

A Review of HIV/AIDS Research in Malaysia

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SUMMARY

Two hundred fifty seven articles related to HIV/AIDS were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000–2013. One hundred seventy one articles were selected and reviewed on the basis of clinical relevance and future research implications. This review of literature has been divided into six sections, namely, epidemiology, risk behaviour, clinical features and opportunistic infections, management, diagnosis and discussion. Wherever possible, the reviewed articles have been presented in a chronological order to provide a historical perspective to the reader as many of the results of earlier publications, which are common knowledge now, were relatively unknown then. Since the early days of the HIV epidemic in Malaysia, there have been rapid advances in the understanding and the management of the epidemic in Malaysia based on the insights derived from the results of these research. These insights are invaluable tools for policy makers, advocates, healthcare providers, researchers and everyone and anyone who are involved in the care of individuals with HIV/AIDS. Attempts have been made to identify gaps in certain research areas with the hope of providing directions for future research in HIV/AIDS in Malaysia.

KEY WORDS: HIV, AIDS, Review, stigma, discrimination, religion, knowledge, attitude, practice, prevalence, incidence, genotyping, phylogenetic studies, most-at-risk-populations

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

This year, 2014, marks the 30th year since the Human Immunodeficiency Virus (HIV) was identified as the causative agent of Acquired Immune Deficiency Syndrome (AIDS). Cure, however, remains elusive and HIV and AIDS have resulted in approximately 30 million deaths worldwide since the first few cases were reported in 1981¹. In Malaysia, the numbers have increased dramatically from the initial three cases of HIV infections reported in 1986 to 91,362 cases of HIV-infections, 16,352 AIDS cases and 12,943 AIDS-related deaths by the end of 2010². Nevertheless, the global scientific community has made great strides in the fight against the epidemic. The introduction of Highly Active Antiretroviral Therapy (HAART) in the early 1990s transformed HIV/AIDS infections from a death sentence to a chronic manageable condition. People living with HIV and AIDS (PLWHA) on HAART can now be expected to live a near normal or normal life.

Malaysia is home to one of the fastest growing HIV epidemics

in the East Asia and Pacific regions. Although the disease was mostly confined within the circle of injecting drug users (IDUs) in the early years, it has since spread to every stratum of society. In 2010, 40% of new reported HIV cases were from heterosexual transmission, a dramatic increase from 27% in 2009. The proportion of women reported with HIV has increased from 4% of new cases in 1995 to 12% in 2005 and 18% in 2010. In 2010, the ratio of housewives and sex workers who tested HIV-positive was 13:1. A report in 2004 estimated that there were 19 new HIV infections per day in youths³. Gender inequity, silence, denial and ignorance continue to fuel the epidemic in Malaysia⁴. However, with several major national initiatives in place, there is evidence to suggest the increase of HIV and AIDS cases in Malaysia may at last be slowing⁵.

The most-at-risk-populations (MARPs) for HIV transmission in Malaysia are the IDUs, sex workers, men-who-have-sex-with-men (MSM), women, transgender people and migrant workers. The estimated prevalence of HIV infections in some of these groups and other important groups of people are shown in Table I.

A systematic review of published and unpublished articles between 1998 and 2003 in developing countries including Malaysia, estimated the prevalence of HIV infection among IDUs was more than 20%²⁰. Roshan *et al*²¹, reported that only 46% of Malaysian blood donors whose blood tested positive for HIV responded to calls from the transfusion medicine units which is a cause for concern; while Tan *et al*²², discussed the cost-effectiveness screening for HIV in the general population with special reference to the mandatory premarital screening for Muslims.

RISK BEHAVIOUR

The risk behaviours attributable to HIV acquisition in several at-risk groups such as sex workers, IDUs, pregnant women, fishermen and MSM are summarised in Table II. Three main survey tools were used in most of these studies: self-administered structured or semi-structured questionnaires or face-to-face interview using a structured questionnaire. The risk behaviours of each group were distinctly different. Among the IDUs, injecting drug use, sharing of injection apparatus, substance abuse at young age, sex with prostitutes, and high risk sexual behaviours were the common denominators^{7,8,23-25}. Among MSM, unprotected anal sex was identified as risk behaviour in all three studies^{12,13,23}. Among fishermen, poor social and parental guidance were identified as significant risk behaviours in addition to drug use and high risk sexual behaviours^{19,26}. Huang *et al*²⁷, discussed the vulnerability of partners of fishermen. In a majority of HIV-infected pregnant women, the only risk factor identified was sexual intercourse with their partners^{15,16,28}.

Table I: Prevalence of HIV in selected groups in Malaysia

Authors	Group	Setting (year)	N	HIV prevalence
Anonymous ⁶	IDU	National HIV Screening Program (2002)	NA	9.67% to 41.19%
Chawarski ⁷	IDU	Treatment seeking subjects in a clinical drug abuse treatment trial	177	19.2%
Chawarski ⁸	IDU	Opiate IDU not-in-treatment in 3 urban areas (2006–2008)	732	27.6%
Fauziah ⁹	IDU	Drug users in 26 rehabilitation centres in Malaysia	6324	12.1%
Anonymous ¹⁰	SW	National HIV Sentinel Surveillance Survey (1996)	NA	6.3%
Anonymous ¹¹	SW	Ad hoc survey (2000)	208 females 136 male transsexuals	6.9% 14.0%
Kanter ¹²	MSM	MSM sex soliciting sites (2011)	517	3.9%
Koh ¹³	MSM	Community based voluntary counselling and testing centre (1998)	433	9.2%
Anonymous ¹⁴	PW	National Surveillance (1998–2002)	NA	0.02–0.04%
Balkis ¹⁵	PW	National Antenatal HIV Screening Programme in healthcare centres in Terengganu (1998–2001)	57,882	0.052%; VT 6.25%
Japaraj ¹⁶	PW	National Antenatal HIV Screening Programme in healthcare centres in Perak and Negeri Sembilan (1997–1999)	26,195 (Perak) 22,524 (Negeri Sembilan)	0.08%; VT 14% (3/21) 0.03%; VT 20% (6/29)
Zahariyah ¹⁷	PW	National Antenatal HIV Screening Programme in healthcare centres in Kedah (1992–2002)	53,380	0.07%; VT 15.8% (3/19)
Khebir ¹⁸	PMS	Premarital HIV screening programme in Johor (2002–2004)	74,210	0.17%
Anonymous ¹⁴	BD	National HIV screening programme for blood donors (2002)	418,118	0.034%
Anonymous ¹⁴	STI	National Surveillance of STI patients diagnosed at health clinics (2002)	1183	6.09%
Anonymous ¹⁴	LDTD	National Surveillance (1999)	NA	1.7%
Anonymous ¹⁴	FM	National Surveillance (2002)	NA	2.7%
Fauziah ¹⁹	FM	Selected fishermen in Terengganu (1997)	542	1.7%

Abbreviations: NA, not available; IDU, intravenous drug user; SW, sex workers; MSM, men-who-have-sex-with-men; PW, pregnant women; VT, vertical transmission; PMS, premarital screening; BD, blood donors; STI, sexually transmitted infections; LDTD, long distance truck drivers; FM, fishermen.

KNOWLEDGE, ATTITUDE AND PRACTICE

Most of the studies on knowledge, attitude and practice related to HIV/AIDS were focussed on MARPs such as MSM, IDUs and pregnant women. Several such studies on other vulnerable groups such as adolescents, students, fishermen, indigenous people (orang asli), factory workers, and healthcare workers were also reported.

