UNIVERSITI PUTRA MALAYSIA

COPY NUMBER VARIATION OF C-C CHEMOKINE LIGAND 3-LIKE 1 (*CCL3L1*), C-C CHEMOKINE RECEPTOR TYPE 5 (*CCR5*) AND *CCR2* POLYMORPHISMS ON THE OUTCOMES OF ANTIRETROVIRAL THERAPY AMONG MALAYSIAN HIV PATIENTS

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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March 2020

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HIV/AIDS is a significant burden in Malaysia, affecting more than 90, 000 of the population. Several host genetic variations have been implicated in the pathogenesis of HIV infection, particularly on HIV susceptibility and disease progression to AIDS. These include *CCR5* and *CCL3L1*, which encode for the CCR5 receptor and the ligand for the CCR5 receptor respectively. However, there is a noticeable discordancy in CD4 count recovery and viral load suppression between individuals during the highly active anti-retroviral therapy (HAART). However, the predictive value of these genetic variants on patients' responses to the HAART is largely unknown. Therefore, the main objective of this study is to determine the impact of *CCL3L1* copy number variation and selected *CCR5/CCR2* polymorphisms on HIV susceptibility, CD4 count recovery and viral load suppression among Malaysian HIV patients during early HAART. Besides, the influence of socio-demographic and clinical factors is also considered. This cross-sectional study involved 182 HIV-positive patients of Malay, Chinese and Indian ethnicities who were attending out-patient clinics of three hospitals in Malaysia and 150 non-HIV (comparative) subjects. A subset of 170 HIV subjects who were receiving the standard first-line HAART regimen with available CD4 count and viral load data were selected for analyses on immunological and virological responses for up to 12 months after the initiation of HAART. Typing of *CCL3L1* copy number used paralogue ratio test (PRT) followed by the copy number validation by microsatellites analyses. *CCR5-Δ32* was genotyped by using PCR while both *CCR5-R223Q* and *CCR2-V64I* were identified by using PCR-restriction fragment length polymorphism (PCR-RFLP). Logistic regression was used to determine the effect of the predictors on achieving the target outcomes of CD4 count ≥500 cells/mm^3 and viral load ≤50 copies/mL. Lower than average *CCL3L1* copy number was associated with an increased risk of acquiring HIV-1 in Malay ethnic. Susceptibility to HIV was also reduced by having the mutant allele of *CCR5-R223Q*. In multivariable analysis after adjustment for socio-demographic and clinical factors, lower than average *CCL3L1* copy number predicted a higher chance of CD4 recovery to ≥500 cells/mm^3 at 8-12 months treatment with HAART. Furthermore, subjects with pre-treatment CD4 count

≥200 cells/mm^3 were associated with at least five times more likely to achieve optimal CD4 recovery in the first 12 months of HAART. Besides, at 8-12 months of HAART, Chinese and Indian subjects were four and seven times respectively more likely to achieve CD4 count ≥500 cells/mm^3 than Malay subjects. Viral load suppression to ≤50 copies/mL was not associated with the *CCL3L1* copy number or *CCR5/CCR2* genetic factors. Rather, the viral load suppression was negatively predicted by pre-treatment viral load ≥100,000 copies/mL and positively predicted by CD4 count ≥200 cells/mm^3 in the first 4-6 months of HAART. In conclusion, both high *CCL3L1* copy number and the mutant *CCR5-R223Q* are the potential factors that prevent HIV infection. The present study also highlights the contribution of low *CCL3L1* copy number, ethnicity and early HAART initiation in order to achieve the optimal CD4 count recovery thus improving the management of HIV treatment.

