HIV/AIDS TREATMENT AND HEALTH-RELATED QUALITY OF LIFE: PATIENTS' PERSPECTIVE AND IMPACT OF ADVERSE DRUG REACTIONS AMONG HIV/AIDS PATIENTS

By

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DEDICATION

To

My Parents-who paved the way

My Wife…….

My Son…….

My Teachers…….

To them, I dedicated this thesis

Of course with this dissertation I would like to thank Almighty Allah for His grace, strength and protection. Despite the fact there were defies in my journey from the beginning, He was always there for me. I would once more like to thank my wonderful family for being such supportive during my studies. I know at times it was tough for them to put up with me, but they were always there for me. I will always be grateful for that because I wouldn't have achieved this without their unmatchable support.

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Syed Imran Ahmed

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACCP	American College of Clinical Pharmacy
ADRs	Adverse Drug Reactions
AHI	Acute HIV Infection
AIDS	Acquired Immunodeficiency Syndrome
ASHP	American Society of Health System Pharmacist
ART	Antiretroviral Therapy/Treatment
ARV	Antiretroviral Medicines
BM	Bahasa Malaysia
BP	Bodily Pain
FAHI	Functional Assessment of HIV Infection questionnaire
GH	General Health Perceptions
HAART	Highly Active Antiretroviral Treatment
HAT-QoL	HIV/AIDS Quality of Life questionnaire
HCP	Health Care Professionals/Providers
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus-type 1
HIV-2	Human Immunodeficiency Virus-type 2
HRQoL	Health Related Quality of Life
IDU	Injecting Drug Use
MAC	Malaysian AIDS Council
MADRAC	Malaysian Adverse Drug Reaction Advisory Committee
MARPS	Most-At-Risk Populations
MCS	Mental Component Summary

MH	Mental Health
MOH	Ministry of Health
MSM-POZ	Men Having Sex with Men- support group
NAP	National AIDS Program
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
OI	Opportunistic Infections
PCS	Physical Component Summary
PF	Physical Functioning
PIR	Paradoxical Immunologic response
PI	Protease Inhibitor
PLWHA	People Living with HIV and AIDS
QoL	Quality of Life
RE	Role Limitations Due to Emotional Problems
RP	Role Limitations Due to Physical Problems
SF	Social Functioning
SF-12	Short Form Health Assessment questionnaire
SPSS®	Statistical Package for Social Sciences
STATA	Statistics and Data software
STDs	Sexually Transmitted Diseases
UNAIDS	Joint United Nation Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VT	Vitality
W.H.O	World Health Organization
WHOQoL	World Health Organization Quality of Life questionnaire

LIST OF APPENDICES

LIST OF PUBLICATIONS

1. **Ahmed SI**, Sulaiman SAS, Hassali MA, Christopher LKC. HIV/AIDS treatment and health related quality of life: Importance of knowing patients' perspective. *HIV & AIDS Rev* 2013; 12 (1): 26-27. doi: 10.1016/j.hivar.2013.02.003.

2. **Ahmed SI,** Sulaiman SAS, Hassali MA, Christopher LKC. Assessing HIV and AIDS Treatment Safety and Health-Related Quality of Life among Cohort of Malaysian Patients: A Discussion on Methodological Approach. *Health Expectations* 2013; DOI: 10.1111/hex.12116.

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6. **Ahmed SI**, Sulaiman SAS, Hassali MA, Hasan SS, Lau HS, Christopher LKC. Factors Associated with Poor CD4 and Viral Load control in Patients with HIV/AIDS. *Journal of Medical Virology (**Under review)***

7. **Ahmed SI**, Sulaiman SAS, Hassali MA, Thiruchelvam K, Hasan SS, Christopher LKC. Acceptance and barriers towards screening: A qualitative perspective of people with HIV/AIDS. *Asia Pacific Journal of Public Health* (***Under review***)

8. **Ahmed SI**, Sulaiman SAS, Hassali MA, Thiruchelvam K, Hasan SS, Christopher LKC. Beliefs and Practices of Complementary and Alternative Medicine (CAM) among people with HIV/AIDS: A qualitative exploration. *European Journal of Integrative Medicine* (***Under review***)

LIST OF PRESENTATIONS

1. **Ahmed SI**, Sulaiman SAS, Hassali MA, Lau HS, Hasan SS, Christopher LKC. HIV & AIDS treatment and patient reported Adverse Drug Reaction. 3rd International Postgraduate Conference on Pharmaceutical Sciences 2014 (iPoPS 2014) 11 - 12 August 2014, University Teknologi Mara (UiTM), Puncak Alam, Selangor, Malaysia. **(Poster)**

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RAWATAN HIV/AIDS DAN KUALITI KEHIDUPAN YANG BERKAITAN DENGAN KESIHATAN: PERSPEKTIF PESAKIT DAN KESAN SAMPINGAN UBAT DALAM KALANGAN PESAKIT HIV/AIDS

ABSTRAK

Kemajuan rawatan antiretroviral (ART) dan perubahan HIV sebagai jangkitan yang kronik, memberi cabaran seperti kesan sampingan ubat (ADRs) yang yang mempengaruhi pematuhan dan pengekalan rawatan dan juga kualiti kehidupan yang berkaitan kesihatan (HRQoL). Oleh yang demikian, penilaian ADRs dan langkah-langkah HRQoL adalah amat penting dalam memaksimumkan keseluruhan hasil rawatan. Penglibatan pesakit secora mendalam tentang rawatan mereka boleh membantu meningkatkan dapatan rawatan serta pemahaman dan kepercayaan pesakit terhadap penyakit, rawatan dan isu-isu berkaitan adalah penting dalam keseluruhan penjagaan HIV.

