GUIDELINES FOR THE USE OF ANTIRETROVIRAL THERAPY IN PAPUA NEW GUINEA

These guidelines were prepared for the Papua New Guinea National AIDS Council and the Papua New Guinea National Department of Health. The Guidelines are designed to ensure that antiretroviral drugs are used in Papua New Guinea in a way that will benefit both individuals and the country overall. The use of these medications will need to be regulated to ensure that the public benefit is not eroded by the development of viral resistance.

The guideline development has been a collaborative effort between the following organisations:

Papua New Guinea National AIDS Council
Papua New Guinea National Department of Health
National HIV/AIDS support project
AUSAID
World Health Organisation
UNAIDS
UNICEF
Port Moresby General Hospital
UPNG
PNG medical society
Burnet Institute

The following individuals were involved in discussions leading to development of these guidelines:

Papua New Guinea National AIDS Council – Joachim Pantumari, David Passirem
Papua New Guinea National Department of Health – Daoni Esorom
National HIV/AIDS support project – John Millan, Greg Law, John McBride
World Health Organisation – Erwin Cooreman, Nopporn Pathanapornpandh
UNAIDS – Nii-K Plange
Port Moresby General Hospital – Goa Tau, Simon Mete, Lloyd Ipai,
UPNG – Evelyn Lavu
Burnet Institute – Stephen Wesselingh
Angau Hospital, Lae – Paison Dakulale

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DRAFT

ABBREVIATIONS

3TC lamivudine
AAFB Acid alcohol fast bacteria (Mycobacteria)
ABC abacavir
AIDS acquired immunodeficiency syndrome
ART antiretroviral therapy
ARV antiretroviral
AZT zidovudine
CD4 T helper cell
CXR Chest X-ray
d4T stavudine
ddI didanosine
EFZ efavirenz also known as EFV
HAART highly active antiretroviral therapy
HIV human immunodeficiency virus
MTCT Mother to child transmission
NAC National AIDS Council
NNRTI non-nucleoside reverse transcriptase inhibitor
NsRTI nucleoside analogue reverse transcriptase inhibitor
NVP nevirapine
OI HIV-related opportunistic infection
PCP Pneumocystis carinii pneumonia
PNG Papua New Guinea
PI protease inhibitor
r low-dose ritonavir boost
sAg surface antigen
SQV saquinavir
TB tuberculosis
TLC total lymphocyte count
UPNG University of Papua New Guine
VCT HIV voluntary counselling and testing
WHO World Health Organization
AZT zidovudine

DRAFT

PURPOSE

The following guidelines have been prepared to guide clinicians in their choice of antiretroviral treatment for HIV infected individuals. The guidelines should be read in conjunction with the WHO document "Scaling up antiretroviral therapy in resource-limited settings. Guidelines for a public health approach" which is available at the web address http://www.who.int. It is envisaged that these guidelines will be used by public, private and NGO sectors and assist the various sectors in their planning for the use of these drugs within the country.

Knowledge about efficacy of various antiretroviral combinations and their adverse effects is rapidly evolving, as is the price structure for individual drugs and drug combinations. These guidelines will therefore be subject to regular review by a panel of experts nominated by the National AIDS Council (NAC), the National Department of Health and the Chief Physician, Port Moresby General Hospital. The guidelines will be published online at http://www.nacs.org.pg/ and print versions will be distributed to all registered prescribers.

WHO SHOULD TREAT

Prescription of antiretroviral therapy is a complex undertaking, and requires a complete understanding of the rationale, pharmacology and adverse effects of medication. In addition the practitioner needs to be knowledgeable about the treatment of coexisting conditions and the treatment of HIV in special patient groups. For this reason the prescription of antiretroviral medication will be restricted to registered medical practitioners who have attended a recognised "prescribers course". The National AIDS Council will run these courses from time to time. A list of registered medical prescribers will be distributed to pharmacies dispensing the medications. Recognition of courses attended elsewhere will be at the discretion of the chairman of NAC to whom application should be made.