Keywords: *CCL3L1*, *CCR5*, CD4 count, viral load, susceptibility, HAART, Malaysia

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

VARIASI NOMBOR SALINAN C-C KEMOKIN LIGAN 3-SEPERTI 1 (*CCL3L1*), C-C KEMOKIN RESEPTOR JENIS 5 (*CCR5*) DAN *CCR2* TERHADAP KESAN-KESAN TERAPI ANTIRETROVIRAL DI KALANGAN PESAKIT HIV DI MALAYSIA

Oleh

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HIV/AIDS merupakan beban yang signifikan di Malaysia, yang menjejaskan lebih daripada 90,000 penduduk. Beberapa variasi genetik pada hos terlibat dalam patogenesis jangkitan HIV, terutamanya terhadap risiko jangkitan dan perkembangan penyakit kepada AIDS. Ini termasuk *CCR5* serta *CCL3L1*, yang masing-masing mengekodkan reseptor CCR5 dan ligan untuk reseptor CCR5. Walau bagaimanapun, terdapat percanggahan yang ketara dalam pemulihan kiraan CD4 dan penurunan beban virus antara individu semasa terapi anti-retroviral sangat aktif (HAART). Walau bagaimanapun, kesan ramalan variasi genetik terhadap tindak balas pesakit terhadap HAART sebahagian besarnya tidak diketahui. Oleh itu, objektif utama kajian ini adalah untuk menentukan kesan variasi nombor salinan pada *CCL3L1* dan polimorfisme *CCR5/CCR2* yang dipilih terhadap risiko jangkitan HIV, pemulihan kiraan CD4 dan penurunan beban virus di kalangan pesakit HIV di Malaysia semasa peringkat awal rawatan HAART. Selain itu, pengaruh faktor sosio-demografi dan klinikal juga dipertimbangkan. Kajian keratan rentas ini melibatkan 182 pesakit HIV-positif daripada etnik Melayu, Cina dan India yang menghadiri klinik pesakit luar dari tiga hospital di Malaysia dan 150 subjek bukan HIV (kawalan). Subset dari 170 subjek HIV yang menerima regimen HAART standard pertama dengan data kiraan CD4 dan data beban virus yang tersedia dipilih untuk dianalisis tentang respon imunologi dan virologi sehingga 12 bulan selepas permulaan HAART. Nombor salinan *CCL3L1* dikira menggunakan ujian nisbah paralogi (PRT) diikuti dengan pengesahan nombor salinan oleh analisis mikrosatellite. Pengesanan genetik *CCR5-Δ32* telah menggunakan tindak balas rantai polimerase (PCR) manakala kedua-dua *CCR5-R223Q* dan *CCR2-V64I* telah dikenal pasti menggunakan polimorfisme panjang pecahan PCR (PCR-RFLP). Regresi logistik digunakan untuk menentukan nilai prediktor untuk mencapai hasil sasaran jumlah CD4 ≥500 sel/mm^3 dan beban virus ≤50 salinan/mL. Bilangan salinan *CCL3L1* yang lebih rendah daripada purata dikaitkan dengan peningkatan risiko mendapatkan HIV-1 dalam etnik Melayu. Risiko jangkitan terhadap HIV juga dikurangkan dengan mempunyai alel mutan *CCR5-R223Q*. Dalam analisis pelbagai pemboleh ubah selepas penyesuaian untuk faktor

sosio-demografi dan klinikal, bilangan salinan *CCL3L1* lebih rendah daripada purata meramalkan kemungkinan pemulihan CD4 yang lebih tinggi kepada ≥500 sel/mm^3 pada 8-12 bulan rawatan dengan HAART. Tambahan pula, subjek dengan jumlah CD4 pra-rawatan ≥200 sel/mm^3 dikaitkan dengan sekurang-kurangnya lima kali lebih tinggi kebolehan untuk mencapai pemulihan CD4 optimum dalam 12 bulan pertama rawatan HAART. Di samping itu, pada 8 hingga 12 bulan rawatan HAART, subjek berbangsa Cina dan India mempunyai empat dan tujuh kali ganda lebih kecenderungan untuk mencapai jumlah CD4 sebanyak ≥500 sel/mm^3 berbanding subjek berbangsa Melayu. Penurunan beban virus kepada ≤50 salinan/mL tidak dikaitkan dengan faktor genetik daripada nombor salinan *CCL3L1* dan CCR5/CCR2. Sebaliknya penurunan beban virus diramalkan secara negatif oleh beban viral pra-rawatan ≥100,000 salinan/mL dan diramalkan secara positif oleh jumlah CD4 ≥200 sel/mm^3 dalam 4-6 bulan pertama rawatan HAART. Kesimpulannya, kedua-dua nombor salinan *CCL3L1* yang tinggi dan *CCR5-R223Q* yang mutan adalah faktor yang berpotensi untuk mengelakkan jangkitan HIV. Kajian ini juga menyerlahkan sumbangan nombor salinan *CCL3L1* yang rendah, etnik dan permulaan HAART pada peringkat yang awal untuk mencapai pemulihan kiraan CD4 yang optimal, seterusnya memperbaiki pengurusan raawatan HIV.

