	190
<b><u>REFERENCES.....</u></b>	<b>196</b>

## LIST OF FIGURES

<b>Figure</b>	<b>Title</b>	<b>Page</b>
Figure 2.1	: Flow of biological sequence information in living organisms .....	8
Figure 2.2	: HIV genomic structure .....	11
Figure 2.3	: HIV life cycle .....	15
Figure 2.4	: Generalized time course of HIV infection and disease .....	18
Figure 2.5	: Phylogenetic tree of the SIV and HIV .....	21
Figure 2.6	: Adults and children estimated to be living with HIV in 2006 .....	22
Figure 2.7	: Adults and children estimated to be newly infected with HIV in 2006 .....	23
Figure 2.8	: Estimated adult and child deaths from AIDS in 2006 .....	23
Figure 2.9	: Generalised relationship between HIV viral copies and CD4 T-cell counts during the typical course of the disease in untreated individuals .....	27
Figure 2.10	(A): Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART Eras (so-called CART) .....	45
	(B): Prognosis According to CD4 Cell Count and Viral Load in the HAART Eras .....	45
Figure 2.11	(A): Resistance by interference with the incorporation of NRTIs .....	48
	(B): Resistance by the ATP-mediated excision of NRTIs .....	48
Figure 2.12	: Mechanism of resistance associated with NNRTIs	49
Figure 2.13	: Structural model of HIV-1-PR, labelled with PI-associated resistance mutations .....	52
Figure 2.14	: Structural model of HIV-1-RT, labelled with NRTI- associated resistance mutations .....	54
Figure 2.15	: Structural model of HIV-1-RT, labelled with NNRTI- associated resistance mutations .....	56
Figure 2.16	: The basic model of HIV viral dynamics .....	61

Figure 3.1	: Schematic of showing the distribution of drug-resistance mutations within the PR and RT genes .....	73
Figure 3.2	: HIV-1 Genotyping Database Model .....	82
Figure 3.3	: HIV-1 Genotyping Database Schema .....	86
Figure 4.1	: The classes of EoR associated with NRTIs, NNRTIs or PIs .....	90
Figure 4.2	: (A): Tracking the trends of CD4 T-cell counts in patients with and without EoR associated with the NRTI class of drugs .....	93
	(B): Tracking the trends of VL in patients with and without EoR associated with the PI class of drugs .....	94
Figure 4.3	: (A): Frequencies of mutations associated with NRTIs .....	101
	(B): Frequencies of mutations associated with NNRTIs .....	102
	(C): Frequencies of mutations associated with PIs .....	102
Figure 4.4	: (A): LOESS curves of the immunological responses correlated with EoR associated with primary-NRTIs mutations .....	104
	(B): LOESS curves of the immunological responses correlated with EoR associated with secondary-NRTIs mutations .....	105
	(C): LOESS curves of the immunological responses correlated with EoR associated with primary-PIs mutations .....	106
Figure 4.5	: (A): LOESS curves of the virological responses correlated with EoR associated with NRTIs associated mutations .....	109
	(B): LOESS curves of the virological responses correlated with EoR associated with PIs associated mutations .....	110
Figure 5.1	: Evolutionary patterns associated with HIV drug resistance ..	121
Figure 5.2	: Multiple sequential evidence .....	124
Figure 5.3	: The distribution of V118I+T215x and other patterns .....	135

## List of Figures

---

Figure 5.4	: The prevalence of two mutational patterns .....	138
Figure 5.5	: Prevalence of the patterns that consist of two mutations .....	139
Figure 5.6	: Prevalence of the patterns that consist of three mutations ...	140
Figure 6.1	: A Simple Bayesian Network .....	155
Figure 6.2	: A Bayesian model of HIV drug resistance dynamics; asterisked parameters are multiple states .....	166
Figure 6.3	: Inductive and deductive reasoning .....	168
Figure 6.4	: Different types of network topologies	170
Figure 6.5	: A Multiply Connected network partitioned into two networks for making inference .....	170
Figure 6.6	: A four-node BN with the four corresponding CPTs .....	172
Figure 6.7	: Initialised version of the BN in Figure 6.6, illustrating the values and messages of $\pi$ and $\lambda$ probability vectors .....	174
Figure 6.8	: An updated version of the BN in Figure 6.7 .....	175