Kajian ini telah dijalankan di Hospital Sungai Buloh. Seramai empat ratus dan empat puluh tiga pesakit HIV/AIDS warganegara Malaysia yang menggunakan rawatan antiretroviral (ART) selama tiga bulan mengambil bahagian dalam kajian ini. Data telah dianalisa menggunakan Statistical Package for Social Sciences (SPSS®) versi 18 and STATA IC® versi 12. Kaedah kualitatif telah digunapakai untuk mendapatkan perspektif pesakit berkenaan penyakit, rawatan dan penjagaan. Temuduga separa struktur telah digunakan untuk menemuduga pesakit dan titik tepu telah dicapai setelah temuduga yang ke 13 dijalankan. Kesemua temuduga telah dirakam dan melalui rangkakerja analisa kandungan piawai.

Sebanyak 44% (n=194) daripada keseluruhan 443 pesakit-pesakit HIV melaporkan ADR, termasuk penurunan berat badan (12.6%), '*lipodystropi*' (12.4%) dan '*neuropeti periferal*' (12%), Tahap CD4 yang menurun (OR 1.72, 95% CI: 1.04-2.86), dan kurangnya perencatan virus (OR 1.87, 95% CI: 1.04 — 3.36) telah meningkatkan kemungkinan terjadinya ADRs. Akibatnya pesakit-pesakit yang mengalami ADRs mengalami sebanyak 2.28 (95% CI: 1.25 – 4.18) risiko yang lebih tinggi dalam ketidak-berkesanan pengawalan CD4. Status pendidikan dan pekerjaan peserta-peserta kajian tidak mendapat pendidikan formal telah mempengaruhi skor rendah yang signifikan bagi 'physical composite scores' (PCS) jika dibandingkan dengan peserta-peserta yang mempunyai pendidikan sekolah menengah (p=0.049) dan yang mem punyai kelulusan ijazah (p=0.003). Pesakit-pesakit yang tidak bekerja juga mempunyai skor yang rendah dalam domain PCS jika dibandingkan dengan pekerja buruh (p=0.003) dan profesional (p=0.006). ADRs juga didapati berkait-rapat dengan HRQoL yang rendah dalam pelbagai domain dan keseluruhan fizikal (p=0.001) dan mental (p=0.013) dalam kualiti kehidupan

Beberapa tema penting telah diperolehi yang menunjukkan perspektif berbeza pesakit-pesakit dalam rawatan HIV/AIDS. Walaupun kebanyakannya memahami HIV/AIDS dan puncanya, terdapat elemen-elemen kerohanian dan juga kurang pengetahuan. Walaupun kesedaran tentang status HIV wujud dalam kalangan pesakit, mereka lebih takut kepada stigma dan diskriminasi. Kesan-kesan sosial dan emosi keluarga telah didapati sebagai elemen-elemen penting yang mengaitkan penyakit dan keengganan untuk melalui proses pemeriksaan. Umumnya peserta-peserta percaya hanya ARTs sahaja rawatan yang sedia ada; kerisauan pada kesan sampingan, kurang sistem sokongan, putus asa, nilai-nilai negatif dan penggunaan rawatan pelengkap

‘complementary’ dan alternatif juga didapati berkaitan dengan rawatan yang dipilih. Hierarki dalam kalangan doktor, masa menunggu untuk mendapatkan temujanji, hormat dan kerahsiaan didapati sebagai elemen-elemen penting yang memberi kesan kepada penerimaan pesakit-pesakit.

Kurang maklumat dan keadaan yang tidak dapat diramalkan berkenaan ADRs terus memberi cabaran kepada pesakit-pesakit HIV/AIDS yang memerlukan fokus dalam penelitian perubatan bagi rawatan HIV. Gambaran kehidupan sebenar berkenaan perspektif pesakit-pesakit terhadap penyakit, rawatan dan penjagaan adalah penting dalam mereka-bentuk dan memperbaiki strategi sedia ada untuk meningkatkan kaedah penjagaan HIV yang perlu diberi lebih perhatian. Strategi seumpama ini adalah penting untuk berdepan dengan usaha negara didalam memenuhi objektif-objektif global di dalam penjagaan HIV

HIV/AIDS TREATMENT AND HEALTH-RELATED QUALITY OF LIFE: PATIENTS' PERSPECTIVE AND IMPACT OF ADVERSE DRUG REACTIONS AMONG HIV/AIDS PATIENTS

ABSTRACT

Advancements in antiretroviral treatment (ART) and shift of HIV as a chronic infection, presents challenges, including adverse drug reactions (ADRs) affecting adherence and retention to care as well as health related quality of life (HRQoL); thus evaluation of ADRs and measures of HRQoL is imperative to maximize the overall treatment outcomes. In addition, greater involvement of the patients in their medical care can benefit treatment outcomes, thus understanding patients' knowledge and beliefs towards disease, treatment and related issues are essential elements in overall HIV care.

