CONSENSUS ON ANTIRETROVIRAL TREATMENT (2nd Edition)

Ministry of Health Malaysia

Academy of Medicine of Malaysia

Malaysian Society of Infectious Diseases and Chemotherapy

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Consensus On Antiretroviral Treatment (2nd Edition)

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Dear colleagues

It has been 3 years since the release of the 1st National Guidelines on Antiretroviral Therapy. The feedback from the 1st edition from medical practitioners have been encouraging and the expert panel valued all comments made. With the many new developments in HIV medicine over the last 3 years, we felt it was time for a review of the guidelines.

The development of the 2nd edition of the Guidelines on Antiretroviral Therapy has been taken over by the Malaysian Society of Infectious Diseases & Chemotherapy (MSIDC). The Organizing Committee had put together 2 experienced expert panels comprising of clinicians and microbiologists who are actively involved with HIV care in this country. The expert panels; one for adult management and the other for paediatrics, were recognizant of new developments in basic science, clinical research, therapeutics as well as current local realities. The most important local development was the significant price reductions of antiretrovirals by some pharmaceutical companies in mid 2001.

The expert panel has taken pains to be specific where they could be but we must acknowledge that individualization of care must always be practiced. It is hoped that this document will guide the clinician in making important therapeutic decisions in managing each individual case. Some new sections have been inserted especially as appendices eg. disease monitoring (esp. with regards to viral load measurements), role of dual nucleoside (suboptimal) therapies and drug interactions. The section on *Reducing maternal-fetal HIV transmission* has been omitted while awaiting the more comprehensive document "*HIV and Pregnancy*" which is expected next year.

As chairman of the Organizing Committee, I would like to express my warmest appreciation for the committee members: Assoc. Prof. Yasmin Malik, Assoc. Prof. Adeeba Kamarulzaman, Dr. Suresh Kumar, Dr. Norliza Ariffin, Dr. Mardziah Alias and Dr. Kamarul Azahar who worked hard writing up the document, collating base documents and working on the logistics of producing a good quality document. I must also express my appreciation to the MISDC and the Academy of Medicine for supporting and sponsoring the document this time round. A word of thanks must also go out to the expert panel members for their time and energy put into the formulation of this document.

Lastly, on behalf of the Organizing Committee, I would like to thank Merck, Sharp and Dohme (M'sia) for the unconditional grant and secretarial support in producing this set of guidelines.

We hope you will find this document useful in providing quality care to HIV-infected patients.

Thank You.

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2nd National Guidelines on Antiretroviral Therapy

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GUIDELINES FOR ADULTS

INTRODUCTION

Recent advances in the knowledge of HIV pathogenesis, the rapid development of potent antiretroviral agents coupled with the availability of more sensitive laboratory tools such as the viral load assays have greatly altered the management of HIV-infected patients. Guidelines for the use of the increasingly complex armamentarium of antiretroviral agents, including new classes of drugs, have been published in many parts of the developed world. Recognizing that it may not be feasible to adopt these therapeutic approaches outlined in these international guidelines, a panel of local physicians involved in the care of HIV-infected patients in this country convened to provide therapeutic recommendations appropriate to our clinical setting. The panel took into account the many different situations faced by HIV-infected patients and their treating doctors with regards to antiretroviral use in this country. Financial constraints and the relative lack of access to laboratory facilities are some of the major considerations that may limit the options for optimum antiretroviral therapy. The fact that recent price reductions of some antiretroviral agents made Highly Active Antiretroviral Therapy (HAART) more accessible, was also taken into consideration in developing these recommendations.

GOALS OF ANTIRETROVIRAL TREATMENT

General goals of antiretroviral therapy [3]

The panel agreed that the general goals of antiretroviral therapy are to prolong survival and decrease morbidity in those infected. An important objective would be to improve the patient's quality of life and reduce the burden that he generates on his family and the community. Maintenance of the family unit would be an important outcome of prolonging the survival of these patients.

In encouraging those who are infected with HIV to seek treatment it is hoped that early identification of HIV infection would lead to a reduction in its transmission within the community.

Finally the general goal of antiretroviral therapy is that it should be affordable and accessible to all those infected.

Specific goals of antiretroviral therapy

The specific objectives of antiretroviral therapy are to suppress HIV replication and to slow down the cycle of immune activation and CD4+ cell destruction as effectively and for as long as possible. The aim would be to reduce plasma viral load to below undetectable levels for a maximum duration and to improve, maintain and prevent the ongoing decline of CD4+ cells.

Ideally, viral load assays and CD4+ cell counts should be used to monitor potent & expensive regimens i.e. HAART. Access to HAART would have little effect if these critical laboratory tests are not available.

SELECTION OF ANTIRETROVIRAL TREATMENT

The guiding principle for selecting antiretroviral therapy is the need for treatment regimens that provide maximum potency and a sustained, durable antiviral response. In situations where optimal therapy aimed at achieving undetectable viral levels is not possible or feasible, the selection of antiretroviral agents should be based on combinations with the 'least penalty' i.e. combinations that are likely to provide maximum clinical benefit and at the same time preserving options for future combination regimes. However, the panel strongly **advocates against the usage of any suboptimal antiretroviral regimens (including monotherapies and dual nucleoside regimens)** as research data unequivocally demonstrates the selection of resistant viral strains with these regimens, which in turn, leads to treatment failure.

Compliance with therapy is one of the major determinants of ensuring a durable response. In all situations the patient must be agreeable and committed to taking what may be a complex and toxic drug regime before commencing therapy.

Given the number of possible drug combinations, it is not possible to recommend which particular regimens are best for treatment of HIV disease. Factors that will influence that decision will include: the condition of the patient (stage of the disease as well as any concomitant illnesses), the potency and adverse effects of the regimen, any concurrent therapies and finally, the cost of the regimen.

At present the antiretroviral drugs that are available in Malaysia (as of August 2001) include (Refer to Appendix A for Drug Details)

I. Nucleoside reverse transcriptase inhibitors (NRTI)

- Zidovudine (*AZT/ Retrovir*) *
- Didanosine (*ddI / Videx*) *
- Zalcitabine (*ddC / Hivid*) *
- Lamivudine (*3TC / Epivir*) *
- Stavudine (*d4T / Zerit*) *
- Combivir (*AZT + 3TC*)

II. Protease inhibitors (PI)

- Indinavir (*Crixivan*) *
- Ritonavir (*Norvir*) *
- Saquinavir – hard gel capsules (*Invirase*)
- Saquinavir – soft gel capsules (*Fortovase*)
- Nelfinavir (*Viracept*)

III. Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- Efavirenz (*Stocrin*)*
- Nevirapine (*Viramune*)

**Antiretroviral drugs currently listed in Ministry of Health drug formulary (August 2001)*

POTENTIALLY DANGEROUS OR INEFFECTIVE COMBINATIONS

I. Antiretroviral Combinations

A list of the side-effects of the drugs is attached in the appendix A.

The following antiretroviral combinations cannot be recommended for reasons of safety or because of insufficient supporting data:

- Didanosine + Zalcitabine — Increased risk of peripheral neuropathy/pancreatitis
- Stavudine + Zalcitabine — Increased risk of peripheral neuropathy/pancreatitis
- Zalcitabine + Lamivudine — *in vitro* evidence of competition for phosphorylation; *in vitro* evidence of cross resistance
- Zidovudine + Stavudine — *in vitro* evidence of competition for phosphorylation

II. Antiretroviral Drug interactions with other drugs[4]

Drugs that should not be used with

protease inhibitors:

- Rifampicin
- Antihistamines – Terfenadine, Astemizole
- Cisapride
- Statins – Simvastatin, Lovastatin
  – Pravastatin and fibrates can be used instead
- Psychotropic – Midazolam, Triazolam

non-nucleosides reverse transcriptase inhibitors:

- Rifampicin – Not recommended with Nevirapine
  Efavirenz can be used but at an increased dose of 800mg/day
- Antihistamines – Terfenadine, Astemizole – Not recommended with Efavirenz
- Psychtopics – Midazolam, Triazolam – Not recommended with Efavirenz

COMMENCING ANTIRETROVIRAL THERAPY – WHEN TO START[4]

Advances in the knowledge of HIV pathogenesis have led to widespread recommendations for early initiation of antiretroviral therapy. Proponents for an aggressive approach to treatment argue that early therapy prevents viral genetic evolution and diminishes the potential for future antiviral drug resistance. A further argument for early treatment is that it will prevent or limit irreversible immune system destruction and may also lead to an earlier restoration of immune function.

However drug toxicities and problems related to incomplete viral suppression (esp. with regards to poor adherence) are some reasons against this aggressive approach.

Over recent years, increasing recognition of the risks associated with initiation of antiretroviral therapy has shifted expert opinion to a more conservative stance concerning the initiation of therapy compared with earlier guidelines. In general, it is now felt that patients with < 350 CD4+ T cells/mm^3 should be offered therapy. This recommendation is based on the substantial

short-term risk of disease progression for untreated patients with < 350 CD4+ T cells/mm^3 at all levels of plasma HIV RNA. In addition, data from observational cohorts suggest that initiation of therapy at a CD4+ T cell count < 200 cells/mm^3 is associated with shorter survival compared with initiation of therapy at higher CD4+ T cell counts[7]. The conservative approach is based on the recognition that robust immune reconstitution still occurs in most patients who initiate therapy with CD4+ T cell counts in the 200-350 cells/mm^3 range, and that toxicities and adherence challenges may outweigh benefits at CD4+ T cell counts > 350 cells/mm^3.

Although the issue of when therapy should be commenced may have taken a more conservative approach, the aim of therapy remains as aggressive ie. maximum viral suppression to get plasma viral loads to below levels of detection using current ultra-sensitive assays.

Recent studies have also highlighted the importance of good drug adherence in maintaining viral suppression and reducing development of resistant viral strains. It is thus imperative that antiretroviral therapy should only be commenced when the patient is committed to long-term treatment[6].

Summary of recommendations on when antiretroviral therapy should be started[4]

Clinical Category	CD4 Count	Viral Load	Recommendation
Symptomatic **• AIDS defining illness** **• Severe Symptoms ***	Any value	Any value	Treat
Asymptomatic	< 200/mm^3	Any value	Treat
Asymptomatic	> 200 but < 350/mm^3	Any value	Treatment recommended
Asymptomatic	> 350/mm^3	> 50,000** copies/ml	Treatment may be initiated #

** Examples include but not limited to*

- *Candidiasis, vulvovaginal: persistent > 1 month, poorly responsive to treatment*
- *Candidiasis, oropharyngeal*
- *Herpes Zoster: more than 1 episode, or involving more than 1 dermatome*
- *Cervical dysplasia, severe or Carcinoma in situ*
- *Constitutional symptoms e.g., fever (> 38.5 °C) or diarrhoea more than 1 month*

The above must be attributed to HIV infection or have clinical course or management complicated by HIV

*** WHO recommendation is in mIU/ml – 2 million copies/ml = 800,000mIU/ml*

 # Some experts recommend initiating treatment since the 3-year risk of developing AIDS in untreated patients is > 30%.

Antiretroviral therapy can be deferred until serious opportunistic infections have been brought under control to reduce risk of drug interactions or adverse drug effects.