## LIST OF TABLES

<b>Table</b>	<b>Title</b>	<b>Page</b>
Table 2.1	: HIV genes and proteins and their functions .....	12
Table 2.2	: HIV/AIDS classification systems provided by WHO and CDC .....	19
Table 2.3	: Comparison of the GTA, PTA and VPA .....	33
Table 2.4	: Primary/secondary resistance mutations associated with PRIs, NRTIs and NNRTI as reported by CREST study ....	35
Table 2.5	: Algorithms for interpreting HIV-1 PR and RT sequences ..	36
Table 2.6	: ARV agents used in the treatment of HIV infection .....	41
Table 2.7	: CART options following virological failure .....	44
Table 3.1	: HIV-1 Genotyping Database Dictionary .....	83
Table 4.1	: CD4 T-cell counts and severity immunosuppression .....	92
Table 4.2	: Frequencies of mutations associated with PIs, NRTIs and NNRTIs .....	100
Table 4.3	: The mean values of CD4 T-cell counts .....	107
Table 4.4	: The mean values of VL .....	111
Table 5.1	: Categories and prevalence of the evolutionary pattern $p_x$ ...	130
Table 5.2	: Evolving mutational patterns in the HIV-RT gene .....	133
Table 6.1	: Primary and secondary resistance mutations associated with PRIs, NRTIs and NNRTI .....	162
Table 6.2	: CD4 levels and the severity of immunosuppression .....	163
Table 6.3	: Variables and states of HIV drug resistance dynamics model .....	164

## ABBREVIATIONS

<b>3TC</b>	Lamivudine
<b>AA</b>	Amino acid
<b>ABC</b>	Abacavir sulfate
<b>AD</b>	Adherence
<b>ADRA</b>	Antiviral drug resistance analysis
<b>AE</b>	AIDS event
<b>AIDS</b>	Acquired immune deficiency syndrome
<b>ANRS</b>	French national agency for AIDS research
<b>APV</b>	Amprenavir
<b>ARV</b>	Antiretroviral
<b>ATV</b>	Atazanavir sulfate
<b>AZT or ZDV</b>	Zidovudine or Azidothymidine
<b>BMI</b>	biomedical informatics
<b>BNs</b>	Bayesian belief networks
<b>CA</b>	Capsid
<b>CART</b>	Combination antiretroviral therapy
<b>CDC</b>	Centres for disease control and prevention
<b>CI</b>	Confidence interval
<b>CM</b>	Codon of mutations
<b>CMP</b>	Category of mutational pattern
<b>CPT</b>	Conditional probability table
<b>CREST</b>	Can resistance enhance selection of therapy
<b>d4T</b>	Stavudine
<b>ddC</b>	Zalcitabine or Dideoxycytidine
<b>ddI</b>	didanosine or dideoxyinosine
<b>DI</b>	Death incidence
<b>DLV</b>	Delavirdine
<b>DNA</b>	Deoxyribonucleic acid
<b>EFV</b>	Efavirenz

<b>EM</b>	Expectation maximisation
<b>EoR</b>	Evolution of resistance
<b>FDA</b>	Food and Drug Administration
<b>FIs</b>	Fusion inhibitors
<b>FPV</b>	Fosamprenavir Calcium
<b>FTC</b>	Emtricitabine
<b>HAART</b>	Highly active antiretroviral therapy
<b>HIV</b>	Human immunodeficiency virus
<b>HIVdb</b>	Stanford university's HIV database
<b>IDV</b>	Indinavir
<b>IN</b>	Integrase
<b>JPD</b>	Joint probability distribution
<b>LOESS</b>	LOcally wEighted Scatter-plot Smoothing
<b>MA</b>	matrix
<b>MDR</b>	Multi-drug resistance
<b>mRNA</b>	messenger RNA
<b>NA</b>	Nucleotide acid
<b>NC</b>	Nucleocapsid
<b>NE</b>	Neutral evolution
<b>NFV</b>	Nelfinavir mesylate
<b>NIH</b>	National Institutes of Health
<b>NIR</b>	Non-responding immunological response
<b>NNRTI</b>	Non-nucleoside reverse transcriptase inhibitor
<b>NRL</b>	National Serology Reference Laboratory
<b>NRTI</b>	Nucleotide reverse transcriptase inhibitor
<b>NS</b>	Negative selection
<b>NVP</b>	Nevirapine
<b>NVR</b>	Non-responding virological response
<b>NWT</b>	non-wild-type
<b>OI</b>	Opportunistic infection
<b>PCR</b>	Polymerase chain reaction
<b>PI</b>	Protease inhibitor
<b>PIR</b>	Positive immunological response