Kata kunci: *CCL3L1*, *CCR5*, kiraan CD4, beban virus, risiko jangkitan, HAART, Malaysia

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I certify that a Thesis Examination Committee has met on 12 March 2020 to conduct the final examination of Irma Izani Mohamad Isa on her thesis entitled "Copy Number Variation of C-C Chemokine Ligand 3-Like 1 (*CCL3L1*), C-C Chemokine Receptor Type 5 (*CCR5*) and *CCR2* Polymorphisms on the Outcomes of Antiretroviral Therapy among Malaysian HIV Patients" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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3TC	lamivudine
AIDS	acquired immunodeficiency syndrome
APC	antigen-presenting cells
APOBEC3G	apolipoprotein B mRNA-editing enzyme, catalytic polypeptide like 3G
ART	antiretroviral therapy
ARV	antiretroviral
AZT	3'-azido-3'-deoxythymidine / zidovudine
Bim	Bcl-2–interacting molecule
bp	basepair
C4	complement component C4
cART	combination-ART
CCL3	C-C chemokine ligand 3
CCL3L1	C-C chemokine ligand 3-like 1
CCR5	C-C chemokine receptors type 5
CCR5-Δ32	CCR5-32 deletion
CCR2	C-C chemokine receptor type 2
CDC	U.S. Centers for Disease Control and Prevention
CGH	comparative genomic hybridisation
CN	copy number
CNPs	copy number polymorphisms
CNVs	copy number variants
CRISPR	clustered, regularly-interspaced, short palindromic repeats
CRF	circulating recombinant form
CTLs	cytotoxic T lymphocytes
CXCL12	C-X-C motif chemokine type 12
CXCR4	C-X-C chemokine receptor type 4
DCs	dendritic cells
DC-SIGN	dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
DEFB	β-defensins
DNA	deoxyribonucleic acid
dNTP	deoxynucleoside triphosphate
ECACC	European Collection of Cell Cultures
EFV	efavirenz
env	envelope
FCGR3B	Fc gamma receptor 3B
FDC	fixed dose combination
FISH	fluorescence in-situ hybridization
FTC	emtricitabine
gag	group specific antigen
gp120	glycoprotein-120
GRGs	genetic risk groups
GWAS	genome-wide association studies
HAART	highly active anti-retroviral therapy
HCV	hepatitis C
HH	human haplotype

HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSPC	hematopoietic stem/ progenitor cells
IA-HOD-IA	Investigator's Agreement, Head of Department and Organizational/ Institutional Approval
IBBS	Integrated Bio-Behavioural Survey
IDU	injecting drug user
IFN	interferon
IN	interleukin
INSTI	integrase strand transfer inhibitors
IRIS	immune reconstitution inflammatory syndrome
IVDU	intravenous drug use
JKEUPM	Jawatankuasa Etika Manusia Universiti Putra Malaysia
KIR	killer cell immunoglobulin-like receptors
LTNP	long-term non-progressor
MAPH	multiplex amplifiable probe hybridization
MCP-2	monocyte chemotactic protein 2
MHC	major histocompatibility complex
MIP-1	macrophage-inflammatory protein 1
MLPA	multiplex ligation-dependent probe amplification
MREC	Medical Research and Ethics Committee
mRNA	messenger ribonucleic acid
MSM	men who have sex with men
MVC	maraviroc
NAHR	non-allelic-homologous recombination
NK	natural killer
NMRR	National Medical Research Registry
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSI	non-syncytium-inducing
OIs	opportunistic infections
OR	odd ratio
ORF	open reading frame
PCR	polymerase chain reaction
PI	protease inhibitor
PIC	pre-integration complex
PLWH	people living with HIV
pol	polymerase
PrEP	pre-exposure prophylaxis
PRT	paralogue ratio test
PWID	people who inject drug
qPCR	real-time PCR
RANTES	regulated upon activation, normal T-cell expressed and secreted
refSNP	reference SNP
RFLP	restriction fragment length polymorphism
RNA	ribonucleic acid
rpm	revolutions per minute
RT	reverse transcriptase
SDF-1	stromal cell-derived factor 1

SI	syncytium-inducing
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
t_0	pre-treatment
t_1	at 4-6 months of HAART initiation
t_2	at 8-12 months of HAART initiation
TBE	Tris/Borate/EDTA
TDF	tenofovir
Th1	type 1 helper T
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRAIL	TNF–related apoptosis-inducing ligand
TRIM5α	tripartite interaction motif 5 alpha
TSG 101	tumor susceptibility gene 101
UGT	uridine diphosphate glucuronyl transferase
UNAIDS	The Joint United Nations Program on AIDS
VL	viral load
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of study

The worldwide trends of human immunodeficiency virus (HIV)/acquired immune deficiency syndromes (AIDS) as well as the unfavourable impact of HIV remain among the major and pressing public health challenges (Cahill & Valadéz, 2013), affecting 36.7 million people around globally (UNAIDS, 2017a). The Asian and the Pacific countries contributed 5.1 million or 14% of the total cases of HIV and AIDS globally. In Malaysia, HIV prevalence is approximately 0.4%, which is equal to 93,089 people (Malaysian AIDS Council, 2016). HIV epidemics in Malaysia involves the most-at-risk or key populations that include men who have sex with men (MSM), people who inject drugs (PWID), sex workers, transgender people, prisoners as well as sexual partners of these key populations (Kilmarx, 2009; UNAIDS, 2017c). Social determinants of health, including being female, poor social-economic status and illiteracy level have been important aspects for control and prevention of HIV/AIDS (Alvarez-Uria, Midde, Pakam, & Naik, 2012; Dean & Fenton, 2010).

A unique feature of HIV viruses is that they replicate themselves using the host machinery system after their genetic material being integrated into host DNA, in the form of proviral DNA (Turner & Summers, 1999). In order to productively infect target cells, the very first step in HIV replicative cycle of HIV involves the binding of HIV to CD4 receptor and to a co-receptor, which is either C-C chemokine receptors type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) (Sierra, Kupfer, & Kaiser, 2005). CCR5 receptor plays a major role during HIV virus entry to host cells by macrophage-tropic or non-syncytium-inducing (NSI) strain at the early events of HIV-1 infection (Bleul, Wu, Hoxie, Springer, & Mackay, 1997; Choe et al., 1996; Deng et al., 1996; Dragic et al., 1996). One of the current antiretroviral therapy approaches is by blocking the CCR5 co-receptor, known as CCR5 inhibitor such as Maraviroc.

Notably, there is a growing number of people living with HIV (PLWH) as HIV patients can live longer due to the effect of taking anti-retroviral treatment (Wang et al., 2016). However, the current antiretroviral therapy (ART) cannot totally eliminate HIV viruses and has many adverse effects. CCR5 receptor is one of the potential target in the effort to cure HIV, by using hematopoietic stem cell gene therapy, which involves transplantation of genetically modified *CCR5* gene to HIV-infected patient (Passaes & Sáez-Cirión, 2014). The insight for *CCR5* genome editing had been derived from the 'Berlin patient', who had underwent a stem cells transplant from human leukocyte antigen (HLA)-matched, homozygous *CCR5* 32 deletion (*CCR5-Δ32*) that leads to undetectable viral load for 20 months post-transplantation without antiretroviral therapy (Hütter et al., 2009; Wang et al., 2016). Furthermore, the development of new HIV treatment modalities are focusing on vaccines and drugs that target the immune systems (Esté & Cihlar, 2010; Passaes & Sáez-Cirión, 2014).