COMMENCING ANTIRETROVIRAL THERAPY – WHAT TO START WITH[4]

When initiating therapy in the patient naive to antiretroviral therapy, one should begin with a regimen that is expected to achieve sustained suppression of plasma HIV RNA (ie. HAART), a sustained increase in CD4+ T cell count, and a favorable clinical outcome (i.e., delayed progression to AIDS and death). Additional consideration should be given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

Antiretroviral therapy comprises of one choice each from Column A and B Drugs are listed in alphabetical, not priority, order		
	COLUMN A	***COLUMN B***
Strongly recommended	n **Efavirenz** n **Indinavir** [9,11] n **Nelfinavir** n **Ritonavir + Indinavir** n **Ritonavir + Saquinavir (SGC/HGC)**	n **Stavudine + Didanosine** [11] n **Stavudine + Lamivudine** [10] n **Zidovudine + Didanosine** n **Zidovudine + Lamivudine**
Recommended as alternative	n Nevirapine n Ritonavir n Saquinavir SGC	n Didanosine + Lamivudine n Zidovudine + Zalcitabine
No recommendation due to insufficient data	n Hydroxyurea in combination with any antiretroviral drugs n Ritonavir + Nelfinavir	
n Saquinavir- HGC Not recommended	n Zalcitabine + Didanosine	n Stavudine + Zidovudine n Zalcitabine + Lamivudine n Zalcitabine + Stavudine
	n All monotherapies whether from Column A or B n All dual nucleoside analogue regimens	

Examples of some possible combinations (not in any order of preference or efficacy)

- ***Stavudine + Didanosine + Efavirenz***
- ***Stavudine + Didanosine + Indinavir + Ritonavir***
- ***Zidovudine + Lamivudine + Efavirenz*** [8]
- ***Zidovudine + Lamivudine + Indinavir + Ritonavir***

The choice of the initial regimen should be carefully chosen as the success of antiretroviral treatment is best seen in treatment-naive patients. Decision on the actual regimen will be influenced by

- u stage of disease
- u prior antiretroviral history
- u concomitant illnesses and therapies
- u ability of the individual to tolerate and comply / adhere with certain combinations
- u adverse effects of the antiretroviral agents
- u the patient's financial situation (ie. affordability) and the cost of the regimen

Thus treatment will have to be individualized.

Notes : Refer to Appendix A for dosages, major toxicities, drug interactions and other special instructions

MONITORING ANTIRETROVIRAL THERAPY

In order to determine the appropriate time for changes in antiretroviral therapy, there must be effective and close follow-up. Monitoring antiretroviral therapy should entail, at least, the following aspects of treatment:

Clinical aspects

The clinical well-being of the patient should be monitored. With effective therapy, clinical signs and symptoms should gradually improve or disappear. Development of new opportunistic infections would often mean treatment failure unless they occur during the first few weeks of treatment. The Karnofsky score (refer to Appendix G) may also be useful in 'quantifying' the patient's health.

Adverse drug effects should also be actively sought so as to ensure good adherence. A check on drug compliance is made regularly and this may include performing pill counts, interviewing family members and parameters like mean corpuscular volume (MCV) if zidovudine is used.

CD4+ / CD8+ cell count

CD4+ / CD8+ cell counts should be regularly monitored i.e. 3 – 6 monthly. Specimens for CD4+ cell measurements should be taken at the same time of day and preferably when the patient is not having an acute opportunistic disease. Sending blood specimens for CD4+ cell counts to the same laboratory will reduce inter-laboratory inconsistencies.

Viral Load assays

Viral load (VL) monitoring is necessary in patients who are on optimal antiretroviral therapy. The first VL assay should be done at least 2 months after initiation of therapy. The expected VL reduction is at least a 2 $\log_{10}$ reduction (ie. 100 fold reduction) by 2 months of therapy. Subsequently VL assays maybe done at 3 monthly intervals if the VL at 2 months achieves the expected results; if not, it should be repeated earlier.

Other laboratory investigations

The other laboratory investigations are requested for the following reasons:

- n Supportive evidence of disease progression
- n Detection of HIV-related complications
- n Detection of adverse drug effects and other therapeutic complications

The common investigations requested at regular intervals include; full blood counts, liver and renal profile, erythrocyte sedimentation rate, creatine kinase (if on zidovudine) and serum amylase (if using didanosine, zalcitabine).

If patients are on protease inhibitors, 6-monthly serum lipid and 3-monthly blood sugar assays should be performed. Hyperglycemia is treated according to standard diabetic protocols. Raised serum lipids should be approached with dietary advice and counseling, failing which lipid-lowering therapy may need to be commenced especially if other risk factors for ischaemic heart disease are present.

CHANGING ANTIRETROVIRAL THERAPY – WHEN TO CHANGE? [4]

Criteria for changing therapy:

- **Failure to suppress plasma HIV RNA to undetectable levels within four to six months of initiating therapy**

  In this regard, the degree of initial decrease in plasma HIV RNA and the overall trend in decreasing viremia should be considered. For instance, a patient with 10^6 viral copies/ml prior to therapy who stabilizes after six months of therapy at an HIV RNA level that is detectable but < 10,000 copies/ml may not warrant a change in therapy.

- **Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance**

  However, the degree of plasma HIV RNA increase should be considered. The physician may consider short-term further observation in a patient whose plasma HIV RNA increases from undetectable to low-level detectability (e.g. ,50 – 5000 copies/ml) at four months. In this situation the patient should be followed very closely. It should be noted, however, that most patients who fall into this category will subsequently show progressive increase in plasma viremia that will likely require a change in the antiretroviral regimen.

- **Any reproducible significant increase, defined as 3-fold or greater, from the lowest point of plasma HIV RNA not attributable to intercurrent infection, vaccination or test methodology except as noted above**

- **Undetectable viremia in the patient receiving double nucleoside therapy**

  Patients currently receiving 2 NRTIs who have achieved the goal of no detectable virus have the option of continuing this regimen or may have modification to conform to regimens in the strongly recommended category. Prior experience indicates that most of these patients on double nucleoside therapy will eventually have virological failure with a frequency that is substantially greater compared to patients treated with the strongly recommended regimes.

- **Persistently declining CD4+ T cell numbers, as measured on at least two separate occasions**

- **Clinical deterioration**

  In this regard, a new AIDS-defining diagnosis that was acquired after the time treatment was initiated suggests clinical deterioration but may or may not suggest failure of antiretroviral therapy. If the antiretroviral effect of the therapy was poor (e.g, <10-fold reduction in viral RNA), then the judgement of therapeutic failure could be made. However, if the antiretroviral effect was good but the patient was already severely immunosuppressed, the appearance of a new opportunistic infection may not necessarily reflect a failure of antiretroviral therapy, but rather a persistence of severe immunocompromise that did not improve despite adequate suppression of virus replication. Similarly, an accelerated decline in CD4+ T cell counts suggests progressive immune deficiency providing there are sufficient measurements to assure quality control of CD4+ T cell measurements.

CHANGING ANTIRETROVIRAL THERAPY – WHAT TO CHANGE TO? [4]

General Principles

Before any change of therapy is initiated, the indication or reason for change must always be borne in mind. The indication for change of therapy will determine the type of changes that need to be made.

It is preferable that antiretroviral agents that have been used before should not be used again. It is preferable that all components of the previous regimen be changed and antiretroviral agents with the least potential for cross-resistance with the previous agents be used as substitutes. If a complete change is not possible, change at least 2 drugs; one of which must include the protease inhibitor.

For adverse effects, intolerance or suboptimal adherence to an otherwise successful regimen (i.e. HIV RNA level below detectable limit), selective substitution of individual identifiable offending component is reasonable. Cross-resistance in this scenario maybe less important.

Suggested Empiric Regimens for Patients Who Failed Antiretroviral Therapy

Prior Regimen	New regimen
2 NRTIs + PI	, 2 new NRTIs plus • NNRTI or • Dual PI (RTV + SQV, RTV + IDV) * , Triple class regimen with : 1 – 2 new NRTIs plus 1 NNRTI plus 1 – 2 new PIs
2 NRTIs + NNRTI	2 new NRTIs plus 1 or 2 PIs
2 NRTIs or monotherapy	2 new NRTIs plus PI or NNRTI

Note : Never add 1 new drug to a failed regime

** Suggested dosages for double PI regimens:*
Ritonavir – 400mg bid + Saquinavir – 400mg bid
Ritonavir – 100 or 200mg bid + Indinavir 800mg bid

Potential Options For Changing Therapy
(IAS-USA Recommendation, JAMA 2000; 283-381)

Reason for Change	Change
Toxicity or intolerance:	
n HIV RNA suppressed below target	Change offending drug (if discernable)
n HIV RNA suppressed but still above target, and fewer than 16wk† on treatment‡	Change offending drug (if discernable)
n HIV RNA above target, more than 16wk† on therapy or prior success§	Change entire regimen
Difficulty with adherence:	
n HIV RNA suppressed below target, but adherence problem present	Change to simplified regimen with equal potency; may substitute single drug if the offending drug is identifiable.
n HIV RNA above target, but less than 8 – 16wk on therapy	Change to simplified regimen with equal potency; may substitute single drug if the offending drug is identifiable.
n HIV RNA above target, more than 8 – 16wk† with therapy or prior success§	Change entire regimen
Virologic failure:	
n Failure to reach target VL within 8 – 16wk† of therapy	Continue current regimen: assess adherence and consider intensification¶
n Failure to reach target VL within 24 – 36wk of therapy	Change entire regimen
n Prior success§ but now confirmed drug failure	Change entire regimen

§ *Prior success refers to patients who previously achieved target viral load but now have confirmed viral load above that target*

† *Actual time to achieve target viral load level (eg, HIV RNA< 50 copies/ml) varies depending on factors such as pretreatment HIV RNA level and regimen potency*

‡ *Attempts should be made to manage toxicity, but if unsuccessful, substitution of equally potent drug is appropriate. (Do not attempt this with suspected abacavir toxicity)*

¶ *For patients treated for 8 – 16wk with substantial reduction and continued decline in viral load (>1.5 $\log_{10}$ decrease) but still not reaching target viral load, intensification may be an option. Before using an intensification strategy, adherence must be carefully assessed.*

GUIDELINES FOR PAEDIATRICS

INTRODUCTION

In Malaysia, the number of HIV infections in women is rising and this trend appears to be reflected in the increasing number of perinatal cases. Perinatal transmission now accounts for most of the children acquiring HIV infection.