Men-Who-Have-Sex-With-Men (MSM)

Kanter *et al*¹² reported 20% of MSM did not believe that HIV is transmissible through insertive or receptive anal sex. Koh *et al*¹³ reported that most MSM practiced oral and anal sex (79.3%, 337/425), had multiple sexual partners (37.9%, 196/425 had between two to five male sex partners and 25.7%, 133/425 had more than six male sex partners in the last six months) and admitted to low rates of condom use during vaginal (20%), anal (13.5%) and oral sex (1.3%). Lim *et al*²⁹ reported alarming rates of unprotected receptive anal intercourse with internal ejaculation (URAIE) among Asian MSM in a large online survey of 10,413 MSM across Asia, including Malaysia.

Prisoners

Bachireddy *et al*³⁰ surveyed 102 opioid-dependent prisoners and reported alarmingly high rates of needle sharing (66%), unprotected sex before incarceration (30%), injecting drug use

(77%) and low proportion of prisoners who believed they needed opioid substitution therapy (OST) after release to prevent relapse (33%). Gill *et al*³¹ reported that knowledge of HIV status had no bearing on high risk sexual behaviours where 73.3% of IDUs continued to practice high risk sexual behaviours despite knowing their HIV status.

Pregnant women

Akmal *et al*³² surveyed 158 pregnant women attending antenatal clinic in Hospital Muar and reported high rates of HIV screening (95%). Among those who declined to be screened, the most common reasons for refusal were feeling of wellbeing, the perception of not being at risk and apathy. Sharifa *et al*³³ surveyed 205 antenatal mothers in western Sabah and reported that a low proportion of them had good knowledge (32.3%), attitude and practice (56.4%) related to HIV/AIDS. These women were younger, better educated and had received health education from health staff. Vinothini *et al*³⁴ conducted a face-to-face survey of 100 pregnant women in an urban antenatal clinic in Malaysia in 1999 and reported good knowledge about HIV/AIDS was positively correlated with higher level of education. The issues of rising HIV infection rates among women and the feminisation of the HIV epidemic were discussed in an article produced by UNICEF and the Malaysian Ministry of Health³⁵.

Table II: Risk behaviours for HIV acquisition in at-risk groups

Authors	Group	Setting (year)	Significant risk behaviours
Chawarski ⁷	IDU	Survey of 177 treatment seeking subjects in a clinical drug abuse treatment trial.	Malay ethnicity Lifetime IDU Needle sharing Lack of condom use during sex
Chawarski ⁸	IDU	Survey of 732 opiate IDUs not-in-treatment in 3 urban centres. (2006– 2008)	Lifetime use of amphetamine type stimulants Lifetime use history of sharing needles
Fauziah ⁹	IDU	Survey of 6324 drug users in 26 rehabilitation centres in Malaysia. (1998)	Injecting drug use Sharing needles Addiction at young age Had sexual exposures Had sex with prostitutes
Dokubo ²³	IDU	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Young age Frequent injections Sharing of needles or syringes
Vicknasingam ²⁴	IDU	Survey of 526 IDUs not-in-treatment from 5 cities in peninsular Malaysia.	Sharing injection equipment Multiple sexual partners
Juita ²⁵	IDU	Case control study of 87 HIV-positive vs 261 HIV-negative drug addicts in a drug rehabilitation centre in Selangor. (1994)	Needle sharing (OR 8.53) Sex with prostitutes (OR 3.7) Homosexuality (OR 4.05) Non-condom use during sex with prostitutes (OR 2.27)
Dokubo ²³	SW	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Brothel work
Kanter ¹²	MSM	Survey of 517 MSM in sex solicitation sites in Kuala Lumpur. (2011)	Unprotected anal sex with casual partner (OR 2.99) Unprotected receptive anal sex (OR 2.71) Group sex (OR 3.7)
Koh ¹³	MSM	Survey of 433 MSM in a community based voluntary counselling and testing centre in Kuala Lumpur.(1998)	Inconsistent condom use during anal sex (OR 3.7)
Dokubo ²³	MSM	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Multiple male sexual partners Receptive anal intercourse Syphilis
Balkis ¹⁵	PW	National Antenatal HIV Screening Programme of 57,882 pregnant women in healthcare clinics in Terengganu. (1998–2001)	93% of HIV positive pregnant women's only risk factor was sexual contact. 66.7% of the husbands were HIV-positive
Japaraj ¹⁶	PW	National Antenatal HIV Screening Programme of 48,719 pregnant women in healthcare clinics in Perak and Negeri Sembilan. (1997–1999)	Multiple sexual partners
Zahariyah ²⁶	PW	HIV antenatal screening programme in Kedah. (1999–2002)	Sexual contact with husbands. Risk factors for husbands include IDU and multiple sexual partners
Fauziah ¹⁹	FM	Survey of 542 fishermen. (1997)	Drug use (marijuana, morphine, heroin) (OR 7.3) Regular and non-regular sex partners Sex with prostitutes
Niza ²⁷	FM	Focus group discussions with fishermen in East Coast of Malaysia.	Early involvement in substance abuse High risk sexual behaviours Poor parental support Lack of social support

Abbreviations: IDU, intravenous drug user; SW, sex workers; MSM, men-who-have-sex-with-men; PW, pregnant women; OR, odds ratio; FM, fishermen.

Table III: Case reports of HIV/AIDS-related conditions

Authors	Case report
Tan <i>et al</i> ¹²⁸	Reported the first 3 cases of disseminated histoplasmosis in patients with AIDS.
Jarmin <i>et al</i> ¹²⁹	Reported a rare case of spontaneous common bile duct perforation due to Mycobacterium tuberculosis in a HIV-positive man and its management.
Kenali <i>et al</i> ¹³⁰	Reported a rare case of concurrent mycobacterial infection and non-Hodgkin's lymphoma at the same site in a patient with AIDS.
Subha <i>et al</i> ¹³¹	Reported a case of Nocardia infection of the mastoid in a patient with HIV.
Wong <i>et al</i> ¹³²	Reported the successful management of pulmonary hypertension using sildenafil in an 18-month old child.
Othman <i>et al</i> ¹³³	Reported a case of intra-abdominal mass due to Penicillium marneffeii in a 7-year-old child with HIV which responded to conventional antifungal therapy.
Chow <i>et al</i> ¹³⁴	Highlighted the risk of fatal lactic acidosis secondary to ART in a report of two cases of HIV-positive patients receiving ART.
Khairy-Shamel <i>et al</i> ¹³⁵	Reported on a case of orbital rhabdomyosarcoma with intracranial extension in a child with HIV that responded to surgery, chemotherapy and reinstatement of ART.
Ketan <i>et al</i> ¹³⁶	Reported a case of pancreatic TB in a HIV-positive patient that mimicked carcinoma.
Fong <i>et al</i> ¹³⁷	Reported a case of cutaneous toxoplasmosis in a HIV-positive patient whose anti-toxoplasma antibody was negative. Histopathological examination, electron microscopy and PCR confirmed the diagnosis.
Isa <i>et al</i> ¹³⁸	Reported a case of renal tubular acidosis in a patient with hepatitis C-HIV-tuberculosis lymphadenitis co-infections and its management.
Nimir <i>et al</i> ¹³⁹	Reported a case of toxoplasma encephalitis in a HIV-positive man who presented with seizure. The diagnosis was complicated by the presence of lung findings suggestive of pulmonary tuberculosis.
Nurfahzura <i>et al</i> ¹⁴⁰	Reported the successful treatment of syphilitic uveitis in several HIV-positive patients.