HIV infection is classified into different stages based on CD4 T-cells count (CDC, 2008; World Health Organization, 2007). HIV virus is the same causative agent that causes AIDS, but the diagnosis of AIDS is made when CD4 cell count < 200 and/or there is the presence of AIDS-defining illnesses (World Health Organization, 2007). The hallmark of HIV-1 infection is the continuous declining of CD4 T cells due to increment in destruction as well as reduction in regeneration of CD4 T cell populations (Douek, Picker, & Koup, 2003). Interestingly, there has been a subset of HIV patients, known as long-term nonprogressors (LTNPs) (Pantaleo et al., 1995), who maintain a normal CD4 count for up to seven years without treatment (Okulicz et al., 2009). CD4 count is an important prognostic factor of individuals starting highly active antiretroviral therapy (HAART) and had been previously used to indicate when to initiate HAART (Egger et al., 2002). With the antiretroviral therapy, CD4 count increases rapidly by approximately 100 cell/mm^3 in the first year of starting HAART (Mocroft et al., 2007).

The entry of HIV virus to host cell leads to a rapid viral replication, known as viral load. The host immune system initially responds to the high viral load by the activation of HIV-1-specific cytotoxic or CD8 T-cells. This HIV-1-specific response leads to an initial decline of viral load few weeks after HIV infection, known as viral set point. However, this HIV-specific CD8 T-cells response is targeted at the dominant viral variant only and is rather limited due to viral immune escape (Goonetilleke et al., 2009). Viral load has been used to monitor response to ART as well as treatment failure (World Health Organization, 2016). During HAART, the viral load is targeted to achieve undetectable level or less than 20 copies/mL (Medical Development Division, 2017). In addition, consistency in viral suppression can minimize risk of viral transmission (Attia, Egger, Müller, Zwahlen, & Low, 2009).

Several host genetic determinants of susceptibility to HIV-1 infection, viral load and disease progression have been identified using classical candidate-gene association studies (O'Brien & Nelson, 2004). One example of how genetic can provide protection to HIV-1 infection is by a deletion mutation on *CCR5* gene, known as *CCR5-Δ32* (Liu et al., 1996). Homozygous *CCR5-Δ32* produces a non-functional CCR5 receptor, thus providing resistance to macrophage-tropic HIV infection (Liu et al., 1996). In addition, the ligand-receptor interaction of C-C chemokine ligand 3-like 1 (CCL3L1)-CCR5 complex had also been recognized to influence variability in CD4 count depletion and baseline viral load particularly in the era before HAART (Gonzalez et al., 2005). Nonetheless, a low pre-treatment CD4 count could also be an important factor preventing full recovery of CD4 counts (Kelley et al., 2009).

CCL3L1 is a ligand to CCR5, which is a HIV co-receptor. The *CCL3L1* gene is known as a multi-allelic gene copy number variant (CNV) because it exhibits a variation in gene copy number (CN) of more than three copies (Girirajan, Campbell, & Eichler, 2011). As one of CNVs gene, it has the potential to alter the gene expression level (Stranger et al., 2007) and have been linked to various types of human diseases including HIV (Usher & McCarroll, 2015; Wain, Armour, & Tobin, 2009). Higher *CCL3L1* CN had been associated with a higher resistance to HIV infection, as this up-regulates the gene expression level and functional chemokine, thereby increasing competition of the HIV virus to the CCR5 receptor (Gonzalez et al., 2005; Townson, Barcellos, & Nibbs, 2002). CNV of *CCL3L1* had also been reported to influence adaptive immune response and immune reconstitution during HAART (Ahuja et al., 2008; Shalekoff et al., 2008). However, some studies had shown no replication or conflicting results in some the disease-association studies, which could be due to the types of genotyping techniques used (Clayton et al., 2005).