Much of the advances in HIV are based on studies carried out in adult patients and limited data obtained from children. However specific clinical trials are currently being carried out in children and they include studies on highly active antiretroviral therapy, viral load monitoring, immunomodulatory therapies and others. For instance, results from recent paediatric trials involving symptomatic antiretroviral-naive patients have demonstrated the superiority of combination therapy of either zidovudine and lamivudine or zidovudine and didanosine (ACTG 152) over monotherapy in terms of virologic and immunologic benefits. Results from the ACTG 338, a study conducted on antiretroviral experienced children, has demonstrated that combination therapy that include a protease inhibitor is virologically and immunologically superior to dual nucleoside combination therapy.

There are however unique considerations in perinatally acquired and paediatric HIV disease:

- most are thought to acquire the infection perinatally i.e. around the time of birth, and therefore raises the possibility of treatment at initial or primary infection
- the infection is acquired when the immune system is developing, thus clinical manifestations and the course of immunologic and virologic markers differ from adults
- treatment in the child will occur in the context of prior exposure to AZT and other antiretrovirals given to the mother as prophylaxis for perinatal transmission and maternal treatment
- differing pharmacokinetics from adults and that changes occur with growth and development
- issues of adherence are a special concern in children

DIAGNOSIS OF HIV INFECTION

In infants (perinatal infection)

For confirmation of positive status, need at least 2 positive tests (i.e. HIV RNA by PCR, p24 antigen, &/or viral culture) performed at separate intervals. The use of p24 antigen alone is not sufficient to diagnose infection in infants aged less than 1 month because of high frequency of false positive assays during this time. In Malaysia, diagnosis of HIV infection in infants is based on PCR technique measuring HIV RNA level. Viral culture is not a routine test as it is more complex and expensive to carry out.

In children of more than 18 months of age

Need at least 2 consecutive positive HIV antibody tests

Not infected (perinatal exposure)

Infection reasonably excluded (less than 18 month) : 2 negative virologic tests at less than 6 months of age, both done more than 1 month of age (one test to be done between 4 to 6 months)

: 2 negative serologic tests, both done at more than 6 months of age, at least 1 month apart, plus no clinical evidence of infection

Infection excluded : Negative serologic test

GOALS OF ANTIRETROVIRAL THERAPY

This would be to decrease viral replication as much as possible for as long as possible resulting in preservation or reconstitution of the immune system and diminishing viral dissemination thereby preventing disease progression and thus leading to improved quality of life and prolonged survival.

The specific results would include :

- general well being,
- optimising growth and development
- reduced opportunistic infections.

Therapeutic Strategy

The aim is to decrease the viral load to as low as possible.

This is achieved by using at least 2 antiretrovirals with no overlapping toxicity plus demonstrated antiviral synergy so as to maximise the length of the response.

Effective management of the diverse needs of the HIV infected infant or child and their families requires a multidisciplinary team approach in a family centred clinic that includes physicians, nurses, social workers, psychologists, dieticians, pharmacists and others.

Knowledge of HIV disease and therapy in children are rapidly evolving. Thus this guideline will need to be reviewed and updated as more advances in HIV infection in children occurs.

Category of Drugs

There are 3 main categories of drugs currently employed in HIV disease. These are the nucleoside reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs) (refer to Appendix A for Drug Details).

Drug Category	Agents	Comments
NRTI	Zidovudine (AZT) Didanosine (ddI) Zalcitabine (ddC) Stavudine (d4T) Lamivudine (3TC) Abacavir (ABC)	Ministry approved drugs that are available at MOH Hospitals : AZT, ddI, ddC, d4T, 3TC
NNRTI	Nevirapine (NVP) Delavirdine Efavirenz	Nevirapine is available as in the syrup form
PI	Ritonavir Nelfinavir Indinavir Saquinavir	Ritonavir is available in MOH Hospitals in the form of suspension and softgel capsule (SGC). Nelfinavir suspension is available. Saquinavir is available in SGC.

General Guidelines

As in adults, combination therapy is used in the treatment of all HIV children. Monotherapy is no longer recommended to treat HIV infection except for the first 6 weeks of life as chemoprophylaxis to prevent perinatal transmission.

The treatment should be tailored to individual needs and constraints.

In HIV infected children with suspected central nervous system (CNS) involvement, consideration should be given to include drugs with good CNS penetration such as zidovudine (AZT), stavudine (d4T) or nevirapine(NVP).

MONITORING DISEASE PROGRESSION

Monitoring of disease progression is currently through immunologic (CD4+), virologic (viral load), and clinical means. Laboratory monitoring is done at diagnosis and every 3-4 months, more often if change of therapy is made or progression of disease occurs.

Clinical

Regular (2 – 3 monthly) follow-up with careful clinical assessment includes evaluating growth and development and careful examination for signs and symptoms of disease progression (refer to Appendix C).

Immunologic (CD4+ T cell)

In infected children and adults, the CD4+ cell count declines as HIV infection progresses, and patients with lower CD4+ cell count have a poorer prognosis than patients with higher counts. It is useful to regard the CD4+ values as indicative of the level of immunosuppression. Recent data indicate that CD4+ percentage and HIV RNA-copy number used together can more accurately define prognosis.

CD4+ counts are age-dependent, being higher in infants and young children than in adults and slowly declining to adult values by 6 years. Therefore age-related definitions of immune suppression are applied (refer to Appendix C). A change in CD4+ percentage, not number, may be a better marker of identifying disease progression in children. Immunologic evidence of immunosuppression occurs when CD4+ percentage values approach <25%. Of concern also is a rapid and substantial drop in CD4+ percentage e.g. 35 to 25% or >30% in < 6 months.

Measurement of CD4+ cell values can be associated with considerable intrapatient variation. For example, intercurrent illness or vaccinations may produce a transient decrease in CD4+ T-cell values. Thus CD4+ measurements are best made when the child is clinically stable. Change or modification of therapy should therefore not be based on a single value but the change in CD4+ value should be substantiated by a second determination with at least 1 week interval between determinations.

HIV RNA concentration assays

Tests for quantification of HIV viraemia are available commercially in Malaysia but are expensive. Although it is recommended that every HIV infected individual be monitored using viral load assays, this may not be possible for the majority of our patients. The following however, are short notes on the tests available, their uses and interpretation:

- u Recent data show that the level of HIV RNA in the plasma accurately reflects the extent of virus replication. Mellors *et al* reported on the correlation of plasma HIV RNA level with disease progression and death and also provided conclusive evidence of the independence of viral load from CD4+ cell counts with regards to prognosis.

- u The HIV RNA pattern in perinatally infected infants differs from that in infected adults. High RNA copy numbers persist in infected children for prolonged periods. In one study[2] HIV RNA levels were generally low at birth (i.e. < 10,000copies/ml) increasing to high values by 2 months, most having > 100,000 copies/ml (range undetectable to nearly 10 million) and then decreasing slowly. After the first year of life, the load slowly declines over the next few years.

- u High HIV RNA levels in infants and children as in adults correlate with disease progression and death.

- u The methods include: RT-PCR and bDNA. Both are comparable with regard to reproducibility and physiologic variability. However these tests cannot be used interchangeably and one test should be used consistently for the same patient. Ideally, the test should be sent to the same laboratory.

Virologic Response

Changes greater than 5-fold (0.7 $\log_{10}$) in infants < 2 years and greater than 3-fold (0.5 $\log_{10}$) in children • 2 years after repeated testing should be considered a significant change. No alteration in therapy should be made as a result of a change in HIV copy number unless this change is confirmed by a second measurement.

COMMENCING ANTIRETROVIRAL THERAPY – WHEN TO START

Prerequisites

- v Intensive education of caregivers and patients about the importance of adherence to the prescribed treatment regimen should be provided before therapy is initiated so that
  - potential problems and solutions can be identified, and
  - frequent follow-up can be provided to assess virologic response to therapy, drug tolerance and adherence

- v Parents or caregivers should be ready to comply with the difficult regimens. Non-adherence to medication allows continued viral replication and encourages the emergence of drug resistance and subsequent treatment failure.

Indications for initiation of ARVT in children with HIV infection

- Clinical symptoms associated with HIV infection, ie. clinical categories A, B or C (refer to Appendix C)

- Evidence of immune suppression, indicated by CD4+ T-lymphocyte absolute number or percentage, ie. immune category 2 or 3 (refer to Appendix C)

- Age < 12 months – regardless of clinical, immunologic or virologic status*

- For asymptomatic children aged • 1 year with normal immune status, two options can be considered:
  - **Preferred approach** : Initiate therapy, regardless of age or symptom status
  - **Alternative approach** : Defer treatment in situations in which the risk for clinical disease progression is low and other factors (e.g. concern for the durability of response, safety and adherence) favour postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic and clinical status. Factors to be considered in deciding to initiate therapy include the following:
    - High or increasing HIV RNA copy number;
    - Rapidly declining CD4+ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression, i.e. immune category 2 (refer to Appendix C);
    - Development of clinical symptoms

** Clinical trial data documenting therapeutic benefit from this approach are not available, and information on drug dosing in neonates is limited. Because resistance to antiretroviral drugs (particularly protease inhibitors) can develop rapidly when drug concentrations fall below therapeutic levels (either as a result of inadequate dosage or incomplete adherence), issues associated with adherence should be fully assessed and discussed with the HIV-infected infant's caregivers before the decision to initiate therapy is made.*

COMMENCING ANTIRETROVIRAL THERAPY – WHAT TO START WITH

Combination therapy is recommended for all infants, children and adolescents who are treated with antiretroviral agents. Combination therapy
- slows disease progression and improves survival,
- results in greater and more sustained virologic response,
- delays development of virus mutations resistant to the drugs being used.

Monotherapy with the currently available antiretroviral drugs is no longer recommended.

Many factors are involved in choice of regimen
- availability of drugs,
- age-appropriate formulations of drugs,
- ability of care giver to comply with complex regimens,
- options available for subsequent treatment if initial regimen fails.

Recommended antiretroviral regimens for initial therapy for HIV infection in children

Preferred Regimen

Evidence of clinical benefit and sustained suppression of HIV RNA in clinical trials in HIV-infected adults; clinical trials in HIV-infected children are ongoing.