The present study was carried out at Hospital Sungai Buloh. Four hundred and forty three Malaysian HIV/AIDS patients, using Antiretroviral Therapy (ART) for at least three months, participated in this study. The data were analyzed using the Statistical Package for Social Sciences (SPSS®) version 18 and STATA IC® version 12. Qualitative methodology was used to explore patients' perspectives on the disease, treatment and care with the help of a semi structured interview guide. A saturation point was reached after the 13th interview. All interviews were audio-recorded and subjected to a standard content analysis framework.

About 44% (n=194) of the total 443 HIV patients reported ADR, among them weight loss (12.6%), lipodystrophy (12.4%), peripheral neuropathy (12%), were frequently found ADRs. Poor CD4 counts (OR 1.72, 95% CI: 1.04 — 2.86), and poor viral suppression (OR 1.87, 95% CI: 1.04 — 3.36) did increase the odds of experiencing ADRs,

consequently patients experiencing ADRs had a 2.28 (95% CI: 1.25 – 4.18) fold greater risk of poor CD4 control. As for QoL, participants with no formal education had significantly lower scores for physical composite scores (PCS) in comparison to those with secondary education (p=0.049) and graduates (p=0.003). Similarly unemployed patients had significantly lower scores under the PCS domain against laborers (p=0.003) and professionals (p=0.006). ADRs were also found significantly associated with lower HRQoL in various domains and overall physical (p=0.001) and mental (p=0.013) quality of life. A number of important themes and subthemes emerged showing patients' perspectives on HIV/AIDS treatment. Generally, participants had acceptable understandings towards the cause of disease; however elements of spirituality were also noted. Though strong beliefs existed towards the benefits of knowing HIV status, fear of stigma and discrimination, social consequences and family emotions were found important elements linked to status non-disclosure and refusal to get screened. Most participants believed in ARTs as the only available treatment; fear of side effects, lack of support system, gross hopelessness, and negative values were found reasons for non-adherence. In addition, strong believes and use of complementary and alternative medicines were found linked to disease treatment. Doctors' hierarchy, appointment waiting time, respect and confidentiality were seen as vital elements affecting patients' satisfaction. Uninformed and unpredictable ADRs continue to challenge HIV/AIDS patients, requiring focus on pharmacovigilance in HIV care. A real life insight about patients' perspectives towards disease, treatment and care is inevitable in designing and improvising existing strategies to enhance areas in HIV care that requires more attention. Such strategies are important to withstand with the country's efforts in meeting global objectives of HIV care.

CHAPTER 1

INTRODUCTION

1.1 Introduction and background to HIV & AIDS

1.1.1 Historical Background

Human immunodeficiency virus (HIV) have been spreading through the human population long before AIDS was first described in 1981 [1], when increasing numbers of young homosexual men succumbed to unusual opportunistic infections and rare malignancies [2]. A retrovirus, now termed human immunodeficiency virus type 1 (HIV-1), was identified as the causative agent of what has since become one of the most devastating infectious diseases to have emerged in recent history [3]. It was in 1986 when a morphologically similar but antigenically distinct virus was found to cause AIDS in patients in western Africa and this new virus was then termed as human immunodeficiency virus type 2 (HIV-2) [4]. Both of these viruses belong to *lentiviruses* family and it is also interesting to know that they are believed to be a result of multiple cross-species transmissions of simian immunodeficiency viruses (SIVs) naturally infecting African primates resulting in gradual immune deficiencies in human being [4]. Chronic immune activation is a hallmark of HIV disease and results in increased viral replication and immune cell depletion, immune cell dysfunction, and aberrant lymphocyte turnover [5], therefore once infected the disease process could result in a clinical latent period of a few years before clinical, constitutional symptoms of disease can be seen [5,6]. This period has a great importance in strategizing behavioral and

pathogenesis based interventions in limiting HIV epidemics as individuals with acute HIV infection (AHI) pose a greater transmission risk than most chronically infected patients, hence prevention efforts targeting these individuals are important for reducing the spread of HIV infection [6–8].

As for disease epidemic sexual transmission, injecting drug use (IDU) and vertical transmission from mother to child are regarded as the major ways of HIV transmission [4,6]. Sexual transmission is still accounted as a major route of HIV/AIDS globally [6], therefore the Joint United Nations Programme on HIV/AIDS (UNAIDS) has targeted a 50% reduction in sexual transmission among low-and middle income developing countries by year 2015 [9].

1.1.2 HIV/AIDS treatment

The unprecedented efforts in the fields of biology, pharmacology and clinical care have contributed to progressively turn HIV infection from an inevitably fatal condition into a chronic manageable disease [10]. Recent advances in antiretroviral therapy (ART) have drastically improved the quality of life for people with HIV infection, however owing to the persistence of latent HIV in the presence of therapy, patients must remain on therapy indefinitely [11].

Despite these unquestioned successes, the problem is far from being resolved: even in countries with full access to antiretroviral treatment, life expectancy of people under

ARV therapy remains lower with respect to that of uninfected people [12]. Furthermore, large populations of HIV infected individuals are not diagnosed, remain untreated or not entered to the treatment at a very late stage of the diseases, represents an infected reservoir that increases risk of HIV transmission. Moreover, the emergence of new comorbidities that may be partly associated with antiretroviral treatment (ARTs) and partly with HIV itself represent a new problem in medical practice [10].