CCR5 is a G-protein-coupled receptor that binds a number of C-C chemokines including CCL3 and CCL3L1 (Hughes & Nibbs, 2018). The protein, which is found on immune cells like macrophages and monocytes, is involved in co-stimulatory signal for T-cell activation (Molon et al., 2005). Most importantly, it serves as co-receptor for macrophage-tropic strains during the early HIV infection (Dragic et al., 1996). CCR5 has a 75% similarity in amino acid sequence as C-C chemokine receptor type 2 (CCR2) (Combadiere, Ahuja, Tiffany, & Murphy, 1996). *CCR5-Δ32* (NC_000003.12:g.46373456_46373487del) and *CCR2-V64I* (NC_000003.12:g.46357717G>A), together with other polymorphisms in the *CCR5* promoter region are tightly linked together and have been used to define *CCR5* haplotype (Mummidi et al., 2000). The *CCR5-Δ32* mutation had been demonstrated to reduce susceptibility to HIV infection and to delay development of the AIDS in HIV-1- infected individuals while the phenotypic effect of *CCR2-V64I* is a slower progression to AIDS (Kostrikis et al., 1998; McDermott et al., 1998; Smith et al., 1997; Tang et al., 2002). Another *CCR5* variant, known as *CCR5-R223Q* (NC_000003.12:g.46373570G>A) is closely associated with *CCR2-V64I* and typically found in the Asian populations (Liu et al., 2007).

1.2 Problem statements

Host genetic variability has been generally accepted to influence the pathogenesis of HIV-1 infection, including susceptibility and disease progression (Fellay, 2009; McLaren & Carrington, 2015). Early study had reported on a small subset of individuals who were resistant to HIV-1 infection regardless of the exposure to the HIV virus (Liu et al., 1996). In addition, the rate of CD4 count depletion can vary among individuals, particularly a small percentage of HIV-infected populations, known as LTNP, who maintain high CD4 T-cell counts for many years and did not progress to AIDS (Pantaleo et al., 1995). Among the most established genetic variants influencing HIV-1 susceptibility and immune response are the mutations on *CCR5/CCR2* and *CCL3L1* genes, which encode the CCR5/CCR2 receptor and the ligand of the CCR5 receptor respectively (Gonzalez et al., 1999, 2005). The *CCR5* haplotypes and *CCL3L1* CN also exhibit race-specific HIV-1 disease-modifying effects, which highlights the need for population or ethnic specific disease association studies (Gonzalez et al., 1999).

However, host genetic determinants of HIV susceptibility are still unknown for the Malaysian population, particularly for the *CCL3L1* CN and the *CCR5/CCR2* polymorphisms. Besides, in this era of HAART, studies on genetic factors that contribute to the variation in the individuals' response to the anti-HIV treatment, in term of immune recovery and viral load suppression are still limited. The phenotypic effects of *CCL3L1* CN and *CCR5/CCR2* polymorphisms on HIV-infected patients of the three major ethnicities in Malaysia are largely unknown. Apart from genetic influence on HIV pathogenesis, there is also a lack of knowledge about the influence of socio-demographic and clinical factors on CD4 recovery and viral load suppression in early response to HAART among Malaysian HIV population.

1.3 Significance of study

First of all, this research will enhance the knowledge on the contribution of genetic diversity on HIV/AIDS pathogenesis among HIV-positive population in Malaysia. The main outcome of this study will add a new element to what is known about CNV of the *CCL3L1* and polymorphisms in *CCR5* and *CCR2* genes as the potential genetic host factors determining HIV susceptibility, immune recovery and viral load suppression following antiretroviral therapy. In addition to the genetic polymorphisms being studied, the impact of other factors including socio-demographic and clinical factors on immune recovery and viral load suppression will also be discovered. Finally, the results of this study can potentially lead to the development of predictive tools or biological markers that would set the stage for personalized HIV medicine, by the generation of genetic risk groups to predict how individuals will respond to the current ART.