- One highly active protease inhibitor (PI) plus two nucleoside reverse transcriptase inhibitors (NRTIs).*
  - Protease Inhibitor (PI)
    - Preferred protease inhibitor for infants and children who cannot swallow pills or capsules: nelfinavir or ritonavir.
    - Alternative for children who can swallow pills or capsules: indinavir
  - Recommended dual NRTI combinations
    - The most data on use in children are available for the combinations of
      - zidovudine (AZT) and dideoxyinosine (ddI), and for
      - AZT and lamivudine (3TC).
    - More limited data are available for the combinations of
      - stavudine (d4T) and ddI,
      - d4T and 3TC, and
      - AZT and zalcitabine (ddC).
  - Examples of these combinations:

NRTI		PI
AZT + ddI		Ritonavir
AZT + 3TC		Indinavir
D4T + 3TC	+	Nelfinavir
AZT + ddC		
D4T + ddI		

- Alternatives for children who can swallow capsules:
  - Efavirenz plus 2 NRTIs
    OR
  - Efavirenz plus Nelfinavir and 1 NRTI.

Alternative Regimen

Less likely to produce sustained HIV RNA suppression in infected patients

- Nevirapine plus 2 NRTIs (AZT + ddI*; AZT + 3TC; D4T + 3TC)
- Abacavir + AZT + 3TC

**(the combination of nevirapine, AZT and ddI produced substantial and sustained suppression of viral replication in two of six infants first treated at age < 4 months)*

Offer only in Special Circumstances

- 2 NRTIs

Not Recommended

Evidence against use because of overlapping toxicity and/or because use may be virologically undesirable.

- Any monotherapy
- d4T and AZT
- ddC and ddI
- ddC and d4T
- ddC and 3TC

CHANGING ANTIRETROVIRAL THERAPY – WHEN TO CHANGE

The following reasons may warrant a need to change antiretroviral therapy:
- treatment failure due to development of viral resistance
- adverse drugs reactions

Adherence problems that may potentially contribute to treatment failure should be addressed and education regarding adherence to the therapy and training in the administration of the prescribed medications should be offered prior to initiation of the new therapy.

The indications for changing antiretroviral therapy is a failure of the current regimen with evidence of disease progression based on clinical, immunologic and virologic parameters :

- **Clinical parameters** warranting a change in therapy are progressive neurodevelopment deterioration, growth failure and disease progression i.e. progression from one clinical category to another based on the CDC 1994 paediatric classification according to the clinical categories.

- **Immunologic parameters** that may warrant a change in therapy include change in immune classification, a persistent decline of five percentile or more in the CD4+ cell percentage in patients with severe immune suppression (as per CDC 1994 classification), and a rapid and significant decrease in CD4+ count.

- **Virologic parameters** for initiating a new therapy include less than a minimally acceptable virologic response after 8-12 weeks of therapy (< 10-fold decrease in viral load from baseline in children receiving 2 NRTIs and a protease inhibitor, and < 5-fold decrease in children receiving two NRTIs), and persistent detectable HIV RNA in children who initially responded with undetectable HIV RNA.

CHANGING ANTIRETROVIRAL THERAPY – WHAT TO CHANGE TO

There are limited paediatric data on alternative antiretroviral drugs currently available. However, some principles can be followed to make new drug therapy decisions in antiretroviral experienced HIV-infected children:

- When therapy is changed because of drug toxicity, drugs with different toxicity and side-effect profiles should be chosen.

- Adherence problems should be fully assessed as a potential cause of treatment failure and emphasis on adherence to the new regimen should be stressed.

- If drug resistance is suspected, change at least two drugs to new agents and the new regimen should include at least three drugs, if possible. Change in one drug or addition of a new drug to a failing regimen is considered suboptimal[15].

- Possible drug interactions and the patient's quality of life should also be considered in the new regimen before therapy is changed in those with advanced disease.

Possible Treatment Options for ART-Experienced Patients

Previous Regimen	Options
2 NRTIs	• 2 New NRTIs* and PI ± NNRTI • 2 New NRTIs and dual PI**
2 NRTIs and NNRTI	• 2 New NRTIs and PI • 2 New NRTIs and dual PI**
2 NRTIs and nelfinavir	• 2 New NRTIs and ritonavir + saquinavir** • 2 New NRTIs and indinavir + NNRTI
2 NRTIs and ritonavir	• 2 New NRTIs and ritonavir + saquinavir** • 2 New NRTIs and amprenavir + nevirapine

*

Initial NRTIs	*New NRTIs*
AZT + 3TC	*d4T + ddI*
AZT + ddI	*d4T + 3TC*
D4T + 3TC	*AZT + ddI*
D4T + ddI	*AZT +3TC*

*** Pharmacokinetic data on dual protease inhibitor (PI) combinations is not available for children. Based on adult data, when used with ritonavir, saquinavir SGC might be given 20 – 30 mg/kg q 12h up to 400mg q 12h. Additional dual PI combinations (nelfinavir + indinavir, nelfinavir + ritonavir, indinavir + ritonavir) are being evaluated in adults, but pharmacologic indications should be determined in children before dosing can be determined.*

ISSUES

- Long term adverse effects of new antiretrovirals especially in children may not yet be completely defined.
- Measures should be taken to ensure greater availability of highly active antiretrovirals to all HIV infected patients in Malaysia
- The provision of viral load monitoring should also be made more accessible to infected patients.

ADDRESSING ADHERENCE ISSUES [12,13,16]

INTRODUCTION

Multiple studies have demonstrated that approximately 50% of all patients, across a wide range of diseases, therapies and individual characteristics, are non-compliant with prescribed treatment regimens. An ACTG study of 76 patients on combination HIV therapy showed that 36% of them missed at least 1 dose within the two weeks prior to the study. Even more worrying, this study was carried out on patients who were early in the course of therapy, when adherence is expected to be best.

Adherence is now recognized as an important issue in antiretroviral therapy. It has been highlighted in the International AIDS Society – USA Guidelines, which state that,

"the ability to maintain long term adherence is a major challenge. Less than excellent adherence may result in virus breakthrough & emergence of drug resistant strains. Even short term non-adherence can lead to virus repopulating in lymph nodes."

In HIV infection, patients are expected to take extremely complex regimens of therapy for prolonged periods of time without the guarantee that such therapy will ultimately be effective in preventing disability or death. This makes it even more difficult to ensure adherence.

This guideline has been prepared to remind doctors of the importance of adherence and the need to discuss thoroughly with the patient this aspect before actually embarking on treatment. It is hoped that the recommendations will help doctors to make successful adherence an achievable goal. Multiple factors have been identified as associated with non-adherence.

In Malaysia, the scenario is different from that in the USA and other developed countries. Lack of finances is a major problem here. Another major issue is the stigma surrounding the disease. This makes secrecy an important factor, causing patients to lack support systems and making the availability of a "safe space" in the workplace and elsewhere a problem. Judgmental attitudes among health care workers are still prevalent.

Therefore, strategies required must target not just the patient, the physician and the treatment regime but also the general community and health care system.

PATIENT FACTORS

Determinants	Strategies
1. Severity of disease and perceived value of therapy ("Health Belief Model").	Empower patient by: a.) patient education related to the disease, the importance of adherence & resistance to therapy. b.) giving pre-written materials with information regarding the drugs they will be on, why therapy is of benefit and why it is being prescribed. Allow for notes to be written by patient during his visit (it has been found that much of what is discussed during the visit is quickly forgotten).
2. Substance abuse, altered mood, poor coping skills, psychiatric illness.	To take this aspect of the patient seriously by a.) referral to appropriate rehabilitation centers, mental health professionals or social service agencies/ NGOs. In order to maximize antiretroviral treatment benefits, substance abuse has to be kept to a 'controllable' level. b.) providing ongoing counseling by health care providers at every clinic meeting.
3. Complexity of regime holidays. dosing agents, based on available therapy.	a.) Close follow-up after initiation of therapy, to sort out problems as they arise and not wait for usual appointment to discuss problems. b.) Ensure that patient truly understands the prescribed regime – v translate if language is a barrier, v use precise terms. e.g. "every 8 hours" rather than "three times a day." c.) Help patient cue pill taking with other routine activities (e.g.: brushing teeth in the morning). d.) Help patient develop special routine for pill taking during changes in normal schedule, e.g. during weekends & e.) Help patient develop simple cards (e.g. color coded cards) showing appearance, timings & number of pills to take. f.) Suggest pill timers, e.g. alarms on watches. g.) Construct regime using minimum number of drugs, when possible, e.g. combination pills & once or twice daily h.) monitoring of treatment progress by patient, e.g. patient to participate in their healthcare by keeping record of their CD4 / viral load counts, weight, nutritional intake, sleep pattern, etc.

4. Decreased social support	a.) Human support within the healthcare team: i) give positive reinforcement (inform patient if CD4 count rise, or viral load drops). ii) give assistance in organizing pill-taking routine. iii) give contact number/ person to approach outside normal appointments. iv) have member of team available to answer questions regarding pill taking schedules or problems with drugs (e.g. the clinic nurse or receptionist). b.) Support within family and work environment: i) help patient break news of diagnosis to family if he/she wishes to. ii) have at least one session with the family, to discuss ways of helping the patient & to allay their fears and clear misconceptions regarding the disease. iii) discuss with family, methods to help with adherence, e.g. reminding patient about his/her medications. iv) support within the work environment is more difficult due to confidentiality. However, if there is a sympathetic friend/ colleague/ office nurse, who is aware of patient's diagnosis, then to include him/her in the discussion. v) provide safe space for rest and privacy in taking medications
5. Influence of alternative therapies and religion. exposure.	a.) Encourage disclosure and discussion between patient & physician so that proper advice can be given on alternative therapies. Many patients spend much of their savings on so-called "cures" & have no money left for therapy. To facilitate open discussion with patient to help them make informed choices & decisions. b.) Establish humane approach from various religious organizations towards patients, so that emotional & psychological support is available – can be facilitated by educating religious workers on disease & methods of
6. Lack of financial support to purchase therapy	a.) Explore financial options with the patient such as EPF, SOCSO, insurance policies, social welfare allowance, family health allowance, etc. b.) Assist patient in getting access from available options (e.g. liaising with EPF/ SOCSO officials, social welfare agencies & NGOs, etc.). c.) To help patient discuss with family members who can assist financially

7. Special paediatric concerns	a. These issues need special consideration : i) Disclosure of diagnosis to paediatric patient ii) Disclosure of diagnosis to baby-sitter/ school b. Discuss the issues listed below prior to starting therapy in older children as adherence may be lacking if they do not understand the need for treatment. Also include caregivers other than parents. i) children refusing to take medications – how to avoid this ii) non-palatable drugs – how to disguise the taste iii) frequent blood taking to monitor progress – parents need to understand this iv) abandoned children – who is responsible v) coping skills of caregivers – set up parent support groups within the clinic cohort etc

CAREGIVER FACTORS

Determinants	Strategies
1. Knowledge/ experience.	a.) More specialized training for staff concerned. b.) Co-management of patients between various caregivers with various skills. c.) Accreditation to centers/ physicians who treat patients with complex antiretroviral regime – an issue to be considered.
2. Attitude of caregivers. by providing adequate education and exposure of health care personnel.	Staff should be trained to be empathetic and non-judgmental
3. Practical skills/ approaches.	a.) Train staff to carry out approaches, such as: i) giving proper instructions to patients (verbal & written), ii) helping patient plan daily routine, iii) incorporating dosage cues, iv) helping patient prepare color coded cards, timers, pill diaries etc, v) giving continuous counseling on medication & side effects, vi) giving positive feedback for successful adherence, vii) identification of non-adherent patients by discussion, viii) carrying out defaulter tracing & reminding patients about appointments & purchasing medications, ix) being accessible to patients via contact numbers, etc. b.) Providing retreat and support groups for caregivers. c.) Review existing technical systems e.g. laboratory problems, such as missing specimens and results.

