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Brief Review

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WHO 2009 GUIDELINES FOR ANTI-RETROVIRAL THERAPHY: ITS IMPLICATION FOR PRIMARY CARE PHYSICIAN

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KEY-LEARNING POINTS

- The HIV epidemic in Malaysia is slowing down but has now spread to spouses and sexual partners of traditional at risk populations, via heterosexual transmission.
- The WHO 2009 guideline advocates starting HAART at CD4 level of 350 cells/mm3, marking a significant departure from starting at CD4 level of 200 cells/mm3 previously.
- The WHO 2009 guideline recommended replacing stavudine with either zidovudine or tenofovir as part of the first line HAART regimen due to the former's adverse effects.
- Early detection of HIV infection and earlier initiation of HAART translates into better quality of life and lower risk of Tuberculosis co-infection.
- Earlier detection of HIV infection requires picking up on subtle signs of the infection as well as employing a host of available diagnostic tests in cases where HIV infection is strongly suspected.
- HIV test should be offered as a part of a routine health check screening. This facilitates early detection of HIV infection and early referral to the hospital for further management.
- Collaboration and communications with non-governmental organizations involved in care of HIV infected people can be a good mean of providing support and counselling to newly diagnosed HIV infected individuals.
- Asymptomatic undiagnosed HIV infected patients may pose a risk for disease transmission to health care workers in the primary care setting. Steps must be taken to minimize the risk of transmission and easy access to post-exposure prophylaxis.
- The primary care physician should be well versed with the many possible drug interactions between HAART and other commonly used medications for other illnesses in order to avoid potentially fatal adverse reactions or treatment failure in patients taking HAART.

Koh KC. WHO 2009 guidelines for anti-retroviral theraphy: its implication for primary care physician. Malaysian Family Physician. 2010;5(2):77-82

The World Health Organization (WHO) recently released several key recommendations on antiretroviral therapy (ART) for adults and adolescents in November 2009. Among the key recommendations for ART are:

- Earlier diagnosis and treatment of human immunodeficiency virus (HIV) in the interest of a prolonged and healthier life.
- Greater use of more patient-friendly treatment regimens.
- Expanded laboratory testing to improve the quality of HIV treatment and care.[1]

According to the 2009 Acquired Immune Deficiency Syndrome (AIDS) epidemic update, new HIV infections have been reduced by 17% over the past eight years. In South East Asia, HIV incidence has declined by 10% in the same period of time. At the same time, there are now more people living with HIV than ever before as people are living longer due to the effective ART while the number of AIDS related death has declined significantly. WHO and UNAIDS estimate that since the advent of effective treatment in 1996, about 2.9 million lives have been saved.[1]

However, of concern is the changing face of the epidemic particularly in East and Central Europe as well as in some Asian countries where the epidemic which used to be driven mainly by injecting drug users and sex workers, is now being increasingly driven by heterosexual transmission.

Since the first few cases of HIV infection were detected in Malaysia in 1986, the rate of new HIV infections reported annually has increased exponentially. At the end of 2008, there were 84,630 reported cases of HIV infections and 14,576 reported cases of AIDS. In keeping with the trend reported by

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WHO, newly reported cases of HIV in Malaysia have been declining from the peak of 6,978 cases in 2002 to 3,692 cases in 2008.

Since 1997, infections among women in Malaysia are up by 11%, and 75% of these patients are between the ages 20 to 39. 60% of these women are married. In addition, 70% of women living with HIV contracted the disease through heterosexual contact. 2006 saw the highest number of female HIV cases reported since the beginning of the national epidemic, forming 15% of new cases that year which represented a 344% jump from the figures in 1997. All these indicate that heterosexual transmission of HIV is becoming a cause for concern, wherein women are now infected by men who acquired HIV infections from either illicit intravenous drug use or from sex with other men.[2,3]