General public, adolescents and young adults

Jasvinder³⁶ surveyed 39,910 Malaysians in 2006 as part of the 3rd National Health and Morbidity Survey and reported high proportions of them were aware of the high risk of HIV transmission when not using condom. Those with the poorest knowledge were from the lower income group, had lower education levels and were rural dwellers. Siti *et al*³⁷, surveyed 520 adolescents aged 15–21 years and reported high scores for knowledge and positive attitude towards HIV/AIDS but also prevalence of misconceptions regarding HIV transmission and gender bias related to sexual behaviour and contracting the disease. Although 72% of the sexually-experienced did not use protection at first sexual intercourse, 80% did not perceive themselves to be at risk of contracting HIV. Jasvinder *et al*, advocated a critical review of existing HIV/AIDS prevention programmes to focus on adolescent risk taking behaviour and sexuality issues, including male-female negotiation skills. Wong *et al*³⁸, reported similar findings in a survey of 1075 young adults aged 15–24 years.

Students

Ahmed *et al*³⁹, reported serious misconceptions, negative attitudes and risk perceptions towards HIV/AIDS among 108 pharmacy students. Chew *et al*⁴⁰, surveyed 170 preclinical and 170 clinical medical students of a public university in Malaysia and reported the former were more stigmatising while the latter were less comfortable handling patients with HIV. Ibrahim *et al*⁴¹, reported improvement of knowledge and attitude after intervention in the form of peer-led education among 276 university students. Jahanfar *et al*⁴², reported similar improvement among 182 secondary school students who received a two-hour talk on sex education. However, in another study on 530 university students who received a four-hour education programme, Jahanfar *et al*⁴³, reported that improvement in knowledge and attitudes towards HIV did not translate into change in risk taking behaviour.

Koh *et al*⁴⁴, surveyed 1020 medical students from several public and private medical universities; and reported that less than 20% had received adequate training to care for PLWHA. Medical students from public universities had more prevalent negative beliefs regarding testing, confidentiality, disclosure and environment of care towards PLWHA compared to students from private universities. However, in providing care to PLWHA, the attitudes were largely positive and non-discriminatory in both cohorts of students. Ni *et al*⁴⁵, surveyed 155 medical students from a university in East Malaysia and reported relatively poor knowledge on HIV/AIDS. Rozina *et al*⁴⁶, surveyed 23,202 university students and reported unsatisfactory level of knowledge and low condom usage (29.8%) among sexually active students. In another survey of 1773 university students, Rozina *et al*⁴⁷, reported only 19.5% were willing to disclose their HIV status to partners or family if diagnosed with HIV infection and only 43% were willing to care for an HIV-infected person in the house.

Fishermen, Orang Asli and factory workers

Fauziah *et al*¹⁹, surveyed 542 fishermen in 1997 and found high proportion of false beliefs such as the belief that HIV is transmissible through shaking hands (44.3%), insect bites (41.0%), and sharing public utilities (50.9%), and that it is curable (39.7%). Anita *et al*⁴⁸, surveyed 2706 Orang Asli and reported that although they made up only 0.5% of the population of Malaysia, they constituted 0.06% of total notified HIV cases. The HIV seroprevalence among them was 0.3%. Although knowledge regarding HIV/AIDS was fair (30–50%), they had negative attitudes towards the disease. In a survey of 3300 factory workers in Negeri Sembilan and Melaka, Anita *et al*⁴⁹, reported they had high levels of knowledge and positive attitude towards HIV/AIDS.

Healthcare providers

A small survey of 34 doctors and 52 nurses revealed that about half of them had fair knowledge regarding post-exposure

prophylaxis (PEP) against HIV⁵⁰. A survey of 450 female surgical-based nurses in a teaching hospital in Kuala Lumpur found that senior nurses and nurses who had received training on universal precaution had higher level of knowledge and more positive attitude towards HIV/AIDS⁵¹. Hasnah *et al*⁵², surveyed 222 healthcare workers and reported that good knowledge on universal precaution was not reflected in practice during a five-day observation in the ward.

Khan *et al*⁵³, surveyed 270 PLWHA regarding their knowledge, attitude and practice on oral hygiene and found most were ignorant about the oral manifestations of the disease and 1/3 of them had negative attitudes towards oral healthcare, and often resorted to various measures to manage oral lesions rather than seek professional care.

CLINICAL FEATURES AND OPPORTUNISTIC INFECTIONS

Opportunistic infections

Articles published in the early 2000s reported patterns of opportunistic infections (OIs) in Malaysian HIV-positive patients that were consistent with research findings from around the world. A retrospective survey of 419 patients in the Kuala Lumpur General Hospital (KLGH) from 1994–2001 found the preponderant age group to be 25–34 years. Half (53%) had CD4 < 200 cells/mm³ at time of diagnosis of OI. The survey also revealed heterosexual contact as the leading risk for HIV transmission, HIV infection via IDU to be directly related to the incidence of tuberculosis (TB) infection, and HIV-related TB was independently correlated with unemployment. The four main AIDS-defining diseases were TB (48%), pneumocystis carinii pneumonia (PCP) (13%), toxoplasma encephalitis (TE) (11%) and cryptococcal meningitis (7%)⁵⁴.

Another retrospective survey on the prevalence of pulmonary OIs in 406 AIDS patients in KLGH in May 2001 found that most of them had CD4 < 200 cells/mm³ (65.1%). Almost half, 40.9% (166/406) had pulmonary OIs with pulmonary tuberculosis (PTB) being the most common (30.1%). Cough (75.3%) and fever (34.3%) were common clinical manifestations. Oral candidiasis was the most common co-infection with AIDS-related pulmonary OIs (39.8%)⁵⁵. Another survey of 205 HIV-infected patients in KLGH from 2001–2002 on the spectrum of OIs found an older preponderant age group of 34–45 years. The median CD4 count was 34 cells/mm³ and sexual contact was the most frequent mode of transmission (78.5%) followed by injecting drug use (30%) and blood transfusion (5%). Oral candidiasis was the most common muco-cutaneous disease and there were significant co-infection with main OIs such as TB, PCP, TE, penicilliosis, and cytomegalovirus (CMV) retinitis. A CD4 count < 100 cells/mm³ at diagnosis of OI was significantly associated with major OIs⁵⁶. A small retrospective study of 59 HIV-positive patients with OI admitted from 2000–2009 reported PCP and toxoplasmosis as the most common OIs⁵⁷.

Tuberculosis

HIV prevalence in patients with TB was estimated to be between 6.3% and 10.5%.^{11,58} Nissapatorn *et al*⁵⁹, reported significant association between HIV-infected injecting drug users and PTB in a survey of 290 patients with HIV-related TB. They reported that 57% patients subsequently were lost to follow-up, 31.8% were successfully treated and 0.8% had died by the end of the study. In another report, Nissapatorn *et al*⁶⁰, found significant association between occupation or mode of HIV transmission and TB infection. Pulmonary tuberculosis was the most common manifestation of TB infection (84.6%, 104/123). The

most common symptoms were fever, cough, sputum or haemoptysis. Narwani *et al*⁶¹, compared 97 HIV-negative and 97 HIV-positive TB patients and reported dissimilarity between the two cohorts in terms of age, family members to room ratio, sex and marital status. Mohammad *et al*⁶², reported that HIV-positive TB patients were less infectious to their contacts compared to HIV-negative TB patients.