SOCIAL / ENVIRONMENTAL FACTORS

Determinants	Strategies
1. Family awareness/ knowledge.	a.) Assist patient in informing family, if desired. b.) Counsel family regarding all aspects of disease. c.) Counsel family on methods of ensuring adherence by giving continuous support, taking active part in patient care & providing financial assistance, when needed.
2. Peer / buddy support.	a.) To set up peer support groups i) within the clinic cohort, ii) by NGOs/community based groups, iii) among patients on therapy. b.) Provide up to date information to patients via these groups. c.) To do counseling and outreach programs via these groups through help- line service and face-to-face counseling.
3. The community as a whole	Increase knowledge and awareness of the general public: i) through public awareness campaigns, forums, seminars, talks etc. ii) through media campaigns presented with a local flavor. iii) with special emphasis on schools & colleges. iv) by ensuring rural population is reached. v) through sufficient information disseminated in vernacular languages. vi) by providing community centers for patients affected by the illness, and halfway homes/ respite care for those in need. NGO involvement is to be encouraged.

HEALTH CARE SYSTEMS

Determinants	Strategies
1. Multidisciplinary approach. friendly to minimize the number of hospital visits & lifestyle interruptions.	a.) Coordinate various disciplines involved, e.g. physician, paediatrician, obstetrician, physiotherapist, dietitian, social worker, etc. The approach should be flexible & user b.) Provide continuity of care from hospital to community, e.g. when a patient is discharged, a community nurse/ NGO worker should be informed for follow-up care. Liaison workers are required for this. c.) Ensure that the information provided to the patient is consistent from one health care worker to another.
2. Evaluation of programs.	There should be : a.) evaluation of all educational programs by health care providers so as to improve the quality of education. b.) ongoing communication between health care system providers, policy makers and PWHAs to ensure all needs are met as best as possible.
3. Needs of Healthcare Worker	To provide care and support to HCWs through supervision, regular meetings, discussion and feedback

CONCLUSION

It is hoped that these strategies, once implemented will help patients adhere to their drug regimes. However, no two patients are alike and all patients need to be assessed individually with regimes tailored to their needs.

The health care provider needs to be committed to helping the patient to be adherent. There needs to be close coordination between patients, caregivers, NGOs and the government, to implement these strategies. No matter how effective the drugs that are available, we need to remember that,

" drugs don't work if people don't take them," and in the case of antiretroviral therapy, " take them correctly".

Guidelines for Post-exposure Prophylaxis [17]

INTRODUCTION

Occupational exposure to HIV among health care workers is an increasingly common problem as the incidence and prevalence of HIV infection in Malaysia continues to increase. Prevention of occupational exposure is a challenge that must be addressed in virtually every medical setting. Despite scrupulous attention to infection control practices, health care workers remain at some risk for exposure. Developing strategies to manage exposed persons is therefore an important priority in every health care setting. Post-exposure care must encompass two main goals 1) to prevent HIV infection among those sustaining exposure 2) to provide information and support during the follow-up interval until infection is diagnosed or excluded with certainty.

Risk for occupational transmission of HIV to HCWs

Prospective studies of HCWs have estimated that the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood is approximately 0.3% (95% CI=0.2-0.5%) and after mucous membrane exposure is 0.09% (95% CI=0.0006-0.5%). The risk is dependent upon factors such as the type of body fluid involved, the type of exposure that has occurred, the volume of fluid involved and the disease stage, and therefore the viral load of the source patient.

Efficacy of post exposure prophylaxis

Studies in animals and humans provide direct and indirect evidence of the efficacy of antiretroviral drugs as agents for post exposure prophylaxis (PEP). There is little direct evidence with which to assess the efficacy of PEP in humans. No prospective studies have been performed and based on the current indirect evidence of PEP efficacy it is unlikely that a placebo-control trial will be performed to demonstrate the efficacy of PEP.

In a retrospective case-control study of HCWs, after controlling for other risk factors for HIV transmission, the risk for HIV infection among HCWs who used Zidovudine as PEP was reduced by approximately 81% (95% CI=43-94%). It should be noted that only a small number of cases were included in this study and the cases and controls were from different cohorts. Failure of zidovudine PEP to prevent HIV infection in HCWs has been reported in at least 14 instances.

Antiretroviral agents for PEP

At present, zidovudine (AZT) is the only agent shown to prevent HIV transmission in humans. There are no data to directly support the addition of other antiretroviral drugs to zidovudine to enhance the effectiveness of the PEP regime. However in HIV infected individuals, combination regimens have proved superior to monotherapy regimens in reducing HIV viral load. Therefore theoretically, a combination of drugs with activity at different stages of the viral replication cycle could offer an additive preventive effect in PEP, particularly for occupational exposures that pose an increased risk for transmission.

Recommendations for the management of potentially exposed HCWs

Every health care setting need to establish a system for prompt reporting, evaluation, counseling, treatment and follow-up of occupational exposures that may place HCWs at risk for acquiring bloodborne infection. Access to clinicians who can provide post exposure care and to the antiretroviral agents for PEP should be readily available.

Exposure management

Immediate post exposure care should emphasize the importance of decontaminating the exposed site as soon as possible. Wounds and skin sites that have been in contact with blood or body fluids should be washed with soap and water; and mucous membranes should be flushed with water. There is no evidence that the use of antiseptics for wound care or expressing fluid by squeezing the wound further reduces the risk for HIV transmission.

Assessment of Infection Risk

After an occupational exposure, the source-person and the exposed HCW should be evaluated to determine the need for HIV PEP. Follow-up for hepatitis B and C virus infections should also be conducted.

Evaluation of exposure

The exposure should be evaluated for potential to transmit HIV based on the type of body substance involved and the route and severity of the exposure. Exposures to blood, fluid containing visible blood or other potentially infectious fluid (e.g. semen, vaginal secretions, cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids) or tissue through percutaneous injury (e.g. needlestick) or through contact with mucous membrane are situations that pose a risk for bloodborne transmission. For skin exposures, follow-up is indicated if it involves direct contact with body fluid as described above and there is evidence of compromised skin integrity.

Evaluation and testing of exposure source

The person whose blood or body fluids are the source of an occupational exposure should be evaluated for HIV infection. If the source is known to have HIV infection, the person's stage of infection and the antiretroviral history should be assessed. If the exposure source is unknown, information about where and under what circumstances the exposure occurred should be assessed epidemiologically for risk for transmission of HIV.

SELECTION FACTORS – BASIC VS EXPANDED PEP REGIMEN

Factors in selection of a PEP regimen

Selection of the PEP regimen should be based on the comparative risk represented by the exposure and information about the source. Most exposures will only require a two-drug regimen using 2 NRTIs. The addition of a third drug, usually a PI should be considered where there is a very high risk for transmission or where drug resistance is suspected.

PEP should be initiated as soon as possible. The interval after which PEP has no benefit has not been defined in human. PEP can be considered even up to 7 days in high risk cases.

PEP Recommendation – Basic and Expanded PEP regime

Regimen Category	Application	Drug Regimen
Basic 2NRTI doses,	Occupational exposure for which there is a recognized transmission risk	4 weeks (28 days) of zidovudine 600 mg/day in divided doses *plus* lamivudine 150mg twice a day
Expanded 2 NRTI + PI	Occupational HIV exposure that poses an increased risk for transmission (e.g. larger volume of blood and/or higher virus titer in blood)	Basic regimen *plus* indinavir 800mg every 8 hours*

**In cases of intolerance to indinavir, efavirenz can be considered*

Occupational exposure to treatment experienced patients

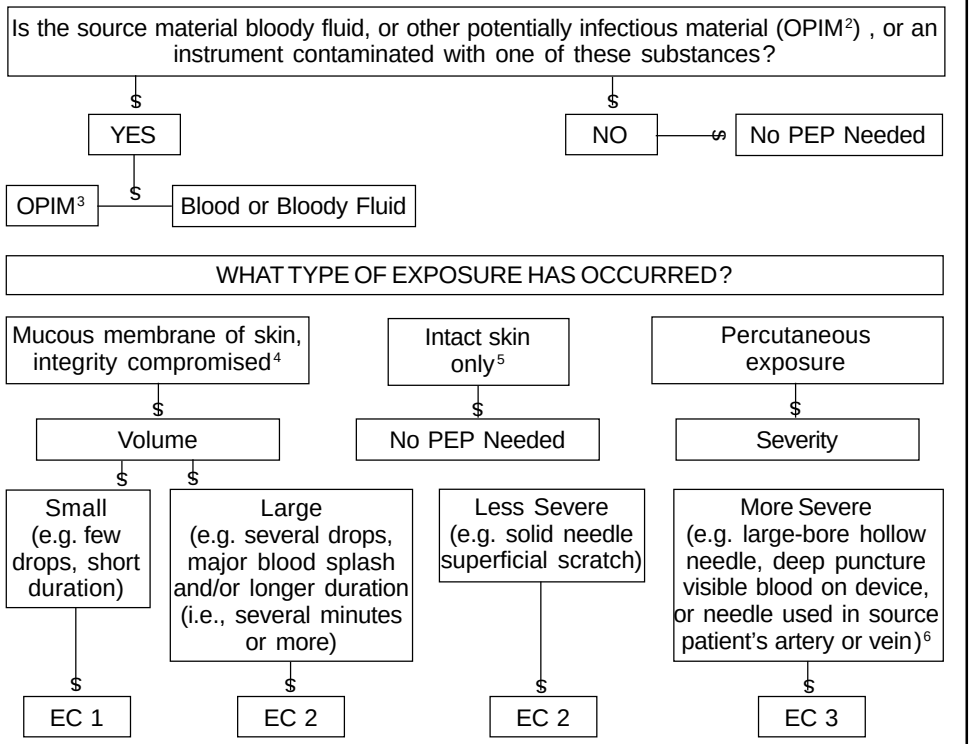
When the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended; expert consultation is advised. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes in the PEP regimen can be made after PEP has been started, as appropriate. Re-evaluation of the exposed person should be considered within 72 hours post exposure, especially as additional information about exposure or source person becomes available.

