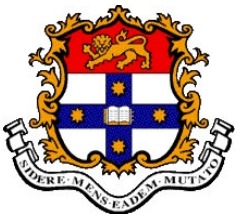


# COMPUTATIONAL METHODS FOR THE ANALYSIS OF HIV DRUG RESISTANCE DYNAMICS

*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**

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**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.

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# 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.

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# 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.

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# ABBREVIATIONS

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

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

| | |
|---|---|
| **PMCC** | Pearson product moment correlation coefficient |
| **Pol** | Polymerase |
| **PR** | Protease |
| **PS** | Positive selection |
| **PTA** | Phenotypic assays |
| **PVR** | Positive virological response |
| **RCG** | Resistance collaborative group |
| **RE** | Resistance emergence |
| **RFLP** | Restriction fragment-length polymorphism |
| **RNA** | Ribonucleic acid |
| **RPAH** | Royal Prince Alfred Hospital |
| **RT** | Reverse transcriptase |
| **RT-PCR** | Reverse transcriptase-polymerase chain reaction |
| **RTV** | Ritonavir |
| **SARS** | Severe acute respiratory syndrome |
| **SPSS** | Statistical Package for the Social Sciences |
| **SQV** | Saquinavir mesylate |
| **STI** | Structured treatment interruption |
| **T-20** | Enfuvirtide |
| **TA** | Toxicity of CART |
| **TAMs** | Thymidine analogue mutations |
| **TDF** | Tenofovir disoproxil fumarate |
| **TMC114** | Darunavir |
| **TPV** | Tipranavir |
| **UNAIDS** | United Nations Programme on HIV/AIDS |
| **vDNA** | viral DNA |
| **VL** | Viral load |
| **WHO** | World Health Organisation |
| **WT** | 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 resistancein patients treated with antiretroviral agents. Abstract No: 95," presented at 18th Annual Conference of the Australasian Society for HIV Medicine, Melbourne, VIC, Australia, 2006.

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