1.4 Objectives

To investigate the relationship of *CCL3L1* copy number variation and *CCR5/CCR2* genotypes on HIV susceptibility, CD4 recovery and viral load suppression following HAART.

The specific objectives include

i. to determine the relationship of socio-demographic and clinical factors on CD4 recovery and viral load suppression following HAART among Malaysian HIV patients (Chapter 4),

ii. to determine the relationship of *CCL3L1* copy number on HIV susceptibility, and CD4 recovery and viral load suppression following HAART among Malaysian HIV patients (Chapter 5),

iii. to determine the relationship of *CCR5/CCR2* polymorphisms on HIV susceptibility, and CD4 recovery and viral load suppression following HAART among Malaysian HIV patients (Chapter 6), and

iv. to generate haplotypes or risk groups based on the relationship of *CCL3L1* copy number and *CCR5/CCR2* polymorphisms on CD4 recovery and viral load suppression following HAART (Chapter 6).

1.5 Hypothesis

i. Socio-demographic and clinical factors are significantly associated with CD4 recovery and viral load suppression following HAART among Malaysian HIV patients.

ii. *CCL3L1* copy number is significantly associated with HIV susceptibility, CD4 recovery and viral load suppression following HAART among Malaysian HIV patients.

iii. *CCR5/CCR2* polymorphisms are significantly associated with HIV susceptibility, CD4 recovery and viral load suppression following HAART among Malaysian HIV patients.

1.6 Conceptual framework of the study

This study had four specific objectives, which were separated into three different objective chapters. In the first objective chapter (Chapter 4), the influence of socio-demographic and clinical factors on immune recovery and viral load suppression were discussed. Consequently, the predictive value of *CCL3L1* CN and *CCR5-CCR2* genotypes on HIV susceptibility, and immune recovery and viral load suppression during HAART were analysed in Chapter 5 and Chapter 6 respectively. The last objective, which is the combined effect of *CCR5* and *CCR2* genotypes and *CCL3L1* CN for the prediction of the susceptibility, and viral load and CD4 count during HAART, were also discussed in Chapter 6. **Figure 1.1** summarised the conceptual framework that has been applied in this study.