STRATIFICATION OF RISK OF TRANSMISSION

Determining the need for HIV post-exposure prophylaxis (PEP) after an occupational expose [1]

(Adapted from Center for Disease Control and Prevention. Public Health Service Guidelines for the Management of Healthcare Worker Exposure to HIV and Recommendations for Post exposure Prophylaxis. MMWR 1988;47 (No.RR-7) : 1-35)

Step 1 : Determine the Exposure Code (EC)



1 *This algorithm is intended to guide initial decisions about PEP and should be used in conjunction with other guidance provided in this report.*

2 *Semen or vaginal secretions; cerebrospinal, synovial, pleural, peritoneal, pericardial, or amniotic fluids; or tissue.*

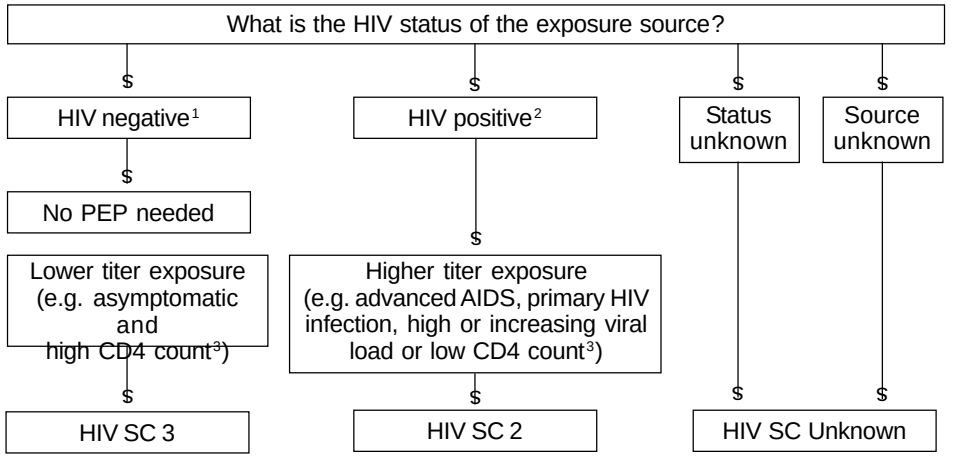
3 *Exposures to OPIM must be evaluated on a case-by-case basis. In general, these body substances are considered a low risk for transmission in health-care settings. Any unprotected contact to concentrated HIV in a research laboratory or production facility is considered an occupational exposure that requires clinical evaluation to determine the need for PEP.*

4 *Skin integrity is considered compromised if there is evidence of chapped skin, dermatitis, abrasion, or open wound.*

5 *Contact with intact skin is not normally considered a risk for HIV transmission. However, if the exposure was to blood, and the circumstance suggests a higher volume exposure, (e.g. an extensive area of skin was exposed or there was prolonged contact with blood), the risk for HIV transmission should be considered.*

6 *The combination of these severity factors (e.g. large-bore hollow needle and deep puncture) contribute to an elevated risk for transmission if the source person is HIV-positive.*

Step 2 : Determine the HIV Status Code (HIV SC)



1 A source is considered negative for HIV infection if there is laboratory documentation of a negative HIV antibody, HIV polymerase chain reaction (PCR). Or HIV p24 antigen test result from a specimen collected at or near the time of exposure and there is no clinical evidence of recent retroviral-like illness.

2 A source is considered infected with HIV (HIV positive) if more has been a positive laboratory result for HIV antibody, HIV PCR, or HIV p24 antigen or physician-diagnosed AIDS.

3 Examples are used as surrogates to estimate the HIV titer in an exposure source for purposes of considering PEP regimens and do not reflect all clinical situations that may be observed. Although a high HIV titer (HIV SC 2) in an exposure source has been associated with an increased risk for transmission, the possibility of transmission from a source with a low HIV titer also must be considered.

Step 3 : Determine the PEP Recommendation

Codes	**Suggested Regimen**
Low Risk (EC1, SC1)	No treatment Monotherapy in selected circumstances
Medium risk (EC1, SC2) (EC2, SC1)	**2NRTI** (Basic regimen)
High risk (EC2, SC2) (EC3, SC1 or 2)	**2 NRTI + PI** (Expanded regimen)
Unknown source or status (Risk for exposure high)	**Monotherapy or 2 NRTI**

Follow-up of HCWs exposed to HIV

POST-EXPOSURE TESTING

HCWs with occupational exposure to HIV should receive counseling, post exposure testing, and medical evaluation regardless of whether they receive PEP. HIV-antibody testing should be performed for at least 6 months post exposure (e.g. 6 weeks, 12 weeks and 6 months)

Monitoring and Management of PEP Toxicity

If PEP is used, drug-toxicity assessment should be performed at baseline and again 2 weeks after starting PEP. Tests should include full blood count, renal liver function tests. Monitoring for hyperglycemia should be included for HCWs whose PEP regimen includes a PI.

Counseling and Education

Although seroconversion following occupational exposure to HIV rarely occurs, the emotional impact of the exposure is often substantial. Therefore access to persons knowledgeable about occupational HIV transmission and who can deal with the many concerns raised is an important element of management.

HCWs should be advised to adopt measures to prevent secondary transmission during the first 6 – 12 week period after exposure. Prevention of sexual transmission, pregnancy and donation of tissue organs and body fluids should be advised. Discontinuation of breast-feeding should also be considered.

Exposed HCWs who choose to take PEP should be advised of the importance of adherence and completion of the prescribed regimen.

APPENDICES

APPENDIX A[14,15,16]

Antiretroviral Drugs Fact Sheet

I. Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Didanosine (ddI) VIDEX Preparations: Paediatric powder for oral solution (must be mixed with antacid): 10mg/ml Chewable tablets with buffers: 25mg, 50mg, 100mg & 150mg Buffered powder for oral solution: 100mg,167mg & 250mg	_____ _____ _____ _____ _____ _____		Possible decrease in absorption of ketoconazole, itraconazole; administer at least 2 hrs before or 2 hrs after ddI. Ganciclovir may increase peak levels of ddI and predispose to toxicity. Administration with protease inhibitors: Indinavir should be administered at least one hour apart from ddI on an empty stomach. Ritonavir should be administered at least 2 hours apart from ddI.	ddI formulation contains buffering agents or antacids. Food decreases absorption: administer ddI on an empty stomach (1 hr before or 2 hrs after a meal). For oral solution: Shake well, and keep refrigerated; admixture stable for 30 days. When administering chewable tablets, at least two tablets should be given to ensure adequate buffering capacity (eg. if the child's dose is 50 mg, administer two 25 mg tablets and not one 50 mg tablet).
Lamivudine (3TC) EPIVIR Preparation: Solution: 10 mg/ml Tablets: 150 mg	Paediatric Dose 4 mg/kg q 12h Neonatal Dose (< 30 days old) Under study in clinical trials: 2 mg/kg q 12H Adolescent/ Adult Dose 150 mg bid	Most frequent: Headache, fatigue, nausea, diarrhea, skin rash, abdominal pain Unusual (more severe): Pancreatitis, neutropenia, increased liver enzymes	TMP/SMX increases lamivudine blood levels; unknown significance. When used with ZDV may prevent emergence of resistance.	Can be given with food. For oral solution: Store at room temperature. Decreased dosage in patients with impaired renal function.

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Stavudine (d4T) ZERIT Preparations Solution: 1mg/ml Capsules: 15mg, 20mg, 30mg & 40mg	Paediatric Dose: 1 mg/kg q12H (up to weight of 30 kg) Neonatal Dose Under evaluation Adolescent/ Adult Dose (60 kg: 40 mg bid 30-60 kg: 30 mg bid	Most frequent: Headache, GI disturbances, skin rashes Uncommon (more severe): Peripheral neuropathy, pancreatitis Other: Increased liver enzymes	Drugs that decrease renal function could decrease clearance. Should not be administered in combination with zidovudine (poor antiretroviral effect).	Can be given with food. Reduce dose in renal impairment. For oral solution: Shake well and keep refrigerated; Solution stable for 30 days.
Zalcitabine (ddC) HIVID Preparations Tablets: 0.375mg & 0.75mg	Usual Dose 0.01 mg/kg q8H Dosage Range 0.005 – 0.01 mg/kg q8H Neonatal Dose Unknown Adolescent/ Adult Dose 0.75 mg tid	Most frequent: Headache, malaise Unusual (more severe) Peripheral neuropathy, pancreatitis, hepatic toxicity, skin rashes, oral ulcers, esophageal ulcers, hematologic toxicity	Cimetidine, amphotericin, foscarnet & aminoglycosides may decrease renal clearance of ddC. Antacids may decrease absorption. Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy.	Give on an empty stomach (1 hour before or 2 hours after a meal). Decrease dosage in impaired renal function.
Zidovudine (AZT) RETROVIR Preparations Syrup: 10 mg/ml Capsules: 25mg, 100 mg & 250mg Tablets: 100mg & 300 mg Concentrate for i.v. infusion/ injection: 10 mg/ml	Usual Dose Oral: 160 mg/m^2 q8H I.V. (intermittent infusion) 120 mg/m^2 q6H I.V. (continuous infusion) 20 mg/m^2/h Dosage Range 90-180 mg/m^2 q6-8H Neonatal Dose Oral: 2 mg/kg q6H I.V. : 1.5 mg/kg q6H Dose in Premature Infants Under study in PACTG 331: 1.5 mg/kg q12H from birth to 2 weeks of age; then increase to 2 mg/kg q8H after 2 weeks of age. Adolescent/ Adult Dose 200 mg tid or 300 mg bid	Most frequent: Hematologic toxicity, including neutropenia, anemia & headache. Unusual: Myopathy, myositis, liver toxicity	Increased toxicity may be observed with concomitant administration of ganciclovir, TMP-SMX, acyclovir, interferon-alpha Decreased renal clearance with cimetidine Fluconazole interferes with metabolism & clearance of ZDV ZDV metabolism may be increased with coadministration with rifampin & rifabutin; clarithromycin decreases concentration of ZDV (administer 4 hrs apart) Phenytoin concentration may increase or decrease. Should not be administered with d4T (poor antiretroviral effect).	Can be administered with food. Decrease dosage in severe renal impairment. Significant neutropenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary. Reduced dosage in significant hepatic dysfunction. Infuse loading doses & i.v. doses over 1 hr. Dilute with D5W to conc. < 4 mg/ml. For i.v. solution: Refrigerated diluted solution stable for 24 hrs.

II. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Nevirapine VIRAMUNE Preparations Suspension: 10 mg/ml (investigational) Tablets: 200 mg	Dose 120-200 mg/m^2 q12H Initiate therapy 120 mg/m^2 given once daily for 14 days. Increase to full dose administered q12H if no rash or untoward effects. Neonatal Dose (through 3 months) Under study in PACTG 356: 5 mg/kg once daily for 14 days, followed by 120 mg/m^2 q12H for 14 days, followed by 200 mg/m^2 q12H Adolescent/ Adult Dose 200 mg q12H Initiate therapy at half dose for the first 14 days. Increase to full dose if no rash or other untoward effects.	Most frequent: Skin rash (some severe), sedative effect, headache, diarrhea, nausea. Unusual: Elevated liver enzymes, rarely hepatitis	Induces hepatic cytochrome P450 3A (CYP3A); auto-induction of metabolism occurs in 2-4 weeks with a 1.5-2 times increase in clearance. Potential for multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Administration with protease inhibitors decreases indinavir concentrations significantly; may also decrease ritonavir concentration. Not known if increased doses of protease inhibitors are needed.	Can be given with food. May be administered concurrently with ddI. For investigational suspension: Must be shaken well; store at room temperature.
Efavirenz STOCRIN Preparations Capsules: 50mg, 100mg & 200mg	Usual Dose: In PI &/or NRTI combination, 600mg od Children (17yrs & under): 13-15kg 200mg 15-20kg 250mg 20-25kg 300mg 25-32.5kg 350mg 32.5-40kg 400mg Children above 40kg to use adult dose	Most frequent: Rash, nausea, dizziness, diarrhea, headache & insomnia Contraindicated with: Terfenadine, Astemizole, Cisapride, Midazolam, & Trizolam	Inducer of CYP3A4 As indinavir levels are decreased when coadministered, the dose of indinavir needs to be increased to 1000mg q8hrs when taken with STOCRIN. Monitoring of liver enzymes recommended when given together with ritonavir. Use with saquinavir as the sole PI is NOT recommended.	To improve tolerability, bedtime dosing recommended during the first 2-4 weeks. May be taken with or without food. Pregnancy should be avoided in women receiving STOCRIN; barrier contraception, in combination with other contracep-tion methods should be considered.

III. Protease Inhibitors

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Indinavir CRIXIVAN Preparations Capsules: 200mg & 400 mg	Dose Investigational: 500 mg/m^2 q8H Neonatal Dose Unknown Adolescent/ Adult Dose 800 mg q8H	Most frequent: Nausea, abdominal pain, headache, asymptomatic hyperbilirubinemia (10%) Unusual (more severe) Nephrolithiasis. Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia and diabetes	Cytochrome P450 3A4 responsible for metabolism. Potential for multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Not recommended for concurrent use: Indinavir increases the drug's metabolism, resulting in increased drug levels & potential toxicity: astemizole, terfenadine, cisapride, midazolam. Indinavir levels significantly reduced with concurrent use: Rifampin. Clarithromycin coadministration increases serum concentration of both drugs. Nevirapine coadministration may decrease indinavir serum concentration. Administration with other protease inhibitors: ritonavir decreases the metabolism of indinavir & results in greatly increased indinavir concentrations.	Administer on an empty stomach 1 hour before or 2 hours after a meal. Adequate hydration required to minimize risk of nephrolithiasis. If coadministered with ddI, give at least 2 hours apart on an empty stomach. Decrease dose in patients with cirrhosis. Capsules are sensitive to moisture & should be stored in original container with dessicant.

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Nelfinavir VIRACEPT Preparations Powder for oral suspension: 50 mg per one level scoop (200 mg per one level teaspoon) Capsules: 250 mg	Dose 20-30 mg/kg tid Neonatal Dose Under study in PACTG 353: 10 mg/kg tid (investigational) Adolescent/ Adult Dose 750 mg tid	Most frequent: Diarrhea Less common: Asthenia, abdominal pain, rash Rare: Hyperglycemia & diabetes	In part metabolized by cytochrome P450 3A4. Potential for multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Not recommended for concurrent use: Astemizole, terfenadine, cisapride, midazolam. Nelfinavir levels are greatly reduced with concurrent use: Rifampin. Administration with other protease inhibitors: nelfinavir increases levels of indinavir; coadministration with ritonavir increases nelfinavir levels 1.5 fold, without change in ritonavir concentrations.	Administer with meal or light snack. For oral solution: Powder may be mixed with water, milk, pudding, ice cream, or formula (for up to 6 hours). Do not mixed with any acidic food or juice because of resulting poor taste. Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes. Tablets readily dissolve in water & produce a dispersion that can be mixed with milk, chocolate milk; tablets can also be crushed & administered with pudding.

DRUG	DOSAGE	MAJOR TOXICITIES	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Ritonavir NORVIR Preparations Oral solution: 80 mg/ml Capsules: 100 mg	Dose 400 mg/m^2 q12H To minimize nausea/ vomiting, initiate therapy at 250 mg/m^2 q12H & increase stepwise to full dose over 5 days as tolerated. Dosage Range 350-400 mg/m^2 q12H Neonatal Dose Under study in PACTG 354. Adolescent/ Adult Dose 600 mg q12H Most frequent:	Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia. Less common: Circumoral paresthesias, increase in liver enzymes. Rare: Spontaneous bleeding episodes in hemophiliacs, Pancreatitis, increased levels of triglycerides & cholesterol, hyperglycemia & diabetes Extensively	metabolized in the liver by CYP3A. Potential for multiple drug interactions. Ritonavir decreases levels of sulfamethoxazole. Increases metabolism of theophylline levels. Increases levels of warfarin & clarithromycin. May increase or decrease digoxin levels. Administration with other protease inhibitors: decreases the metabolism of indinavir & saquinavir & results in greatly increased concentrations of these drugs; increases nelfinavir concentration 1.5 -fold. For full details of drug interactions, consult product insert.	Administration with food increases absorption. If administered with ddI should be administered 2 hours apart. Oral capsules must be kept refrigerated. For oral solution: Must be kept refrigerated & stored in original container; can be kept at room temperature if used within 30 days. To minimize nausea, therapy should be initiated at a low dose & increase to full dose over 5 days as tolerated. Techniques to increase tolerance: Mix oral solution with milk, chocolate milk, ice cream. Dulling the taste buds before administration by chewing ice.
Saquinavir INVIRASE (hard capsule) FORTOVASE (soft-gel capsule) Preparations Capsule: 200mg	Usual Dose: Adolescent/ Adult Dose: 1200mg tid (Fortovase) 600mg tid (Invirase) in PI combination, 400mg bid (Invirase)	Most frequent: Diarrhea, nausea, headache & rash	Drugs that induce CYP3A4 may reduce saquinavir levels. Rifampicin reduces saquinavir levels greatly and should not be used in combination. Contraindicated Drugs: Terfenadine, Astemizole, Cisapride, Ergot Alkaloids, Trizolam, Midazolam, Rifampin. Drugs that increase saquinavir levels: Ritonavir, Ketoconazole, Nelfinavir, Delavirdine.	Administer with meal (high fat meal preferred)

APPENDIX B

1993 Revised Classification System For HIV Infection And Expanded Surveillance Case Definition For AIDS Among Adults And Adolescents[2]

CD4+ Cell Category	Clinical Category A	Clinical Category B	Clinical Category C
1. 500 cells/mm^3	A1	B1	C1
2. 200-499 cells/mm^3	A2	B2	C2
3. < 200 cells/mm^3	A3	B3	C3

Category A Conditions	Category B Conditions	Category C Conditions
n No symptoms n Acute HIV infection (resolves) n Generalized lymphadenopathy	n Bacillary angiomatosis n Oropharyngeal candidiasis n Vulvovaginal candidiasis: persistent, frequent, or poorly responsive to therapy n Cervical intraepithelial neoplasia II or III n Constitutional symptoms : fever, diarrhea > 1 month n Oral hairy leukoplakia n Herpes zoster : multiple episodes or involving > 1 dermotome n Idiopathic thrombocytopenic purpura n Listeriosis n Pelvic inflammatory disease : particularly if complicated by tubo-ovarian abscess n Peripheral neuropathy	n Candidiasis of bronchi, trachea, lungs or esophagus n Invasive cervical cancer n Coccidioidomycosis, disseminated or extrapulmonary n Cryptococcosis, extrapulmonary n Cryptosporidiosis, (intestinal infection > 1 month duration) n Cytomegalovirus disease (excluding liver, spleen or lympth nodes) n HIV-related encephalopathy n Herpes simplex : chronic ulcer > 1 month duration, or bronchitis, pneumonitis, or esophagitis n Histoplasmosis : disseminated or extrapulmonary n Isosporiasis : > 1 month's duration n Kaposi's sarcoma n Burkitt's lymphoma n Immunoblastic lymphoma n Primary lymphoma of the brain n *MAC * or M. kansasii*: disseminated or extrapulmonary n *M. TB* : any site n *Mycobacterium*: other species or unknown species, isseminated or extrapulmonary n *Pneumocystis carinii* pneumonia n Recurrent pneumonia n Progressive multifocal leukoencephalopathy n *Salmonella* septicemia, recurrent n Toxoplasmosis of the brain n Wasting syndrome due to HIV

Source : CDC, 1992.

**MAC – Mycobacterium avium-intracellulare complex*

APPENDIX C

1994 Revised HIV Paediatric Classification

I. Clinical categories

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly Symptomatic

Childrien with two or more of the following conditions but none of the conditions listed in categories B and C:

- v Lymphadenopathy (- 0.5cm at more than two sites; bilateral=one site)
- v Hepatomegaly
- v Splenomegaly
- v Dermatitis
- v Parotitis
- v Recurrent or persistent upper respiratory infection, sinusitis or otitis media.

Category B: Moderately Symptomatic

Children who have symptomatic conditions other than those listed for category A or category C that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to the following:

- v Anaemia (< 8gm/dL), neutropenia (1,000/mm^3), or thrombocytopenia (< 100,000mm^3), persistent • 30 days
- v Bacterial meningitis , pneumonia, or sepsis (single episode)
- v Persistent oropharyngeal candidiasis (i.e thrush)
- v Cardiomyopathy
- v Cytomegalovirus infection with onset before age 1 month
- v Diarrhea, recurrent or chronic
- v Fever lasting >1 month
- v Hepatitis
- v Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1year)
- v HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- v Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- v Leiomyosarcoma
- v Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- v Nephropathy
- v Nocardiosis
- v Toxoplasmosis with onset before age 1 month
- v Varicella, disseminated (i.e., complicated chickenpox)

Category C : Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a category B condition).