1.1.3 HIV/AIDS in post HAART era

A milestone in the history of HIV disease has been the availability of new classes of drugs in 1995-96, allowing the introduction of combination ARTs i.e. Highly Active Anti-Retroviral Therapy (HAART) and the gradual evolution of HIV infection into a chronic, usually non-fatal condition [13]. Ever since HIV has been recognized; reduction in viral load with increase in CD4 cell counts remained as the prime objectives of antiretroviral treatment along with the enchantment in health related quality of life and reduction in the impact of HIV transmission in the community. No matter how we define, the principal goal of HIV treatment is to prevent or reverse the progression of clinical illness [14].

There is no doubt that the unprecedented increase in the access to HIV treatment even in resource-limited settings has definitely contributed towards the global improvement in epidemics and HIV/AIDS related morbidity and mortality. This made possible due to virological suppression that occurs in approximately 70% of patients during the first

regimen of HAART [15], thus making infected individuals' immunologic reconstitution possible [16,17]. Many factors contribute to immunological enhancements and virological suppression in making HAART as an effective tool [18] against HIV and AIDS and it was found that patients who present with advanced HIV infection and high levels of viral replication continue to be a challenge in the highly active antiretroviral treatment (HAART) era [19,20]. This become an important point of concern as substantial number of patients start their first-line antiretroviral therapy at an advanced stage of the disease [21].

It is widely accepted that for HIV-positive persons on HAART, high levels of adherence to treatment regimens are essential for promoting viral suppression and preventing drug resistance [22], also since complete cure for HIV infection is not yet possible, treated people have to maintain lifelong adherence and facing the risk of delayed drug toxic effects [10]. In reality HAART poses many challenges to patients' life affecting the outcome of these successes. Though many factors can contribute to such challenges including drug toxicities [23], it has been suggested that a lower pre-HAART, CD4 count nadir may lead to a greater risk of experiencing drug related toxicities. In addition the frequency of a paradoxical immunologic response to HAART, defined as viral suppression without CD4 cell-count improvement, has also been reported in the literature as 8 to 42%, and around 15% in most occasions [20,24]. Therefore timely HIV diagnosis and induction of HAART remained a crucial step in determining the success of antiretroviral therapy. Looking into this the world health organization in its 2013 guidelines for antiretroviral therapy has recommended earlier

initiation of antiretroviral therapy (ART) at CD4 500cells/μl or less for all adults and children above 5 years [25]. It further recommended initiation of ARTs irrespective of CD4 cell count or clinical stage for people co-infected with active tuberculosis disease or hepatitis B virus with severe liver disease, pregnant women, people in serodiscordant partnerships, and children under 5 years of age [25].

1.2 Current status of HIV/AIDS

1.2.1 Disease epidemics

According to UNAIDS global AIDS epidemics report 2013; globally 35.3 million [32.2 million–38.8 million] people were living with HIV indicating that about 75 million [63 million–89 million] people have been infected with HIV since the beginning of epidemics [9]. During the recent years there has been an extraordinary increase in access to HIV treatment, care and facilities even in resource-limited settings where antiretroviral medications were previously unavailable, which has definitely contributed towards a global improvement in epidemics and HIV/AIDS related morbidity and mortality. As a matter of fact a 33% decline of new HIV infection was reported compare to the year 2001, however this positive news is not limited to the newly diagnosed infection as in 2012, also almost 1.6 million [1.4 million–1.9 million] people died from AIDS-related causes worldwide compared to 2.3 million [2.1 million–2.6 million] in 2005 [9]. Sub-Saharan Africa with South and South-East Asia remained as top two regions accountable for most people living with HIV and HIV related deaths

[9]. Therefore though it is true that the number of globally newly infected people is declining, the burden of the epidemic continues to vary considerably between countries and regions [26].

1.2.2 Developed versus developing world

It is indeed a great success as extraordinary escalation in access to HIV treatment even in resource-limited settings has been witnessed in recent years, and according to World Health Organization (WHO) data, access to antiretroviral drugs in low-middle income countries had rose 10 fold [9]. However in high-income countries, antiretroviral drugs have long been widely available and access to treatment has had a prominent impact on HIV-related mortality and introduction of HAART had resulted in decline of as much as 85% in the mortality rate in HIV infected patients [27]. As the antiquity of HIV/AIDS has taken long time before in 1983 a retrovirus was (later named as human immune-deficiency virus) found responsible for causing this disease in human being [28], it was developing countries, particularly in sub-Saharan Africa, continued to bear the full brunt of an unchecked AIDS pandemic [2]. In the initial twenty five year history of this disease ninety-five percent (95%) of infections and deaths occurred in developing countries due to various factors [28], owing to the fact that dealing with the scientific, clinical, political, economic, and social problems posed by HIV/AIDS will continue to be a major struggle beyond the capacities of developing countries.