Mohammad *et al*⁶³, explored the clinical features, radiological findings and outcomes of treatment in 149 HIV-positive TB patients and found that 80% (117/149) had PTB, 20% had extrapulmonary TB (ETB), 45% had cough, 51% had sputum smear positive, 55% had radiological findings (localised, military, diffused infiltrates, opacities) on chest radiograph, 5.4% had pleural lesions, 5.5% had mediastinal or hilar lesions. During the survey period, 38.9% died. The median survival time from treatment initiation was 13.5 weeks (range 1–56). Majority (74%) died without completing the six-months of anti-TB therapy.

Velaiutham *et al*⁶⁴, found no correlation between Mantoux test, sputum culture and CXR severity in HIV-positive TB patients. They also reported higher incidence of sputum smear negative, sputum culture positive and non-reactive tuberculin skin test in these patients. Pulmonary tuberculosis was the most common manifestation (63%) followed by ETB (22%), and PTB + ETB (15%). Tuberculosis adenitis was the most common ETB presentation. Chest radiograph findings ranged from moderate to severe in sputum acid fast bacilli (AFB) negative patients. Kooi *et al*⁶⁵, reported that AIDS patients with CD4 count < 200 cells/mm³ were more likely to present with atypical radiographic appearance of PTB.

Nissapatorn *et al*⁶⁶ reported the similarities and differences between PTB and ETB in HIV-infected patients in a survey of 406 HIV-positive TB patients. Both groups had similar mean age and most had CD4 count < 200 cells/mm³. For PTB, cough and haemoptysis (88%) were the most common symptoms; the lungs were most commonly affected (89%) and 42% were successfully treated with six months anti-TB therapy. For ETB, lymphadenopathy (33.5%) was the most common symptom; miliary TB was the most common disease location (55.6%) and 43% were successfully treated with nine months anti-TB therapy. Among patients who defaulted therapy, a higher proportion (87%) had PTB. No multidrug resistant (MDR)-TB or relapse cases were detected in this study. Naing *et al*⁶⁷, performed a meta-analysis study and found significant association between HIV and ETB (OR 1.3), and between CD4 count < 100 cells/mm³ and ETB (OR 1.3).

Toxoplasmosis

Diagnosing *Toxoplasma gondii* infection in HIV-positive patients based on serological results can be challenging. Shamilah *et al*⁶⁸, reviewed the immunofluorescent antibody test (IFAT) results of 2554 sera of HIV-positive and HIV-negative patients between 1995–1997. The authors considered IgG titre cut-off point of 1:>64 by IFAT to be highly suggestive of current toxoplasmosis. They reported an overall prevalence of 26.3% with a significantly higher prevalence in HIV-positive (31.3%) compared with HIV-negative (24.3%) patients. Nissapatorn *et al*⁶⁹, compared the toxoplasma IgG serology results of 100 HIV-positive patients and 203 healthy blood donors. They reported toxoplasma IgG seroprevalence of 21% and 28.1% in HIV-positive patients and blood donors, respectively. There was no significant association between seroprevalence of toxoplasma IgG with possible risk factors such as contact with felines, consumption of undercooked meat, and history of blood transfusions in both groups. The mean CD4 count in HIV-

positive patients in this study was 202.23 cells/mm³. The CD4 count was not associated with seropositivity for toxoplasma antibodies in HIV/AIDS patients.

Nissapatorn *et al*⁷⁰, determined the anti-toxoplasma IgG levels by ELISA technique in 301 sera of HIV/AIDS patients. They reported seroprevalence of 41.2% (124/301). Higher seroprevalence were found in Malays (57.9%) compared to Chinese (38.7%) and Indians (29.6%). No association between toxoplasma IgG seroprevalence and CD4 count was found.

Nissapatorn *et al*⁷¹, reported toxoplasma IgG seroprevalence of 51.2% (208/416) in a survey of 406 HIV-infected patients and 14.9% (31/208) were diagnosed with active toxoplasma encephalitis (TE) while 10.6% (22/208) had chronic (latent) toxoplasma infection. The most common symptom was headache (67.7%). Computed tomography (CT) brain scan findings included multiple lesions (87.5%), hypodense lesion (66.7%) and frontal region (41.7%). Significant association was found between CD4 count and TE (PR 2.6, *p* = 0.019). After six weeks of anti-TE therapy, relapsing TE was detected in 9.7% cases.

Nissapatorn *et al*⁷², surveyed 505 HIV-infected patients and reported a toxoplasma IgG seroprevalence of 44.8% (226/505). Out of the 88.7% (448/505) with no TE, 44.4% (199/448) showed toxoplasma seropositivity. In contrast, 11.3% (57/505) had TE; out of which 47.4% (27/57) showed toxoplasma seropositivity. Six-point-five percent (17/260) who received primary prophylaxis (cotrimoxazole) and 0.7% (1/137) who received HAART developed TE. The most common symptom was headache (56%). The CT findings included multiple lesions (96.4%), hypodense lesion (66.7%), and parietal region (39.3%). The median CD4 count was 25 cells/mm³. The CD4 count of < 100 cells/mm³ was significantly associated with development of TE.

A comprehensive review of toxoplasmosis in HIV/AIDS in 2009 reported the prevalence of latent toxoplasma infections in HIV-infected patients varied between 3–97%⁷³. Prevalence was related to ethnicity, certain risk factors, and reactivation of toxoplasma infection. In the pre-HAART era, TE was the most common focal cerebral lesion in approximately half of toxoplasma-seropositive AIDS patient with toxoplasma infection. Infection of the eyes, lungs, heart and the spinal cord has been reported. The introduction of HAART resulted in marked decrease in overall incidence. Toxoplasma encephalitis was significantly associated with neurological immune restoration inflammatory syndrome (NIRIS)⁷³.

Parasitic infections

Asma *et al*⁷⁴, examined the stool samples of 346 HIV-infected individuals and reported the prevalence of intestinal parasitic infection (IPI) as 37.9% (18.8% protozoa and 7.5% helminths), and 50.4% had multiple parasitic infections. Low CD4 count of < 200 cells/mm³ was associated with IPI. Lono *et al*⁷⁵, reported that HIV-positive individuals were three times at risk to acquire microsporidium infection compared to HIV-negative individuals (OR 3.2). The overall prevalence was 8.5% (21/247). Nissapatorn *et al*⁷⁶, produced a comprehensive review of the challenges in the diagnosis and therapy of parasitic infections in HIV-infected individuals.

Fungal infections

A survey of 96 patients with cryptococcal infections from 2003–2004 showed that HIV was the major underlying illness in 37.5% (36/96) of them. The predominant species were *Cryptococcus neoformans var gubii* followed by *C. gatti*.