## Abbreviations

---

<b>PMCC</b>	Pearson product moment correlation coefficient
<b>Pol</b>	Polymerase
<b>PR</b>	Protease
<b>PS</b>	Positive selection
<b>PTA</b>	Phenotypic assays
<b>PVR</b>	Positive virological response
<b>RCG</b>	Resistance collaborative group
<b>RE</b>	Resistance emergence
<b>RFLP</b>	Restriction fragment-length polymorphism
<b>RNA</b>	Ribonucleic acid
<b>RPAH</b>	Royal Prince Alfred Hospital
<b>RT</b>	Reverse transcriptase
<b>RT-PCR</b>	Reverse transcriptase-polymerase chain reaction
<b>RTV</b>	Ritonavir
<b>SARS</b>	Severe acute respiratory syndrome
<b>SPSS</b>	Statistical Package for the Social Sciences
<b>SQV</b>	Saquinavir mesylate
<b>STI</b>	Structured treatment interruption
<b>T-20</b>	Enfuvirtide
<b>TA</b>	Toxicity of CART
<b>TAMs</b>	Thymidine analogue mutations
<b>TDF</b>	Tenofovir disoproxil fumarate
<b>TMC114</b>	Darunavir
<b>TPV</b>	Tipranavir
<b>UNAIDS</b>	United Nations Programme on HIV/AIDS
<b>vDNA</b>	viral DNA
<b>VL</b>	Viral load
<b>WHO</b>	World Health Organisation
<b>WT</b>	wild-type

## PUBLICATIONS FROM THESIS

1. A. A. Mazari, A. Y. Zomaya, M. Charleston, H. Salem, A. Maher, and R. J. Garsia, "Immunological and virological responses correlated with evolution of resistance in patients treated with antiretroviral agents. Abstract No: 95," presented at 18th Annual Conference of the Australasian Society for HIV Medicine, Melbourne, VIC, Australia, 2006.
2. A. A. Mazari and A. Y. Zomaya, "A Brief Overview of Grid Activities for Bioinformatics and Health Applications (Chapter 20)," in *Parallel Computing for Bioinformatics and Computational Biology*, A. Y. Zomaya, Ed. NY, USA: John Wiley & Sons, 2005.
3. A. A. Mazari, A. Y. Zomaya, M. Charleston, and R. J. Garsia, "A Novel Algorithm for Adaptive and Neutral Evolutionary Patterns Associated with HIV Drug Resistance," The fifth ACS/IEEE International Conference on Computer Systems and Applications (AICCSA-07), [Accepted], Amman, Jordan, 2007.
4. A. A. Mazari, A. Y. Zomaya, M. Charleston, and R. J. Garsia, "Bayesian Networks for Modelling HIV Drug Resistance Dynamics, [Extended Abstract]," The fifth ACS/IEEE International Conference on Computer Systems and Applications (AICCSA-07) [Accepted], Amman, Jordan, 2007.
5. A. A. Mazari, A. Y. Zomaya, M. Charleston, H. Salem, A. Maher, and R. J. Garsia, "Lability of Antiretroviral Drug Resistance Mutations—Correlates with Immunological and Virological Responses," *Current HIV Research* [Accepted], 2007.
6. A. A. Mazari, A. Y. Zomaya, M. Charleston, and R. J. Garsia, "Adaptive and Neutral Evolutionary Mutations at the HIV-RT Gene Associated with Resistance to NNRTIs," the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2007), [Submitted], Sydney, Australia, 2007.