It was until the year 2000 when The International AIDS Conference in Durban, South Africa, proved a turning point which put the AIDS crisis in the developing world back on the front page of newspapers around the world, growing sentience among the general population and government leaders and raising a cry heard around the world [2]. This demanded a unique and truly global response to meld the resources, political power, and technical capacity of wealthy countries with the needs and capacities of developing countries [28]. As presented in the yearly global epidemic reports by UNAIDS, the developing world especially Sub-Saharan Africa, South Asia and South-East Asia still facing greater challenges in managing the epidemics of HIV/AIDS while the developed world has already witnessed a declining or steady levels to growing HIV epidemics [9,26]. Therefore the focus in dealing AIDS epidemic varied between developed and developing world, where developed world activities involve managing the predictable effects of any potent therapy, toxic effects and drug resistance rather than scrambling to provide basic care as in the case of developing nations [29].

1.2.3 Global challenges and strategies in controlling HIV/AIDS epidemics

The human immunodeficiency virus and its incurable acquired immunodeficiency syndrome pose greater challenges despite the commendable achievements in recent years. As it is clearly evident and expected that the global prevalence of this disease would definitely going to increase in the coming years [9,30], there is a strong need for planning better strategies towards prevention and treatment of this disease. The first two decades of HIV/AIDS were marked with exploring disease and its treatment while the

epidemics were continuously growing at an alarming rate resulted in worse situations in Asian and African countries [31], now it is the time to deal with the issues still challenging the world especially developing countries for which better HIV surveillance programs are inevitable. There is an ever greater need to apply the concept of "Treatment for prevention", requiring multiple preventive measures to curb the disease epidemics [32].

Though "zero new infection, zero discrimination and zero AIDS related deaths" remained as visionary global agenda of UNAIDS much work has to be done in context to growing HIV/AIDS related challenges and epidemics in various parts of the world. In order to continue this journey UNAIDS has set certain targets to be achieved by the year 2015, including reduction in HIV transmission, AIDS related mortalities and morbidities as well as reduction in stigma and discriminations towards HIV patients [26].

1.3 HIV/AIDS in Malaysia

1.3.1 Historical background

History of HIV/AIDS in Malaysia started when first cases were reported in 1986 [33–35], since then country has seen considerable challenges in managing this disease [34]. Although initially IDUs were the main driving force of HIV epidemics in this country [34,36], at present it is still concentrated within most-at-risk populations (MARPS)

especially among IDU, sex workers and transgender population [33]. With the universal advancements in managing HIV/AIDS the country has witnessed significant reduction in new HIV cases by more than half from 28.4 per 100,000 populations in 2002 to 11.42 cases per 100,000 populations in 2013 [9,34]. In the year 2013, there were 3,393 new cases were reported at an average of 9 cases per day though it is significant but lesser since the epidemic reached its peak in 2002 (6,978 cases) [34].

1.3.2 Current Status

By the end of the year 2013, about 86324 patients were living with status of HIV and the country had reported a cumulative 101,672 HIV cases, 20,235 AIDS cases and 16,340 deaths related to HIV/AIDS, thus giving reported PLWHA of 85,332 cases. Although male patients are mainly accounted for HIV epidemics in this country but the proportion of women reported with HIV has also increased dramatically in the last decade [34,36]. As the epidemic spread the pattern progressively shifted towards increasing infection rates in female with male/female ratio from 9.6 in 2000 to 4.5 in 2010 to 3.7 in 2013. As explain earlier another important aspect is the shift of infection epidemics from IDUs to sexual transfer which is evident by increasingly more sexual transmission with IDU/sexual transmission ratio now declined from 3.9 in 2000 to 0.3 in 2013 with about 34.3% reported cases were among young individuals aged between 13 to 29 years [34]. The Malaysian Ministry of Health has a separate HIV/STI (sexually transmitted infection) sector working as national AIDS program (NAP) and county's improved control of HIV epidemics is due to a multi-sector AIDS response involving various departments and ministries [34]. In addition to government efforts, Malaysian

AIDS Council (MAC) also works with many partner organizations with a vision of building "society free from the negative impact of HIV and AIDS where the AIDS epidemic is under control through comprehensive prevention, treatment, care, support and impact alleviation services particularly for the most vulnerable and marginalized populations" [37].

1.3.3 Challenges in HIV/AIDS care

While significant progress has been made in the country's response to HIV/AIDS, scaling up prevention, treatment and care to meet universal access goals remain a challenge in this country. The Ministry of Health, Malaysia in its 2014 global AIDS response report [34] has highlighted key challenges in HIV management including;

a) Increase knowledge and awareness among younger population towards risky behavior.
b) Scaling up HIV testing for better management
c) To curb sexual transmission of HIV
d) Coverage and integration of various service sectors including primary health.
e) To improvise TB/HIV care
f) Elimination of mother to child transmission (MTCT)
g) Public –private partnership for better HIV control
h) To eliminate stigma and discrimination towards HIV/AIDS

Many factors including gender inequity, silence, denial [38] and ignorance fuel the epidemics in Malaysia. In addition urban and rural children and adolescents' vulnerability to HIV further increases, therefore children with HIV/AIDS have been reported to have faced stigma and exposed to and experience acts of discrimination leading to many challenges [36].