Cryptococcosis in children was uncommon⁷⁷. Nor Hayati *et al*⁷⁸, reported the successful management of *Penicillium marneffei* infection in 20 AIDS patients. Forty-five percent had acquired HIV through heterosexual intercourse and 40% from IDU. Median CD4 count was 10 cells/mm³. Diagnosis was made from blood cultures and four skin biopsy samples. Nine patients were aware of their HIV status at time of diagnosis, four were on HAART but were not compliant. All except one had other concurrent OIs, the most common being oral candidiasis (95%, 19/20) and TB (30%, 6/20). Common presenting features included typical skin lesions, fever, anaemia, and hepatomegaly. Median length of hospital stay was 19 days. All were successfully treated with intravenous amphotericin B at induction and switched to itraconazole (80%) or fluconazole as maintenance (20%). No relapses or mortality were reported at the end of scheduled therapy and at third month review.

Sexually transmitted infections (STI)

Choon *et al*⁷⁹, surveyed 132 HIV-positive individuals presenting with STI from 1992–1998 and reported males outnumbered females by 4.5 to 1, the preponderant group was 20–40 years (82.5%), 53.0% (70/132) were single, 34.1% married, 7.5% divorcees, 97.7% were heterosexuals, 53.3% male patients patronised prostitutes, 50 (37.9%) were IDUs; of which 24 had multiple sex partners, 48.2% (53/109) had one or more STIs, 31.9% had history of one STI and 3.6% had two STIs in the past. Fifty six (42.4%) had developed AIDS while 13 had passed away at the time of the study. The main mode of HIV transmission was heterosexual contact. The prevalence of STI was high.

Dermatological manifestations

Jing *et al*⁸⁰, surveyed 182 HIV-positive patients and reported prevalence of mucocutaneous disorders (MCD) of 71.4% (130/182). All had low CD4 cell counts and AIDS-defining illnesses. The common manifestations were generalised hyperpigmentation (35.7%), papular eruptions (29.1%), xerosis (27.5%), seborrhoeic dermatitis (19.2%) and psoriasis (7.7%). The most common infections were oral candidiasis (35.7%), tinea corporis and onychomycosis (9.9%) and herpes (4.3%). Kaposi sarcoma was rare. Mucocutaneous findings were useful clinical predictors of HIV infection or a sign of advanced HIV infection. Rosnah *et al*⁸¹ reported that oral candidiasis was the most common mucocutaneous manifestation in children before starting ART. The frequency of mucocutaneous manifestations was proportionate to the severity of immune depletion.

Nissapatorn *et al*⁸², surveyed 174 patients with AIDS-related skin diseases (mean CD4 count 100.5 cells/mm³) and identified two main categories of skin conditions, namely the predominant group of infectious mucocutaneous manifestations such as seborrhoeic dermatitis (6.3%), ichthyosis (0.6%), tumours (1.8%), sexually transmitted diseases (0.6%); and the minority group consisting of drug-related skin conditions (0.6%).

Progressive encephalopathy

Hamid *et al*⁸³, followed up 55 HIV-positive children and found the incidence of progressive encephalopathy to be 18.2% (10/55). All presented with hepatosplenomegaly, lymphadenopathy, and abnormal deep tendon reflexes while five had impairment of brain growth. Low CD4 count and percentage were associated with progressive encephalopathy.

Psychiatric disorders

Tung *et al*⁸⁴, surveyed 89 patients using the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and

Depression Scale (HADS); and reported lower depression rate among HIV-positive patients in Malaysia compared to countries in the West. Patients dependent on others for support, non-alcoholic drinkers and being a female were identified as significant predictors for depression. In contrast, Shane *et al*⁸⁵, surveyed 41 HIV-positive patients using the Mini International Neuropsychiatric Interview (MINI) questionnaire and the WHO Quality of Life (QOL) questionnaire; and reported 51% of them had psychiatric morbidity, 21% had depression associated with hepatitis B infection and poor social support. Depression was correlated with psychological wellbeing on WHOQOL. Psychiatric morbidity, including suicidality, was associated with CD4 count < 200 cells/mm³. The Malay version of the survey tool developed by WHO specific for people infected with HIV to assess their quality of life, the WHOQOL-HIV BREF, was validated by Saddki *et al*⁸⁶.

Muhammad Muhsin *et al*⁸⁷, compared 200 HIV-positive and 200 HIV-negative prisoners using the Structured Clinical Interview for Diagnosis Statistical Manual of Mental Disorders-IV (SCID-1) and found extremely high prevalence of mental illness and substance use disorders, especially opioid dependence in HIV-positive prisoners. HIV infection was significantly correlated with age, ethnicity, marital status, history of injection drug use, lifetime duration of incarceration, substance abuse, polysubstance abuse and non-substance induced psychiatric disorders. Prisoners with triple diagnosis (psychiatric disorders, substance use disorders and HIV) spent 46.7 cumulative lifetime months in prison compared to those with only one psychiatric diagnosis. No difference was found between those with two psychiatric diagnoses and those with only one psychiatric diagnosis. HIV infection and triple diagnoses were not associated with violent offenses.

Hasanah *et al*⁸⁸, surveyed 271 HIV-positive patients using the Functional Assessment of HIV Infection (FAHI) and HADS to determine the socio-demographic, clinical and psychological factors influencing QOL in these patients. They reported that the psychological and social wellbeing of patients were more affected than their physical wellbeing. Heterosexual route of HIV transmission was associated with lower social wellbeing but not in IDUs. Lua *et al*⁸⁹, surveyed 30 caregivers of patients with HIV/AIDS using the Malay Caregiver Quality of Life (MCQoL) questionnaire and reported favourable psychometric properties among them.

Opportunistic pneumonias and hepatitis E

Tengku *et al*⁹⁰, conducted an extensive review of the common HIV-associated opportunistic pneumonias and the management of PTB, PCP and recurrent bacterial pneumonias. Ng *et al*⁹¹, reported the seroprevalence of anti-HEV antibodies in 21/145 HIV-1 infected subjects was 14.4% (10.5% IgG and 4.1% IgM). The most likely route of transmission was faecal.

Predictors of death

Lubis *et al*⁹², surveyed data of 845 HIV-positive patients from 1989–2009 and reported age 50 and older, secondary and tertiary education, unemployment, AIDS on presentation, single and double drugs antiretroviral (ART) regime, and inability to achieve viral load of ≤ 50 copies/ml despite being on ART were significant predictors of death.

MANAGEMENT

HIV-TB co-infection

Marzuki *et al*⁹³, reported the prevalence of drug-induced hepatitis in a survey of 473 patients with TB was 9.7% (46/473).

HIV and ETB were significant risk factors for development of drug induced hepatitis. Ismail *et al*⁹⁴, in a survey of 219 HIV-TB patients, reported slightly more than half (53.4%) achieved successful outcomes (cure, completed therapy). Unsuccessful outcomes (death, default therapy, treatment failure) were associated with IDUs (OR 2.72), not being on HAART (OR 5.1), lymphadenopathy (OR 2.01) and poor nutritional status (OR 4.61). In another study of 227 HIV-TB patients, Ismail *et al*⁹⁵, reported 23.3% of them had died at the end of the study; out of which 40% died within 2 months of diagnosis. Survival at 2, 6, and 12 months after starting anti-TB therapy was 90.7%, 82.8% and 78.8%, respectively. Death was associated with Malay ethnicity, CD4 count < 200 cells/mm³, presence of three or more OIs, not being on HAART and leucocytosis.