ART was first made available in Malaysia in 1989 and since then much effort has been put in to ensure its availability to the population via infectious diseases clinics in major hospitals and primary health clinics with family medicine physicians trained in HIV medicine. In 2006, the Malaysian government made nationwide two significant initiatives, namely the Methadone Maintenance Therapy (MMT) and the Needle Syringe Exchange Program (NSEP) targeted at intravenous drug users in an effort to encourage the use of clean sterile syringes and needles to feed their habits. In the same year, first-line ART without cost was made available for all eligible HIV infected citizens. These initiatives are starting to bear fruit as more HIV infected individuals can now access the beneficial effects of treatment and the rate of HIV infection amongst intravenous drug users has declined.[3]

Most doctors trained in treating HIV in Malaysia follow the 2006 Antiretroviral (ARV) guidelines released by WHO which recommended that all patients start ART when their CD4 count (a marker of a person's immunity status) falls to 200 cells/mm3 or lower, at which point many already show symptoms of HIV disease and other opportunistic infections. The standard ART regimen of choice currently practiced in Malaysia includes the combination of two nucleoside reverse-transcriptase inhibitors (NRTIs), typically either zidovudine (AZT) + lamivudine (3TC) or stavudine (d4T) + 3TC with a non-nucleoside reverse-transcriptase inhibitor (NNRTI), typically either nevirapine (NVP) or efavirenz (EFV). There is also a generic triple-drug combination which is low cost and widely available called SLN (stavudine + lamivudine + nevirapine). However, since 2006, studies and trials have demonstrated that earlier initiation of ART reduces death rates and improved quality of life of HIV infected individuals.[4-7] The 2009 WHO guidelines now recommend initiation of ART at the CD4 threshold of 350 cells/mm3 for all HIV positive patients, including pregnant women, regardless of symptoms. This marks a significant departure from the 2006 recommendation of starting ART at CD4 level less than 200 cells/mm3. An earlier start to ART boosts the immune system and reduces the risks of HIV related death and disease. It also lowers the risk of HIV and tuberculosis transmission.[8]

The 2009 WHO guidelines also recommended the phasing out of stavudine (d4T) as first-line therapy because of its long term irreversible side effects which include severe peripheral neuropathy, disfiguring lipodystrophy and risk of fatal lactic acidosis.[1] Instead, WHO recommended that AZT or tenofovir (TDF) to be used as they are less toxic and are equally effective alternatives. While AZT is readily available in Malaysia, TDF is available to carefully selected patients on a case-to-case basis.

In the last couple of years, more affordable generic tenovir (TDF) and the fixed dose combination drug, tenovir-emtricitabine, are now available making it a very attractive first-line drug as part of the NRTI backbone of a triple-drug ART regimen. This particularly true in patients with hepatitis B-HIV co-infections as TDF has potent activity against both viruses while in patients with hepatitis C-HIV co-infections on treatment with ribavirin and peg-interferon for chronic hepatitis C, tenofovir in combination with lamivudine (3TC) is favoured over AZT + lamivudine because AZT induced anaemia is higher with ribavirin which may affect the success of hepatitis C treatment. Some treatment naïve patients who are concerned about the disfiguring effects of lipodystrophy, which is a problem with stavudine, are requesting either to have TDF as part of their first-line ART regimen while patients already on ART regimen containing d4T are requesting for it to be replaced with TDF.

In addition, the 2009 WHO guidelines also recommended greater access to CD4 testing and the use of viral load monitoring to improve the quality of HIV treatment and care. In Malaysia, while CD4 testing is available in most major hospitals, HIV viral load testing is only available in very few selected tertiary health care centres. This discrepancy is mainly due to the high cost of the latter which require sophisticated laboratory equipments. The WHO is aware of this limitation and therefore added that "access to ART must not be denied even if these tests were not readily available" in its recommendation.[1]

The recommendations, if adopted, will result in greater number of people needing treatment for HIV infection. The associated costs of earlier treatment may be offset by decreased hospital costs, increased productivity due to fewer sick days, fewer children orphaned by AIDS and a drop in HIV infections. On the other hand, if the guidelines are followed blindly without careful selection of patients, usually based on their readiness to be on life long therapy, follow up and commitment to strict adherence to the ART regimen, it may result in high rates of non-adherence and therapeutic failure rates.