1.4 HIV/AIDS and Quality of life

1.4.1 Quality of life (QoL) & Health related quality of life (HRQoL)

WHO defines *quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns* [39]. While quality of life (QoL) is a broad concept that incorporates individual's perceptions of factors affecting his or her general well-being, health related quality of life (HRQoL) focuses specifically on quality of life related to health. WHO defines the concept of HRQoL as, "*a state of complete physical, mental and social well-being and not merely the absence of disease of infirmity*." In recent years, interest in measuring HRQoL increased with the publication of more HRQoL studies. QoL is in fact, a concept that incorporated all factors affecting a person (economic status, social functioning, self-satisfaction and well-being) while HRQoL focuses more on QoL related to health. Major aspects of HRQoL include physical, social, emotional and cognitive functioning; mobility and self-care; patient perception of health; and symptoms[40]. Patrick and Erickson broadly defined HRQoL as the

"value assigned to the duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy [41]

1.4.2 Importance of HRQoL among HIV/AIDS patients

As discussed earlier despite the global decline in number of people newly infected with HIV/AIDS, many nations are still fronting challenges with expending epidemics, hence despite much of the news on HIV/AIDS is encouraging in present era, challenges sill remain [26]. Numerous factors contribute to this high prevalence; from low levels testing and linkage to care and prevention, to poor retention in care and adherence to antiretroviral treatment [42]. Though much has been achieved in terms of treatment outcomes due to the global solidarity in the AIDS response during the past decade [26], the chronicity of HIVA/IDS still poses challenges to patients' life [43]. Therefore until the day HIV/AIDS cure will be possible, delay in HIV/AIDS related mortality and related complications with improve quality of life (QoL) will remain as main outcomes of the treatment and in order to achieve this, equal and active participation of patient in the whole process of treatment is imperative. This accentuates on assessment of patient perspective and understanding toward disease and its management [44].

Health-related quality of life is increasingly recognized as an important outcome and as a complement to traditional biological end points such as mortality. Unless a cure is found the majority of PLWHA will continue to suffer from this disease and its treatment with serious impact on quality of life [45–47]. Therefore, development, assessment and

implementation of a reliable and valid cross cultural quality of life measure is necessary that can be used not only to assess the physical and medical needs of PLWHA, but also their psychological, social, environmental, and spiritual determinants in wider context of better disease management.

HRQoL has emerged as an important issue in the management of HIV infection. HIV infected patients generally demonstrate a HRQoL that is lower than that of the general population, similarly those with AIDS reported lower HRQoL than patients with other chronic conditions like cancer or depression. Assessment on HRQoL has been found to be effective in enhancing communication between patients and health care providers [27], where it has allowed patients to review those areas of HRQoL that most concern to them. This could also be used to track changes in functional status over time, especially in monitoring treatment effects [48]. Therefore monitoring HRQoL can also help to determine whether adverse effects outweigh value of desired clinical response. [40,49].

1.5 Adverse drug reactions (ADRs) and HIV/AIDS

1.5.1 Adverse drug reactions and HRQoL

Detection, monitoring and managing ADRs are essentially integral part in any field of medicine and HIV/AIDS is not different from that [50]. It is well established that HAART employs range of acute and chronic adverse drug events affecting patients' adherence and resulting in issues related to patient overall compliance [51,52]. Similar to other chronic illnesses, HIV/AIDS patients' experienced ADRs affect HRQoL, a

prime therapeutic objective of HIV/AIDS treatment. Studies have reported that these medications are associated with significant safety concerns including serious ADRs, with both short- and long-term effects, affecting many organ systems, which may damage confidence in any national ARV program and affect patient adherence [53,54]. It is logical and expected that most of the time these patients are provided with expert care on the co-morbidities in addition to disease itself, however a routine assessment and evaluation of ADRs can help in devising more effective treatment programs which in turn can help in addressing issues like adherence and poor quality of life among HIV/AIDS patients, since long-term complications of this disease are multifactorial and can be related to the virus itself or to adverse effects of antiretroviral therapy [55]. Adherence to treatment is closely linked to the occurrence of ADRs and it would be pointless simply changing the medications without addressing the adherence barriers. It is thus imperative that clinicians clearly understand ADRs, readily recognize them in their patients and manage them effectively [56,57].

HIV-infected persons normally complained of adverse effects due to antiretroviral therapy ranges from fatigue, pain, nausea and vomiting, skin rashes, sleep disturbances, sexual dysfunction, and body image issues and many more [48,55,58–62]. All these adverse effects definitely interferes with their normal daily activities and hence exerting impact on patients' overall quality of life [38,46,63,64].

1.5.2 Importance of measuring ADRs and HRQoL

Living with HIV/AIDS, affects not only the physical health but also the mental and social well-being of infected individuals. HIV can no longer be defined as simply a virus but a social and historical event on how patients survive along with HIV. Issues that include personal safety, human rights and other aspects of political and social infrastructure can radically affect patients' quality of life [40]. The assessment of HRQoL as an outcome of management has increased since its introduction in late 1940s. It has the potential to facilitate patient's care by constructing better management and care plan for the patients. Monitoring and optimizing HRQoL may improve adherence to therapy, therefore HRQoL measures serve as an important gadget in evaluating patients' well-being and health improvement. The purpose of assessing HRQoL is mainly to discuss on issues that are particularly relevant to patients with HIV/AIDS, and also to provide an overview of common research based HRQoL assessment tools used in patients population [49]. Therefore, routine clinical assessment of health related quality of life in persons with HIV infection is vital. It has the potential to improve care by assessing and monitoring treatment effects, enhancing communication between patients, and also tracking back their functional status over time [40,49].