Injecting Drug Users (IDUs)

Several articles highlighted the failure of national drug rehabilitation programmes and punitive response to the drug problem in Malaysia and the successful piloting and implementation of the harm reduction policies and programmes including the drug substitution therapy and needle and syringe exchange programme (NSEP) in 2005⁹⁶⁻⁹⁸. The inclusion of the health aspects of illicit drug use in Malaysia's drug policies resulted in better access to HAART, reduction in HIV risk behaviour and greater social benefits including increased employment⁹⁸. Nevertheless, tension between law enforcement and public health as overall drug policy is based on abstinence and zero tolerance remains a challenge⁹⁷. Sarnon *et al*⁹⁹, reported favourable reception of the NSEP among IDUs. Degenhardt *et al*¹⁰⁰, discussed the positive impact of the shift from punitive law enforcement approach to evidence-based treatment in Malaysia, an effect not seen in other countries like Russia and the USA. A review by Mesquita *et al*¹⁰¹, traced the course of development of the HIV/AIDS epidemic among people who inject drugs (PWID) in the Western Pacific and Asia and WHO's role in supporting these responses.

In a review of evidence for effectiveness, cost-effectiveness and coverage of ART for IDU with HIV in several countries with the very highest burden of IDUs, including Malaysia, Wolfe *et al*¹⁰², reported disproportionately low access to ART among IDUs which was attributed to systemic and structural obstacles restricting treatment access. They highlighted the need for integration of ART with opioid substitution and TB treatment, increase peer engagement in treatment delivery and reform harmful policies to improve ART coverage of IDUs.

Chou *et al*¹⁰³, explored the responsibility attribution, defined as 'how an individual perceives the cause of their HIV/AIDS infection', and its relationship to coping styles of IDUs with HIV/AIDS. They identified four homogenous attribution groups among IDUs in Malaysia – external, fatalistic, internal and indeterminate. A combination of self-esteem, social support and religiosity mediate the relationship between responsibility attribution and coping behaviours. Suresh *et al*¹⁰⁴, highlighted the important role of non-governmental organisations (NGOs) in pushing for implementation of harm reduction policies and programmes in Malaysia through the formation of a state-NGO alliance to dialogue with opposition from mainly Muslim religious groups. A study by Koh *et al*¹⁰⁵, laid to rest a prevalent myth popular among IDUs in Malaysia that efavirenz ingestion can lead to a false positive urine cannabis test thus negating the need for letter-of-certification by healthcare providers to be used by IDUs in the event of a drug raid.

Prisoners

Choi *et al*¹⁰⁶, surveyed 102 HIV-infected prisoners within six

months of release from incarceration and reported four major concerns among them: staying out of prison (60.8%), remaining off drugs (39.2%), finding employment (35.3%) and obtaining HIV care (32.4%). High levels of stigma, including negative self-image and public attitudes-related stigma were independent barriers to obtaining HIV treatment. Factors associated with higher likelihood of identifying more re-entry challenges included previous incarcerations (OR 3.2), higher HIV-related symptoms (OR 2.0), and higher public attitudes-related stigma (OR 2.5). They pressed for more targeted interventions (effective drug treatment, HIV care and public awareness campaign) to stem the HIV epidemic and improve the health outcomes among HIV-infected prisoners in Malaysia. The same sentiment was echoed by Copenhaver *et al*¹⁰⁷, in their study involving interviews with HIV-positive prisoners and their healthcare providers. Wickersham *et al*¹⁰⁸, reported HIV-positive prisoners on higher dose of methadone at the time of release from prison were associated with greater retention on methadone-maintenance therapy (MMT) after release to the community. Optimisation of MMT doses with proper monitoring are required prior to re-entering the community from prisons.

Fu *et al*¹⁰⁹, evaluated 100 HIV-infected prisoners in two of the largest compulsory drug detention and rehabilitation centres in Malaysia. None of the prisoners had access to ART during detention, only 9% received HIV-related clinical assessment or care, nearly 25% had symptoms of TB but were not screened, 95% met criteria for opioid dependence, none had access to opioid substitution therapy (OST) during detention, 86% reported current craving, 87% anticipated relapsing to drugs after release and 14% had suicide ideation. There were significant unmet health needs and high risk of morbidity and mortality while in detention.

Transsexuals (*Mak Nyah*)

Teh *et al*¹¹⁰, interviewed 15 *Mak Nyahs* from five major towns in Malaysia and reported HIV problem as critical in this group. Knowledge of HIV/AIDS was poor and the practice of safe sex was low. HIV/AIDS was not considered a primary problem. Finding employment and discrimination were more important issues. They faced constant harassment from enforcement authorities for prostitution. There were no HIV prevention activities in many parts of Malaysia to cater to their needs.

Health clinics and NGOs

Foong *et al*¹¹¹, interviewed healthcare providers in two major HIV/AIDS clinics in Malaysia and identified gaps in providing care to HIV-positive patients in primary care setting. The gaps included lack of treatment and consultation facilities, lack of availability and accessibility to information, lack of publicity on available facilities, lack of communication and inter-professional working, and the need for more effective coordinated efforts with clear leadership. It was suggested that nurses may have a greater role to play.

Azwa *et al*¹¹², conducted a comprehensive review of the management of HIV in pregnancy with special emphasis on ART strategies and obstetric care in a middle income country. Musa¹¹³ discussed the successes and challenges faced in the running of a half-way home established for the care of women and children with HIV/AIDS.

Children with HIV

Mohd *et al*¹¹⁴, surveyed 95 HIV-positive children on ART aged 1–18 years. They reported that almost all did not achieve the recommended energy intake for their age groups and almost half had vitamin A and selenium deficiencies. Nasir *et al*¹¹⁵,

reported that children on protease inhibitors had lower body weight, low HDL-C but less selenium deficiency. A comprehensive review of 1301 children in Asia in the TREAT Asia (Therapeutics Research, Education, and AIDS Training in Asia) report¹¹⁶ reported 10% of Asian children were on second-line ART. The median age at second-line initiation was 120 months (range 78–145). Better use of current first-line regimens and broader access to heat-stable, paediatric second-line and salvage formulations were needed. Earlier diagnosis of treatment failure was of little use unless providers and patients had access to appropriate drugs for children to switch to.

HIV-positive refugees

Mendelsohn *et al*¹¹⁷, compared the adherence to HAART in 153 refugees and 148 host community clients at a public clinic in Kuala Lumpur. Similar proportion between refugees and host community clients in terms of < 95% adherence and unsuppressed viral load was reported. Refugees in protracted asylum situations were able to sustain good treatment outcome and should be included in the HIV strategic plans of host countries.

Antiretroviral therapy (ART)

Hasan *et al*¹¹⁸, asked 325 HIV-positive patients on ART to describe their experiences of adverse drug reactions (ADRs) and identify drug-drug-interactions. The common ART agents used were lamivudine (64.6%), zidovudine (40.6%) and efavirenz (42.5%). Common ADRs were fatigue, allergic reactions, weight loss, dry mouth and memory loss. Females, non-complementary and alternative medicine users and age younger than 50 years were associated with higher ADRs. Forty-four cases of category-D drug-drug-interactions were identified in the study. In another study, Hasan *et al*¹¹⁹ reported 78.2% (254/325) had used complementary and alternative medicine but 68% did not disclose this to healthcare professionals. The most common complementary and alternative medicine used were vitamins and supplements, herbal products and massages.