WHEN TO START TREATMENT

The National AIDS Council recommends that HIV-infected adolescents and adults should start Antiretroviral therapy when they have:

• WHO stage IV of HIV disease (clinical AIDS), regardless of the TLC;

• Advanced WHO stage III disease (Characterized by HIV wasting, chronic diarrhoea, prolonged fever, atypical pulmonary tuberculosis, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis), regardless of the TLC;

• WHO stages II or III of HIV disease with TLC below 1200/mm^3.

WHO clinical staging is attached as appendix 1

If CD4 cell count is available the additional criteria may be used

• WHO stages I, II or III of HIV disease, with a CD4 count below 200/mm^3.

BASELINE TESTS

Full blood count
Electrolytes, Hepatic transaminases
Glucose
Syphilis serology
Sputum for AAFB and/or CXR
Hepatitis B sAg
Pregnancy test in women of reproductive age

WHAT DRUGS TO USE

The use of fixed drug combinations is recommended wherever possible to facilitate compliance and minimise the potential for the development of viral resistance

Recommended first line therapy

Zidovudine (AZT) /Lamivudine (3TC) /Nevirapine (NVP)
Or
Stavudine (D4T) /Lamivudine (3TC) /Nevirapine (NVP)

The combination of AZT/3TC/NVP is generally preferred. D4T may be associated with more mitochondrial toxicity and more common appearance of lipodystrophy. AZT, on the other hand, is associated with anaemia due to bone marrow toxicity in 5-10% of patients. If measurement of Haemoglobin is not routinely available, or if the Haemoglobin prior to initiation of therapy is less than 80 g/L (without a correctable cause), the combination of D4T/3TC/NVP would be preferred. Both combinations have equivalent potency. The fixed dose combination of AZT/3TC/NVP is slightly more expensive than D4T/3TC/NVP. Nevirapine is given as a single daily dose for the first 14 days to reduce toxicity. This can be achieved using a Nevirapine containing triple combination tablet at night and a dual combination tablet without the Nevirapine in the morning, for the first 14 days.

Recommended second line therapy

For drug toxicity

Substitution of single agents can be made if drug toxicity occurs and can be ascribed to a component of the triple therapy given as first line. For example, the AZT containing regimen can be changed to the D4T containing regimen if significant anaemia occurs. Efavirenz may be substituted for Nevirapine if a patient develops a moderately florid rash, but should not be given if there is mucosal ulceration or systemic effects associated with the rash. Nevirapine can be changed to ABC or SQV/r if hepatotoxicity or severe rash occurs.

Table 1. Drug substitution for toxicity

Primary drug regimen	Single-drug substitution for toxicity
AZT+3TC+NVP	*If AZT toxicity:* D4T + 3TC + NVP
	If NVP toxicity: AZT + 3TC + (EFZ or ABC or SQV/r)
D4t+3TC+NVP	*If D4T toxicity:* AZT + 3TC + NVP
	If NVP toxicity: D4T + 3TC + (EFZ or ABC or SQV/r)

For drug failure

Failure of a drug regimen is usually on the basis of viral resistance, and can only be confirmed by documentation of a rising viral load. In the absence of this measurement, a lack of clinical response after 6 months of treatment in a patient adherent to medication is likely to be due to viral resistance. If the treatment failure is due to non-adherence, consideration should be given to discontinuation of therapy.

For viral resistance it is recommended that all 3 drugs be changed. For the 2 first line therapies listed the two-second line therapies for drug failure would be

D4T/DDI/SQV/r (avoid this combination in pregnancy)
Or
AZT/DDI/SQV/r

Table 2. Drug substitution for regimen failure

If the failing regimen is…	Then switch to …	Unless…
AZT + 3TC + NVP	ddI + D4T + SQV/r	If patient has already been on D4T and switched due to toxicity, switch to: ddI + ABC + SQV/r
D4T + 3TC + NVP	ddI + AZT + SQV/r	If patient has already been on AZT and switched due to toxicity, switch to: ddI + ABC + SQV/r
If failure is due to non-adherence consider cessation of therapy (2^{nd} line therapies are far more complex and likely to fail with poor adherence. Drug costs are considerably higher)		

PREVENTION OF OPPORTUNISTIC INFECTIONS

Cotrimoxazole PCP prophylaxis (one single strength tablet daily) should be given to all patients meeting the clinical criteria for commencement of ART's or, when available, the CD4 cell count is less than 200 cells/mm^3. Prophylaxis can be ceased after 12 months for patients who have had a sustained clinical response.