1.6 Patients' perspective on Disease, Treatment and Care

1.6.1 Importance of exploring Patients' Perspective

Lack of information and understandings about disease and drugs in usage have been highlighted among most significant reasons why HIV/AIDS individuals do not adequately follow their treatment [32,63,65]. Beliefs about health and illness, in particular about the necessity of medication to ward off illness and concerns about potential medicine-related adverse events have been found to be influential in both HIV and other disease areas. The emic perspectives are useful for examining when we are seeing things from our own point of view and when we are trying to understand someone else's view of things, which shows the meaning that people attached to things from their own cultural perspective [66].

1.6.2 HIV/AIDS and Patients understandings

Patients with chronic diseases might be expected to encounter increasingly complex barriers given the need for long-term care and treatment and it is clear that these barriers can have very serious consequences in terms of delayed treatment, inappropriate healthcare-seeking behaviors, poor adherence to the treatment regimens or even a decision to forego treatment [67]. HIV/AIDS is widely recognized as a chronic illness within HIV care, but is often excluded from chronic disease lists outside the field. Patient related principle elements of chronic disease management such as understanding illness & wellness, health promoting behaviors, preventing transmission are some of the

essential elements in the integrated framework of chronic HIV care [68]. Therefore exploring such elements can help improvising existing HIV/AIDS treatment program by incorporating patients' perspectives into it since such perceptions influences their health-seeking behavior and can complicate their treatment outcomes [67]. This in turn can help in optimizing patient care as well as dealing issues of non-compliance, delay in treatment, screening refusal etc.

1.6.3 Use of Qualitative methods in HIV/AIDS

The use of qualitative methods is becoming more common in medical research in general and HIV/AIDS in particular [69–71]. Undeniably, some researches have suggested that qualitative research is fundamental to our understanding of the socio-behavioral aspects of HIV disease [72]. Studies in various parts of the world have revealed poor patient understandings and beliefs towards HIV/AIDS, in addition to numerous barriers to HIV screening; however only limited data is available as many of them focuses particular aspects in HIV care. Various aspects of HIV care related to PLWHA understandings and point of view including disease transmission and screening [73], refusal to screening [74], spirituality in relation to HIV/AIDS care [75], status disclosure [76] and adherence [77] etc. have been explored by using qualitative methods and generated useful data that helped in better understanding of the issues involved. In addition patients' needs, satisfaction and quality of life have also been learnt through qualitative findings [78].

1.6.4 Qualitative studies on HIV/AIDS in Malaysia

As reported earlier, Malaysia has seen a decline in annually reported new cases of HIV/AIDS [33], however despite this achievement the disease postures many challenges to the society and individual patients [34]. Malaysia is a country with extensive cultural and ethnic diversities with range of spiritual traditions and believes [34,79]. Also in the presence of complementary medication and treatment systems, evaluating patients' perspective towards HIV/AIDS and related issues is undeniably important and will definitely help in better understanding of real life issues faced by PLWHA. Another strong reason for need of such explorations is the fact that studies have found deficits in the spectrum of engagement in HIV care including late diagnosis, suboptimal linkage to and retention in HIV care, insufficient use of antiretroviral therapy, and suboptimal adherence to therapy, posturing significant barriers to achieving optimal treatment outcomes [18].

1.7 Summary

Acknowledging the historical global impact of HIV/AIDS epidemics although significant achievements have been made in terms of controlling disease epidemics globally and access to care facilities, there are still considerable challenges exist in controlling disease epidemics in resource limited developing nations [26] as well as the social impact of this disease in many societies. People infected with HIV/AIDS are still facing many defies due to stigma, discrimination and social injustice in various parts of the world [26]. In 2011 United Nations political declaration on HIV and AIDS therefore pledged to intensify global efforts in elimination HIV/AIDS and in order to achieve that specific targets were set to be achieved by the year 2015 including measures to curb HIV epidemics and its impact on patients' life [26]. Though such ambitious targets and commitments is more of global political agenda, it has lesser meanings and importance for individual HIV/AIDS patients who continue to struggle with their fight against disease as well as the right to live without stigma, discrimination and other forms of social injustice in the societies.

Considering HIV/AIDS as one of the greatest menace for mankind in the modern history of medicine the reasons for its sudden emergence, epidemic spread, and unique pathogenicity have been a subject of intense study since HIV was first discovered [4]. Therefore, unquestionably there is an ever greater need to intensify more contextualized findings from developing countries casing various aspects of disease and patients life as much of the data unfortunately still comes from developed part of the world [80]. In conclusion HIV/AIDS is now a disease driven by social inequalities and comprehensive

interventions that demonstrate how the adverse demographic and psychosocial factors affect PLWH are a fundamental part of a truly effective therapeutic strategy [46]

The modern history of medicine has witnessed a devastated epidemic of HIV/AIDS during the past three decades that has not only resulted in millions of death around the globe but with greater impressions on societies. With the advent of HAART the face of this disease has been greatly modified and it has become a chronic disease [77,81], with increased life expectancy for affected patients [77]. However this treatment causes many challenges to patients' life [82,83] which require understanding and rectification from care providers and planners. Though much have been achieved in terms of disease epidemic and its impact on both patient and societies in develop world [9], socio-economic disparities between developed and developing world and various other forms of health disparities are undeniably a major cause of failure in controlling disease epidemics in developing world and which also poses challenges in achieving global HIV outcomes [26,30,84–86].