Hejazi *et al*¹²⁰, surveyed 334 HIV-positive adults on ART and reported abdominal obesity prevalence of 36.5%. Risk factors associated with abdominal obesity included older patients (OR 1.05), higher fasting plasma glucose levels (OR 1.19) and higher body mass index (OR 1.43). In another survey of 2738 adult HIV-positive patients, Hejazi *et al*¹²¹, reported high prevalence of metabolic abnormalities, including elevated levels of serum triglyceride, LDL-C, total cholesterol and fasting plasma glucose levels. Protease inhibitors use (OR 2.3) and alcohol consumption (OR 2.7) were associated with elevated triglyceride levels in these patients.

Lian *et al*¹²², surveyed 128 HIV-positive patients newly started on ART and reported AIDS-defining illnesses (ADIs) still occur especially in patients with CD4 count < 100 cells/mm³ at HAART initiation. The most common ADIs were pulmonary tuberculosis, extra-pulmonary tuberculosis and *Pneumocystis carinii* pneumonia.

Yagoub *et al*¹²³, explored the key determinants of adherence to HAART in a survey of 925 HIV-positive patients on HAART. Poor adherence was associated with diarrhoea, vomiting, forgetfulness, use of herbal medications or religious treatment, and long travel distance to obtain medications. Good adherence was associated with the use of alarm clocks, acceptance of HIV status, self-efficacy, older age, higher education level, and higher income. Effective treatment of adverse effects, discouraging the use of alternative treatments, counselling, use of alarm clock and easier access to HAART were needed to improve adherence.

CULTURE AND RELIGION

In a 2005 editorial, Kamarulzaman¹²⁴ discussed the challenges of managing the HIV epidemic in a multicultural and predominantly Islamic Malaysia. Since then, the challenges have remained relatively unchanged. The success from implementing harm reduction strategies to curb HIV transmission in IDUs was not seen in MSM and sex workers¹²⁵. Homosexuality is culturally frowned upon and is often hidden. Majority of MSM may be married adding to the challenge to design appropriate intervention strategies among MSM¹²⁶. Wong *et al*¹²⁷, surveyed 2271 Malaysians aged 18–60 years and reported poor knowledge was not the root causes of HIV stigma and discriminatory attitudes but rather ethnicity was the strongest correlate of knowledge of HIV transmission, self-stigma, and public stigma attitudes.

CASE REPORTS

A handful of case reports of patients with rare HIV/AIDS-related conditions have been published including several case reports on the challenges in diagnosis and management. These are summarised in Table III.

DIAGNOSIS

Genotyping and Phylogenetic Studies

Circulating recombinant forms (CRF)

A fascinating picture of the evolution of the HIV epidemic in Malaysia at the molecular level was made possible through genotyping and phylogenetic studies with the discovery of various subtypes of the HIV-1 virus that spread from one at-risk population group to other groups and ultimately into the general population. In 2000, Saraswathy *et al*¹⁴¹, reported HIV-1 B, C and E subtypes were identified among Malaysian IDUs with predominance of the B subtype. The CRF subtype B was also identified as the dominant subtype in IDUs by Tee *et al*¹⁴². They went on to describe the discovery of CRF33_01B disseminating widely among various risk populations in Kuala Lumpur between 2003 and 2005 as well as the discovery of the emergence of intersubtype recombinants CRF01_AE/B suggesting a new circulating form in Kuala Lumpur which had emerged as early as the mid-1990s, predominantly in IDUs. CRF01_AE/B were the progenitors of CRF33_01B¹⁴³⁻¹⁴⁶.

Lau *et al*¹⁴⁷, in 2007 reported the discovery of HIV-1 isolate 06MYKLD46, a possible second generation HIV-1 recombinant derived from CRF33_01B. A year later, Lau *et al*¹⁴⁸, and Wang *et al*¹⁴⁹, reported evidence of rapid and extensive HIV-1 evolution in the region with the discovery of several novel recombinant forms of HIV-isolates, namely 07MYKL47, 07MYKL48 and 07MYKL49. In 2010, Lau *et al*¹³³, reported evidence for possible biological advantages of the newly emerging HIV-1 CRF from Malaysia (CRF33_01B) compared to its progenitors (CRF01_AE and subtype B). In 2012, Ng *et al*¹⁵⁰, reported the discovery of novel HIV-1 CRF54_01B from three epidemiologically unlinked subjects of different risk groups in Malaysia suggesting that the new CRF may have potential in bridging HIV-1 transmission among different risk groups in South East Asia (SEA). Similarly, Chow *et al*¹⁵¹, reported the discovery of a novel HIV-1 genotype phylogenetically linked to CRF33_10B identified in three epidemiologically unrelated persons in Malaysia. They suggested that the discovery may contribute to HIV-1 molecular surveillance and future vaccine development in the SEA region. In the same year, Mohamad *et al*¹⁵², reported the emergence of CRF33_01B as the predominant subtype and a high frequency of primary mutations among HIV-1 infected children after failure of ART in Kelantan.

In 2013, Ng *et al*¹⁵³, reported that the HIV-1 subtype B and CRF01_AE were predominant and contributed to about 80% of total HIV-1 infections among MSM in Malaysia, of which 12 monophyletic clusters were identified. Bayesian coalescent analysis estimated that the divergence times for these clusters were mainly from 1995–2005. In the same year, Chow *et al*¹⁵⁴, reported that the founder lineages of CRF33_01B were likely to have first emerged among IDUs in the early 1990s before spreading exponentially to various high and low-risk populations (including children who acquired infections from their mothers) and became endemic later on during the early 2000s. Their findings provided notable genetic evidence indicating the widespread expansion of CRF33_01B among IDUs and into the general population.

Oyomopito *et al*¹⁵⁵, reported that patients infected with CRF01_AE have reduced immunologic response to therapy at 12 months compared to subtypes B infected counterparts. Clinical deterioration was associated with low baseline CD4 counts and older age. Major drug resistance mutations among antiretroviral (ARV) treated patients with detectable viral load was reported by Tee *et al*¹⁵⁶, in 2005. Resistance was greatest with non-nucleoside reverse transcriptase resistance and least with protease inhibitor. Ong *et al*¹⁵⁷, studied the molecular diversity of HIV-1 and surveillance of transmitted drug resistance among treatment naïve patients, five years after introduction of ART in Kuala Lumpur between 2008 and 2010. They found the predominant circulating HIV-1 genotypes were CRF-01_AE (51%; 51/100) and CRF33_01B (17%; 17/100). Transmitted drug resistance among ART-naïve patients was low five years after the introduction of HAART¹⁵⁷⁻¹⁵⁹. In 2011, Sungkanuparph *et al*¹⁶⁰, reported prevalence of patients with one or more drug resistance mutation was 13.8% in a multicentre HIV-1 drug resistance monitoring study suggesting that primary HIV drug resistance was emerging after rapid scaling-up of ART use in Asia. Chitra *et al*¹⁶¹, reported that the increase of beta-2 microglobulin and reduced absolute CD4, CD8 count, CD4/CD8 ratio and leucocytes count in HIV patients who were non-adherent to HAART may have a contributory role in the immune progression of HIV with interruption of HAART. Beta-2 microglobulin plays an important role in the diagnosis of HIV and might indicate HIV progression.

Other genotyping studies

Tan *et al*¹⁶², reported cryptococcal and Mycobacterium tuberculosis immune restoration disease (IRD) coincided with peaks in the proportion of activated T-cells, pathogen-specific gamma-interferon responses and reactive plasma IgG. However, Sumathoth *et al*¹⁶³, later reported that the level of antibody to mycobacterial antigens did not predict IRD.