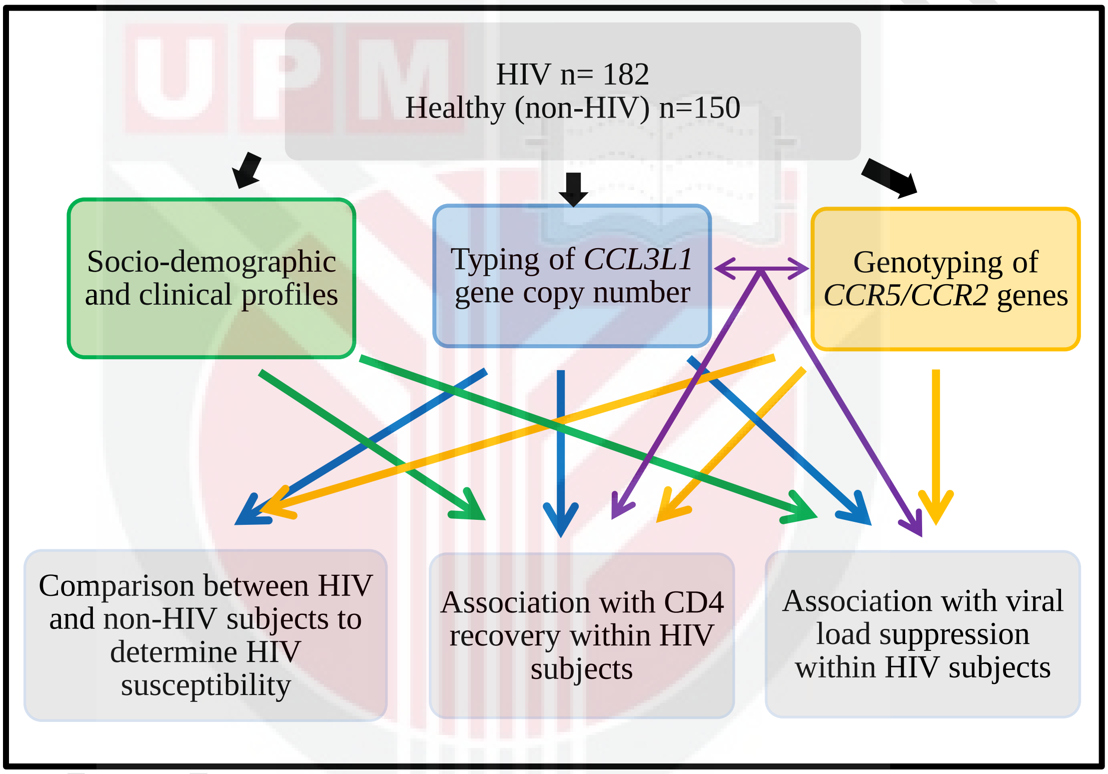

Figure 1.1: Conceptual Framework

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She had previously worked as houseman officer in Hospital Kajang for several months. However, due to her hearing condition at that time, she decided to continue her studies to pursue her ambition as a medical lecturer. While completing her Ph.D, she had worked as a part-time lecturer teaching Pharmacology subject at Royal College of Surgeon Ireland-Perdana University. In the future, she imagines herself as an expert in Pharmacology and Pharmacogenetics field, as combination of her Medical, Pharmacology and Human Genetics qualifications, to contribute to the personalised and precision medicine.

LIST OF PUBLICATIONS

List of article publications

Mohamad Isa II, Abu Bakar S, AbRahman AK. Ethnicity as predictor of immune reconstitution among Malaysian HIV-positive patients treated with highlyactive antiretroviral therapy. J Med Virol. 2020;1–9.https://doi.org/10.1002/jmv.25680

Mohamad Isa II, Jamaluddin J, Achim NH, Abubakar S. Population-specific profiling of *CCL3L1* copy number of the three major ethnic groups in Malaysia and the implication on HIV susceptibility [published online ahead of print, 2020 Jun 1]. *Gene*. 2020;754:144821. doi:10.1016/j.gene.2020.144821

Impacts of *CCR5* gene variants on HIV susceptibility and response to antiretroviral therapy among Malaysian HIV patients (submitted)

List of proceedings/conferences and others

Irma Izani Mohamad Isa, Nurfarahin Hanini Achim, Ahmad Kashfi Ab Rahman, Azureen Azmel, Suresh Kumar Chidambaram, Siti Dalila Adnan, Cheah Yoke Kqueen, Zulkefley Othman and Suhaili Abu bakar. *Influence of Socio-Demographic and Viral Transmission Mode on Early CD4 Count and Viral Load among HIV Patients with Anti-Retroviral Therapy*. 4th National AIDS Conference, 28-30 September 2018, Swiss Garden Hotel Kuala Lumpur. (Poster presentation)

Irma Izani Mohamad Isa, Nurfhaezah Khairil Wahidin, Nur Sakinah Matnor, Ahmad Kashfi Ab Rahman, Cheah Yoke Kqueen, Zulkefley Othman and Suhaili Abu bakar. *Prevalence of 32 Basepairs Deletion Mutation of CCR5 Gene (CCR5-Δ32) among HIV-1 and Healthy Populations in Malaysia*. 4th National AIDS Conference, 28-30 September 2018, Swiss Garden Hotel Kuala Lumpur. (Poster presentation)

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Path to a more tailored HIV treatment, Three-Minute Thesis (3MT) Competition, Faculty of Medicine and Health Sciences, 6th March 2019

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