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Prior to the release of the 2009 WHO guidelines on ART, many infectious diseases specialists in Malaysia have initiated ART for HIV positive patients at a higher CD4 threshold than 200 cells/mm3, typically at a CD4 level between 250 cells/mm3 and 350 cells/mm3. Unfortunately, many HIV positive people present at a late stage of the disease to the hospital, when their CD4 cell counts are well below 200 cells/mm3. In addition, the lack of health awareness in the general population, limited access to acceptable anonymous HIV testing facilities as well as poor human and financial resources have resulted in not many asymptomatic HIV infected people to be diagnosed early.

In the light of the 2009 WHO guidelines on ART, what are the implications for general practitioners in this country? Primary care physicians can play a major role in ensuring wider access to diagnosis and treatment of HIV in this country, in line with the guidelines. There are at least three areas where primary care physicians can play a role:

1. Early detection, counselling and referral of HIV infection

Because of the shift in the dynamics of HIV transmission from injecting drug users to heterosexual transmissions, primary care physicians need to be aware that the traditional 'image' of a possibly HIV infected individual which is a Malay man between 20 to 40 years old who is either unemployed or is an odd job worker and engages in intravenous drug use, may not always be true. Instead, the apparently healthy looking house wife or elderly gentleman with no obvious risk factors for HIV infection may in fact be infected with HIV. If these asymptomatic HIV positive people could be diagnosed early and referred for early initiation of ART before serious damage to their immune system occurs, they stand to greatly benefit in terms of continual well being and improved quality of life.

While careful history taking may elicit certain risk factors such as being the spouse of a injecting drug user and meticulous physical examinations may yield subtle clues to possible HIV infection such as poor wound healing, seborrhoeic dermatitis and longer recovery time from simple ailments such as upper respiratory tract infections, the more efficacious method of diagnosis would be to offer HIV and other sexually transmitted illnesses (STI) screening tests as part and parcel of a comprehensive health screening package. Currently, these tests are usually not part of the normal health screening package offered by private laboratories and general practitioners.

A number of recent studies have led to a growing clarion call to the "test and treat" strategy which is straightforward: test everyone, and treat those who are infected with HIV. The rationale behind this strategy includes a dramatic reduction in the 'community viral load' (defined as the mean of the most recent viral load of all reported HIV infected individuals in a particular population) which is associated with decrease in new HIV diagnoses.[9] Another study demonstrated that ART prevents HIV transmission by as much as 92% in sero-discordant couples where the HIV positive partners on ART have undetectable viral load.[10]

While the Enzyme-Linked Immunosorbent Assay (ELISA) screening test for HIV is highly sensitive and specific, it is not infallible. False negative in the face of severe HIV infection has been reported.[11] In patients who show obvious signs of immunosuppression with known risk factors but have negative HIV ELISA tests, it would be prudent to refer the patient to a centre where more sophisticated tests such as the Western Blot, p24 or HIV viral load could be done.

Early diagnosis should ideally be accompanied by early counselling on the various support systems available for people newly diagnosed with HIV. The principle of privacy and confidentiality must be upheld at all times. Besides the treatment facilities available in most major hospitals in the country, there are many well established non-governmental organizations with personnel well trained in managing HIV infected individuals, such as the Malaysian AIDS Council, the Kuala Lumpur AIDS Support and Services (KLASS) and the PT Foundation. Sometimes referral for psychiatric support may be necessary to deal with depression. Primary care physicians may want to establish communication links with these organizations for referral purposes.