II. Immune categories (based on age specific CD4+ T-cell count and percentage)

	< 12 months		1 - 5 years		6 - 12 years	
Immune category	No./μβL	%	No./μL	%	No./μL	%
Category 1 No suppression	• 1,500	• 25	• 1,000	• 25	• 500	• 25
Category 2 Moderate suppression	750 - 1,499	15 - 24	500 - 999	15 - 24	200 - 499	15% - 24
Category 3 Severe suppression	< 750	< 15	< 500	< 15	< 200	< 15

APPENDIX D

Use of CD4+ counts and viral load assays

I. Use of $CD4^+$ / $CD8^+$ counts (*CD=cluster differentiation*)

Normal Ranges

$CD4^+$	:	500-1400/mm^3
$CD8^+$	:	180-865/mm^3
$CD4^+$ / $CD8^+$ Ratio	:	1.1-3.5

Calculation

$CD4^+$ counts (using Flow Cytometry) = WBC ∞ %lymphocytes ∞ %$CD4^+$ cells

Note

To avoid influence of change in WBC, use %$CD4^+$s :

e.g. > or equal 29% = $CD4^+$ count > 500/mm^3
14-28% = $CD4^+$ count 200-499/mm^3
< 14% = $CD4^+$ count < 200/mm^3

Remember

- *The test must be done within 48 hours after blood collection. **Do not ship** if the blood sample is expected to reach the laboratory **after** 48 hours.*
- *The counts are **highly variable**. They vary*
  - *: widely between labs*
  - *: even from hour to hour in some HIV-infected people*
- *They are also significantly influenced by*
  - *: other intercurrent infections,*
  - *: alcohol intake*
  - *: even pregnancy*
- *Note as well that, in some cases persons with less than 50 or 100 remain healthy; conversely some with relatively high counts (over 400) are quite ill.*

II. Use of Viral Loads

Relationship between HIV RNA copies / ml and log_{10} HIV RNA values

Copies / ml	Log_{10}	Copies / ml	Log_{10}	Copies / ml	Log_{10}
100	2.00	10,000	4.00	100,000	5.00
500	2.70	15,000	4.18	150,000	5.18
1,000	3.00	20,000	4.30	200,000	5.30
1,500	3.18	25,000	4.40	250,000	5.40
2,000	3.30	30,000	4.48	300,000	5.48
3,000	3.48	35,000	4.54	350,000	5.54
4,000	3.60	40,000	4.60	400,000	5.60
5,000	3.70	45,000	4.65	425,000	5.63
7,500	3.88	50,000	4.70	450,000	5.65
9,000	3.95	75,000	4.88	500,000	5.70

Note : *Fold variation is obtained by dividing the larger HIV RNA level in copies / ml by the smaller HIV RNA level in copies / ml*

e.g. If start at 100,000 copies / ml,

Log_{10} drop	*n-fold change*	*Copies remaining*
0.3	*2-fold*	*50,000*
0.5	*3-fold*	*33,000*
1.0	*10-fold*	*10,000*
1.5	*30-fold*	*3,300*
2.0	*100-fold*	*1,000*

Summary Comparison of 2 quantitative HIV RNA Assays

Generic Form	RT-PCR	Branched-chain DNA (bDNA)
Product	Amplicor HIV-1 Monitor	bDNA Version 2.0
Manufacturer	Roche	Bayer (formally Chiron)
Standard Detection range (copies / ml)	400 to 750,000	500 to 1,000,000
Lower limit of detection (next generation test)	20 copies / ml	20 copies / ml
Comparison of results	1.8 times those with bDNA	0.56 times those with RT-PCR
Specimen volume (ml)	0.5	0.5
Specimen collection	EDTA	EDTA
Specimen preparation*	Separate plasma in **< 6** hours of collection, and freeze prior to shipping	Separate plasma in **< 4** hours of collection, and freeze prior to shipping
Shipping	Frozen plasma on dry ice for overnight courier	Frozen plasma on dry ice for overnight courier
Available in	Hospital Kuala Lumpur Malaysian Liver Fdn. HUKM UMMC	Malaysian Liver Fdn

Remember

- *Infected CD4+ cells have an average life span of < 2 days and that of HIV particle is < 1 day. **Do not delay** specimen preparation and shipping
- As the assay kits are continually making improvements, it is sensible to choose one particular assay and use it exclusively.
- It's a technical variation if there's < 0.3 log_{10} (2-fold drop) change.
- Reflect real change in viral burden if there's > 0.5 log_{10} (3-fold drop) change.

APPENDIX E

Safety and Toxicity of Individual Drugs in Pregnancy [4,18]

Drugs	FDA pregnancy category	Long term animal carcinogenicity studies	Animal teratogen studies
Zidovudine (AZT)	C	Positive (rodent, noninvasive vaginal epithelial tumours)	Positive (rodent-near lethal dose)
Zalcitabine (ddC)	C	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose
Didanosine (ddI)	B	Negative (no tumours, lifetime rodent studies)	Negative
Stavudine (d4T)	C	Not completed	Negative (but sternal bone calcium decreases in rodents)
Lamivudine (3TC)	C	Negative (no tumours, lifetime rodent studies)	Negative
Nevirapine	C	Not completed	Negative
Delarvirdine	C	Not completed	Positive (rodent-ventricular septal defect)
Efavirenz	C	Not completed	Positive (cynomologus monkey-anencephaly, anophthalmia,microopthalmia
Indanavir	C	Not completed	Negative (but extra ribs in rodents)
Ritonovir	B	Positive (rodent, liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir	B	Not completed	Negative
Nelfinavir	B	Not completed	Negative

FDA pregnancy categories:

I Adequate and well controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimester)

II Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted

III Safety in human pregnancy has not been determined. Animal studies are either positive for fetal risk or have not been conducted. Thus the drug should not be used unless the potential benefits outweighs the potential risk to the fetus

IV Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

APPENDIX F

Role of double nucleosides in the era of HAART

Since the introduction of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), the goal of antiretroviral therapy has been to achieve maximal viral suppression. Data that demonstrates residual viral replication when plasma HIV-1 RNA is above 50 copies / ml has underscored the risk of developing viral resistance, if maximal viral suppression is not achieved. Dual nucleoside regimens have not been able to achieve adequate viral suppression to ensure sustainable antiviral control. At best, there maybe a 1-1.5 $\log_{10}$ plasma viral load reduction which often rebounds between 6 -18 months.

Since treatment failure is inevitable, dual nucleoside regimens are no longer recommended. The panel is unanimous in recommending that suboptimal therapies like dual nucleoside regimens should not be used except in very exceptional situations. This may be considered in patients who have very limited financial resources and are unable to access Highly Active Antiretroviral Therapy (HAART). For these patients, dual nucleoside regimens may be considered as a 'time-buying' exercise; especially when their CD4 cell counts are < 100-200 cells. The fact that the therapy will fail with time must be adequately explained to the patients and their significant others. Commencing dual nucleoside regimens as starting regimens will also limit future antiretroviral options for HAART if it does become accessible then. Current treatment policy of the Ministry of Health does not support the usage of dual nucleoside regimens.

Unanimous recommendation of expert panel:

The preferred treatment strategy in Malaysia in 2001 is :

Highly Active AntiRetroviral Therapy (HAART)

APPENDIX G

Karnofsky Performance Status Scale

	Scale	Description
Able to carry on normal activity; no special care is needed	100	Normal, no complaints
	90	Able to carry on normal activity, minor symptoms or signs or disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work; able to live at home; cares for most personal needs; a varying amount of assistance is needed.	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled, requires special care and assistance
	30	Severely disabled, hospitalization is indicted although death is not imminent
	20	Hospitalisation is necessary, very sick, active supportive treatment necessary
	10	Moribund, fatal processes progressing rapidly
	0	Dead

Karnofsky DA, et al. Cancer 634-656; 1984

APPENDIX H

HIV Websites and Support Groups

I. Websites

http://www.hivatis.org
HIV/AIDS Treatment Information Service website
CDC Guidelines on
Adult and Adolescent treatment
Paediatric treatment
Perinatal guidelines
PEP
Non occupational exposure
Prevention of OI
Tuberculosis in HIV

http://hopkins-aids.edu/publications/book/book_toc.html
Medical Management of HIV Infection
by John G. Bartlett, M.D. and
Joel E. Gallant, M.D., M.P.H.

http://hiv.medscape.com/Home/Topics/Aids/AIDS.html
Several CME articles on HIV

II. HIV Support Groups

Malaysian Aids Council
No. 12 Jalan 13/48A
The Boulevard Shop Office
Off Jalan Sentul, 51000 Kuala Lumpur
Tel: 03-4045 1033
Fax: 03-4042 6133

24 hours Infoline
on HIV/AIDs: 03-707 7007
Counseling: 03-4043 9711

Antiretroviral Treatment:
Toll Free Line: 1800-881848
Homepage: htp://www.mac.org.my

Persatuan Pengasih Malaysia
Rumah Pengasih
3201 -A Jalan Syers
Off Langgak Tunku
Bukit Tunku, 50480 Kuala Lumpur
Hotline: 03-62013179
Fax: 03-62013013
E-mail:khidmat@pengasih.hikmah.net

Pink Triangle Foundation
7C-1, 1st Floor Jalan lpoh Kecil
Off Jalan Raja Laut
50350 Kuala Lumpur
or
P.O.Box 11859
50760 Kuala Lumpur
Tel: 03-4044 4611
Fax : 03 -4044 4622
E-mail: isham@pop7.jaring.my
Positive Living e-mail : plbaru@hotmail.com

Pertubuhan Wanita Dan Kesihatan Kuala Lumpur
Tingkat 7
Wisma Kraftangan
Jalan Tun Perak
50050 Kuala Lumpur
Tel: 03-2692 6861
Fax:03- 2692 6877
Email:wake@tm.net.my

Community AIDS Service Penang
C-05 Ground Floor
Kornpleks Masyarakat Penyayang
Jalan Utama, 10560 Penang
or
P.O.Box 1206
10850 Penang
Tel: 04-229 9566
Fax:04-2297412
E-mail: casp@tm.net.my

Federation of Family Planning Association Malaysia
81 -B Jalan SS- 1 515A
47500 Subang Jaya
Selangor Darul Ehsan
Tel: 03-5633 7514 / 516 / 528
Fax: 03-5634 6638
E-mail: ffpam@po.jaring.my
Homepage: http://www.ffpam.org.my

Malaysian CARE
Pusat Kebajikan Good Shepherd
Lot 389 8.8km Jln Hulu Kelang
68000 Ampang Selangor (Secretariat)
Tel: 03-4256 8715
Fax: 03-42514044
Email:mcare@po.jaring.my
Homepage:http://www.mcare.org.my

The Buddies Of Ipoh
(A project of The Family Planning Association, Perak)
(Address of Family Planning Association Perak)
58A-60A Regat Sri Cempaka
Tawan Cempaka, 31400 lpoh, Perak
Hotline: 05-5467633
E-mail:hivbuddiesipoh@hotmail.com

Kuala Lumpur AIDS Support Services Society (KLASS Society)
54, Jalan 3/18C,
Taman Mastiara,
Jalan Ipoh, Batu 5 1/2
51200 Kuala Lumpur
Tel: 03-62531684
Fax: 03-62531076
E mail: faithcentre89@hotmail.com

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