Malaysia is a multiethnic and multi religious country with Muslims predominates [34,38], with in the wider perspective of this, the country has made significant progress in controlling HIV/AIDS epidemics however challenges remained. Dealing with an illness like HIV/AIDS which has its impact on both patient as well as society is not an easy thing to be achieved when require to dealt with people from various religious and cultural backgrounds. Through challenges are there, Malaysia has made great inroads in controlling its HIV/AIDS epidemic, considering issues surrounding HIV are exceedingly sensitive, engaging with religious leaders is certainly no small feat [79],

however there is a need to focus on areas in HIV care that remained unexplored or neglected, in order to withstand with global response to the disease.

1.8 Problem Statement

There is no doubt about the overall positive impact of HAART in managing HIV & AIDS, however the face change of HIV/AIDS as a chronic infection/disease presents challenges for patients and health-care professionals, and measures of QOL can provide important information in behavioral and clinical studies of ARTs [64]. In the era of new antiretroviral treatments that have dramatically reduced both morbidity and mortality, a primary goal is to maximize function and wellbeing in the everyday life of HIV-infected patients. To be able to do so, it would be important for clinicians and policy makers to identify factors that influence health-related quality of life (HRQoL) [87].

Due to the well-established antiretroviral toxicities experienced, poor adherence and compliance is often seen among HIV/AIDS patients [23], with decreased health related quality of life. Many factors including socio-demographics, comorbidities, traditional and complementary medication use could also increase the likely hood of ADR incidents [46,50,88] and hence monitoring ADRs and measuring quality of life should have been considered as integral part of any HIV program. The initial two decades of HIV/AIDS were more focused on drug discovery and optimizing treatment outcome and therefore the importance of drug safety monitoring was over- shadowed by the need to develop potent therapies capable of arresting a fatal disease process [50].

Qualitative researches in health care are gaining popularity in providing better understandings from both patients and health care professionals perspectives [89]. Due to the fact that qualitative researches provided more descriptive, contextually rich data it has enabled us to appreciate the elusiveness and complexity of HIV-related behaviors and the importance of lifestyle and culture in determining crucial factors affecting patients' life and outcome of an HIV care program. In addition it has also proved invaluable in formative research and development, especially in mapping the profiles of difficult- to-access social networks of target populations [71]. Furthermore it can help in clarifying issues and phenomenon found in quantitative findings and help us fill in the gaps in our knowledge and understandings [71,90].

CHAPTER 2
LITERATURE REVIEW

2.1 HIV/AIDS and adverse drug reactions

There is no doubt that HAART significantly reduces morbidity and mortality among PLWHA, however, the HAART associated adverse drug reaction often adversely affecting the QoL of these patients. This in turn, reduces patients' adherence to HAART regimen and raises other issues of compliance and patient retention to care. Although all antiretroviral drugs carry ADR profile, protease inhibitors are among the most common causing adverse drug reactions [48,55,91]. A study by Tramarin et al concluded that HIV/AIDS patients with PI induced diarrhea had significantly lower scores in all quality of life domains compared to those without diarrhea ($p<0.05$), therefore study recommended significant adverse effect of diarrhea on quality of life should be considered when choosing the appropriate antiretroviral drugs regimen [92]. Lipodystrophy a syndrome, is characterized by abnormal body fat redistribution and metabolic abnormalities, is often manifested with enlarged abdomen, thinning of extremities, buffalo hump and sunken facial cheeks, is regarded as an important adverse effect of HAART [29,48,50,53,55,81,91,93–95], which had been identified to significantly reduce QoL among HIV/AIDS patients [64,96–102]. In a study involving 125 patients with lipodystrophy symptoms, there were more than 40% of patients experienced pain, physical limitation, poor health status and lower QoL [96], similarly a study by Nicholas et al concluded that quality of life is affected by HIV symptoms and that lipodystrophy-related symptoms may negatively affect quality of life [96].

Lipodystrophy has increase fear of HIV patients in taking ART and a recent published paper found that 85% of patients with lipodystrophy reported that changes have been noticed by family, friends and work colleagues. Disfigurement caused stigma, and attractiveness; it also influence social relations and lead to anxiety and depression [99,101]. Similar findings were reported in a Rwandan study shown that, females especially claimed that body fat redistribution negatively affected their physical and emotional health [103]. Qualitative studies have also found psychosocial implications of lipodystrophy on HIV individuals and have found it to be associated with problems with personal and family relationships and social isolations [98].

HIV patients at the beginning of their antiretroviral treatment can frequently show a wide variety of adverse drug effects such as skin rashes, hyperpigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiforme, toxic epidermal necrosis or Stevens-Johnson syndrome, hence early identification and management of these including identification of the causative agent, are vital to prevent the progression of these reactions [58]. In addition to patients reported toxicities, long term toxicities of antiretroviral medications presents greater challenges and raising issues related to medication and treatment adherence [23].

Concomitant use of traditional herbal remedies with HAART has also been found to adversely affect the effectiveness of treatment regimen and QoL among PLWHA. In study done in Zimbabwe, concomitant use of herbal remedies with antiretroviral drugs (ART) found significantly more incidences of skin rash (odds ratio = 2.5, p-value =