Primary care physicians can also play a major role in helping to destigmatize the disease by raising awareness of the disease via health posters, counselling and health education to allay the fears of the people so that they may be more willing to be come forward to be tested for HIV. Promoting HIV testing as part and parcel of an annual health screening tests that are normally done now could be one possible way to achieve this. In addition, all women diagnosed as being pregnant at private clinics or laboratories should be offered HIV and STI testing as is the practice in public hospitals.

2. Practice of Universal Precautions

Because it is almost impossible to tell if a patient who presents to a primary health physician for ailments unrelated to HIV such as cuts and bruises from trauma or motor-vehicle accidents, is in fact infected with HIV; staff working in these clinics must be educated on the practice of universal precautions to avoid possible occupational related HIV transmission. Consequently, the unsafe or even dangerous practice of reusing syringes and sutures or needles, improper disposal of paraphernalia contaminated by body fluids, and performing minor surgical procedures without proper protection should be avoided. Needle-prick injuries from these unsafe practices are possible with potential for transmission of HIV.

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It is recommended that all primary health care clinics have a carefully drawn out algorithm in the event of a needle-prick injury to ensure speedy diagnosis of possible HIV transmission as well as early access to post-exposure prophylaxis.

3. Drug-drug interactions

As access to ART becomes more accessible, HIV positive individuals will invariably live longer. Studies have demonstrated that a HIV positive individual started early on ART with access to proper care and monitoring can expect to live between 20 to 50 years from the time of ART initiation.[12] A possible consequence to this is that these individuals will go on to develop other age related or ART related diseases such as diabetes mellitus, dyslipidemia and ischemic heart disease. Chronic smokers may develop chronic obstructive pulmonary disease, while alcoholics may develop liver diseases.

These chronic diseases would necessitate the use of anti-hyperglycemic agents, cholesterol lowering agents and other medications on top of their ART. A substantial number of HIV infected people from the younger age group also indulge in recreational drug use such as ecstasy and amphetamine abuse.

Table 1: Interactions between illicit drugs and ARVs

Drug	Interaction/Effect	Recommendations
Amphetamines	Increases RTV levels, can increase toxicity	Do not prescribe RTV or RTV-containing regimens even in low doses if there is amphetamine use
Barbiturates	Barbiturates such as phenobarbital can induce CYP3A4 (i.e. more rapid drug clearance)	Consider avoiding other potent CYP3A4 inducers such as EFV or NVP in patients misusing barbiturates
Benzodiazepines (depending on the bdz used)	PIs can cause over-sedation; NVP can cause withdrawal	Avoid concurrent use of alprazolam, midazolam and triazolam with all PIs, NVP and EFV
Cocaine	PIs and EFV increase levels - can cause overdose; NVP can cause hepatotoxic metabolite	Interactions can lead to increased hepato-toxicity; clinicians should monitor closely
Codeine	PIs can increase or decrease metabolism an dlead to: possible overdose or possible loss of analgesia	NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
Heroin	NFV and RTV can cause withdrawal	NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
MDMA (Ecstacy), GHB (gamma hydroxybutyrate)	RTV can increase drug level and lead to toxicity	Clinicians should not prescribe PIs even in low doses if patients report MDMA or GHB use; MDMA/RTV use can be fatal
Morphine	NFV, RTV lead to withdrawal and loss of analgesia	NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
Phencyclidine (PCP)	PIs and EFV can lead to toxicity	Use PIs cautiously and they may lead to PCP toxicity; clinicians should monitor closely
THC/Marijuana	PIs may increase concentration; NNRTIs may decrease concentration	No clinically significant interactions have been reported

Source: World Health Organization. HIV/AIDS treatment and care for injecting drug users. Clinical protocol for the WHO European Region. Copenhagen, Denmark, WHO, 2006 (http://www.euro.who.int/document/SHA/WHO_Chapter_5_web.pdf).