Lim *et al*¹⁶⁴, and Iqbal *et al*¹⁶⁵, reported the predominance of *Cryptosporidium parvum* subgenotypes signified the possibility of zoonotic as well as anthroponotic transmissions of cryptosporidiosis in HIV-infected individuals. Lim *et al*, also reported the first detection of *C. hominis*, *C. meleagridis*, *C. felis* and *Giardia* in Malaysian HIV/AIDS patients.

Other Diagnostic Methods and Laboratory-Based Research

In 2000, Jayaram *et al*¹⁶⁶, reported the value of fine needle aspiration cytology (FNAC) in the diagnosis of bacterial, fungal and high grade lymphoma including phenotyping in HIV-positive patients who presented with lymph node enlargement. In 2008, Zaidah *et al*¹⁶⁷, reported the superiority of the polymerase chain reaction (PCR) over microscopy in identifying *C. parvum* infection and its usefulness in the determination of the true prevalence and epidemiology of *C. parvum*. Al-Darraj

*et al*¹⁶⁸, evaluated the single GeneXpert MTVB/RIF assay against the acid-fast bacilli (AFB) smear microscopy and the gold standard BACTEC MGIT 960 liquid culture in 125 HIV-positive prisoners. The single GeneXpert assay outperformed AFB smear microscopy but has low screening sensitivity of 53.3%. Lee *et al*¹⁶⁹, evaluated the use of the dried blood spot (DBS) method as a tool to detect HIV, hepatitis B and C infections. They concluded that although the DBS was an ideal choice as a screening tool, its use was restricted by the need to use different cut off values for validation of test positivity. Chew *et al*¹⁷⁰, reported the results of a longitudinal study exploring the role of chemokines in IRD and sensory neuropathy.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Studies on the prevalence of HIV in many of the most-at-risk-populations in Malaysia have provided reliable insights into the magnitude of the problem in Malaysia (Table 1). These statistics are useful to guide the implementation of prevention and treatment strategies in these groups, especially in a resource-limited setting. Logically, greater proportions of resources should be allocated to groups with higher HIV prevalence such as the injecting drug users, sex workers and MSM⁶⁻¹³. In practice, however, resources have often been allocated for programmes such as the premarital HIV screening for Muslims that have very low yield of HIV positive detection despite screening a large population^{18,22}. This policy ought to be re-evaluated as it is not only potentially discriminative as the policy does not apply to non-Muslims, it is also clearly a policy borne out of political or religious expediency rather than evidence-guided use of limited resources. Incidence studies in various-at-risk groups are sorely lacking in Malaysia as are prevalence studies in other marginalised groups such as the transgender people, migrant workers and refugees.

Risk behaviours for injecting drug users in Malaysia have been well documented and they are consistent with the findings of studies conducted in other countries^{7-9,23-25}. On the other hand, there is little or no data about the prevalence of HIV and risk behaviours in many of the marginalised communities in Malaysia such as sex workers, MSM, transgender people, migrant workers and refugees. Identifying risk behaviours in these groups can help guide the formulation of risk-reduction strategies tailored specifically for each of these groups. The successes of the opioid substitution therapy and needle and syringe exchange programmes among intravenous drug users are prime example of tailored strategies targeted at identified risk-behaviours⁹⁶⁻¹⁰⁰. The knowledge, attitude and practice studies in Malaysia have largely been focussed on students, adolescents and pregnant women^{32-35,39-47}.

Although at least 24 AIDS-defining illnesses have been identified¹⁷¹, most of the research in Malaysia have largely focussed on only a few of the common conditions associated with HIV/AIDS such as tuberculosis, toxoplasmosis, and fungal infections. Case reports of patients with rare manifestations of conditions related to HIV/AIDS and the management strategies used for these conditions should be encouraged. A neglected area of research is the complex issue of managing HIV-hepatitis B and C co-infections especially with recent advances in the management of hepatitis B and C infections where cure is possible.

In conclusion, 30 years after the identification of HIV as the causative agent of AIDS and 28 years after the first few cases of

HIV were reported in Malaysia, the HIV epidemic is here to stay and continue to be a major public health concern. Although we have achieved substantial success in slowing the epidemic, particularly among injecting drug users, a significantly large proportion of at-risk populations in Malaysia remain vulnerable to the epidemic.

SECTION 3: FUTURE RESEARCH DIRECTION

More incidence and prevalence studies should be conducted on marginalised groups such as the transgender people, migrant workers and refugees. Studies should also be conducted to identify the factors that help fuel the rise of heterosexual transmission of HIV infections in recent years in the population.

Future knowledge, attitude and practice studies should focus on less studied groups such as the injecting drug users, MSM, sex workers, transgender people, migrant workers, and refugees. Outcome studies on the effectiveness of destigmatising strategies are needed.

Research on the management of HIV-HBV and HIV-HCV co-infections in Malaysian patients should be carried out since there is lack of data in this area. Studies on children living with HIV is also an important aspect to look into. Health economic studies are vital to assess the need for pre-marriage screening.

A large number of studies have identified problems in the management of specific groups of patients with HIV/AIDS such as those with HIV-TB co-infection, injecting drug users and prisoners⁹³⁻¹¹⁰. Outcome studies based on strategies to address the identified problems should be done. The findings of outcome studies are vital to affect policy change. More research is needed to address the problem of access to ART, particularly among prisoners and refugees. Research in developing strategies to improve adherence to ART, the key to success in managing HIV infection, is needed to provide insight into what works and what does not in the local context.

Studies and case reports on the use of post-exposure prophylaxis (PEP) for HIV beyond the confines of healthcare personnel are needed in order to affect a policy change to extend PEP to people who are exposed to HIV in a non-healthcare setting such as condom failure, victims of sexual abuses and rape, and homosexual and bisexual men with multiple sex partners.

Another potential area for research is the use of ART as a pre-exposure prophylaxis (PrEP) strategy, particularly in MSM and sex workers. Pre-exposure prophylaxis may indeed prove to be the key to controlling the spread of HIV within these groups and the general population, just as harm reduction policies and programmes had done to control the HIV epidemic in IDUs. The use of PrEP may be a reasonable alternative to sperm-washing and child adoption for discordant couples who wish to conceive. As patients on ART are able to live longer, research on the long term effects of ART and other causes of morbidity and mortality in these patients should be conducted. Adverse effects associated with older ARTs should be highlighted in case reports in order to push for the availability of newer and safer drugs. Outcome studies on early intervention with ART and the short and long term benefits of ART are needed in order to widen the scope of coverage for treatment of HIV in the population.

Non-governmental organisations (NGOs) and advocacy groups working for people living with HIV/AIDS must publish articles describing their works and the successes from their works, not only for the sake of posterity but also as leverage in obtaining crucial funding and support as well as serve as guides for other NGOs and groups.

More laboratory-based research need to be done especially in the areas of diagnostics. A reliable biomarker to predict, diagnose and manage immune-reconstitution syndrome in HIV-positive patients newly started on ART remains elusive and requires more research. Although genotyping and phylogenetic studies have provided useful insight to the evolution of the HIV epidemic in Malaysia at a molecular level, studies must now focus on translating this knowledge from the bench to the bedside in a clinically relevant fashion, in terms of identifying potential drug-resistance based on viral genotyping, molecular surveillance and vaccine development^{138,146}.

More research is needed to provide solid and reliable evidence that can be used to affect policy changes and formulate workable treatment and prevention strategies.

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