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All these would create a new therapeutic dilemma: that of possible drug-drug interactions. For instance, prescribing ergotamine for migraine in a HIV positive patient who is on protease inhibitors as part of his ART can lead to fatal consequences as protease inhibitors can raise ergotamin levels in the body to toxic levels by inhibiting its metabolism. Similarly, nevirapine hastens the clearance of drugs metabolized via the cytochrome P450 pathway in the liver such as ketoconazole, oral contraceptives, anti-histamines, statins, and antiepileptics such as phenytoin or carbamazepine which in turn may result in under-dosing.

Careful drug history should be elicited from HIV infected patient on ART by the attending primary care physician in order to avoid potential adverse effects from drug-drug interactions.

In conclusion, primary care physicians have a significant role in early diagnosis of HIV infected people, ensuring wider access to early ART, ensuring the welfare of health care workers attending to possible HIV positive patients and safe long term follow up of HIV positive patients needing medications for non-HIV related ailments.

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Table 2: Interactions between drugs commonly used to treat PLWHA and ARVs

Medication	Actions/Uses	Interactions with ARV medications
Psychotropic medications		
Alprazolam (benzodiazepine)	Sedative	Alprazolam clearance decreased by 41%; clinicians should avoid concurrent use of certain benzodiazepines (alprazolam, midazolam and triazolam) with all PIs and EFV
Desipramine	Tricyclic antidepressant (TCA)	Desipramine clearance decreased by 59%
Fluoxetine (SSRI)	Treatment of depression and compulsive disorders	Ritonavir increased by 19%
St John's wort (herb)	Antidepressant	IDV decreased by 57%; do not co-administer to patients taking PIs or NNRTIs
Valproic acid	Anticonvulsant	AZT increased in preclinical studies
Other medications		
Carbamazepine	Anticonvulsant	
Fluconazole	Antifungal	Potential for bidirectional inhibition by some azole antifungal antibiotics and PIs. Monitor for toxicities and dose adjustments. Toxicity and antifungal outcomes observed with NNRTIs
Phenobarbital	Anticonvulsant	Barbiturates are potent inducers of CYP3A4. Clinicians should consider avoiding co-administration of other potent inducers (e.g. EFV and NVP)
Phenytoin	Anticonvulsant	Some interactions; monitor for toxicities and dose adjustments
Rifampicin	Anti-TB	PIs contraindicated. Rifampicin should not be co-administered with LPV, NFV, SQV. Rifabutin may be potential alternative
Sildenafil	Erectile dysfunction agent	No effect of sildenafil on PIs. Ritonavir increases sildenafil level 10-fold. Saquinavir increases sildenafil level 3-fold. Use cautiously (lowest dose every 48 hours) and monitor for adverse effects

Source: World Health Organization. HIV/AIDS treatment and care for injecting drug users. Clinical protocol for the WHO European Region. Copenhagen, Denmark, WHO, 2006 (http://www.euro.who.int/document/SHA/WHO_Chapter_5_web.pdf).

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Bad news for dietary supplements: *folate, vitamin B6, vitamin B12 and omega-3 fatty acids do not prevent cardiovascular events in adults with prior cardiovascular disease.*

Galan P, Kesse-Guyot E, Czernichow S, *et al*. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ. 2010;341:c6273. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2993045/pdf/bmj.c6273.pdf

2501 adult patients with a history of myocardial infarction, unstable angina, or ischaemic stroke, were randomized to receive vitamins (folate, vitamin B6, B12) or omega 3 fatty acids or placebo and followed up for 4.7 years.

Allocation to B vitamins lowered plasma homocysteine concentrations by 19% compared with placebo, but had no significant effects on major vascular events (hazard ratio, 0.90, 95%CI 0.66 to 1.23, p=0.50). Allocation to omega 3 fatty acids increased plasma concentrations of omega 3 fatty acids by 37% compared with placebo, but also had no significant effect on major vascular events (hazard ratio 1.08, 95%CI 0.79 to 1.47, p=0.64).