TREATMENT OF OPPORTUNISTIC INFECTIONS

HIV infected patients presenting with opportunistic infections should have these infections treated prior to commencement of ART. The availability of Fluconazole to treat Cryptococcosis and severe candidiasis is a requirement for adequate treatment of these opportunistic infections.

PEOPLE WITH TUBERCULOSIS AND HIV COINFECTION

It is recommended that people with TB/HIV Co infection complete TB therapy before beginning ARV treatment unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e. if the CD4 count is below 200/mm^3 or if disseminated TB is present). If a person needs TB and HIV treatment concurrently, first-line treatment options include AZT/3TC or d4T/3TC plus either a NNRTI or ABC. If a NNRTI regimen were used, EFZ would be the preferred drug, as its potential for aggravating the hepatotoxicity of TB treatment appears smaller than that of NVP. However, its dosage should be increased to 800

mg/day. Except for SQV/r, protease inhibitors are not recommended during TB treatment with rifampicin because of their interactions with this drug.

Table 3. Recommendations for HIV treatment in patients with Tuberculosis

Clinical status of patient	Recommendations for ART
Uncomplicated TB, patient otherwise well	Defer ART until TB treatment complete
Complicated or disseminated TB, patient moderately unwell	Defer ART for 2 months then, if patient not improving, start AZT/3TC/EFZ (800mg/day)
High likelihood of HIV disease progression or death during treatment of TB	Introduce ART once TB treatment established. Use AZT/3TC/ABC or AZT/3TC/EFZ (800mg/day)

TREATMENT OF HIV IN PREGNANCY

Every pregnant woman in Papua New Guinea should have access to Voluntary Counselling and Testing (VCT) for HIV.

HIV infected pregnant women who meet the criteria for initiation of ART should be offered treatment. Treatment should be delayed until after the first trimester, if this can be done safely. Drugs that should not be administered during pregnancy include Efavirenz and the combination of D4T/DDI.

Women who do not otherwise qualify for treatment of HIV should be given antiretroviral treatment prior to delivery (AZT/3TC/NVP) to reduce the risk of perinatal transmission. AZT/3TC/NVP can be initiated early, at about 34 weeks gestation, or at the onset of labour. Early commencement of ART should only be undertaken if high levels of adherence are certain. Where there is the necessary medical and non-medical support for the administration, ART should be given until breast-feeding is completed, when the ongoing need for therapy is evaluated. Under normal circumstances therapy would be stopped.

Figure 1. Approach to prevention of HIV vertical transmission

Range of options for MTCT prevention

- MINIMUM- Single dose AZT/3TC/NVP at onset of labour and single dose NVP to baby
- OPTIMAL- Continue ART for duration of breast feeding to prevent post natal transmission

Where there is support for counseling and adherence

- Start ART at 34 weeks to lower risk of perinatal and in utero transmission

Infants born to HIV infected mothers should receive one dose of Nevirapine syrup 2mg/kg within 72 hours of birth. If the mother received her first dose of AZT/3TC/NVP less than one hour prior to delivery the infant should be given 2mg/kg of Nevirapine as soon as possible after delivery and receive an additional dose after 48 hours.

PAEDIATRIC GUIDELINES

All infants born to HIV-infected mothers should be followed up, fully immunized and given nutritional support. They should all receive Cotrimoxazole prophylaxis, at least for the first six months and preferably for the first 12 months of life in order to prevent PCP. If an infant

becomes symptomatic, virological testing should be performed, if available, in order to determine the HIV infection status.

Clinical staging for HIV infection in children is different from adults and normal ranges for CD4 cells are higher, therefore a decision to initiate ART will be based on different criteria to adults. The initiation of ART is not recommended in asymptomatic HIV-infected infants under 18 months of age.

The choice of first-line ART for children follows the same principles as in adults, with additional considerations about pharmacokinetic data and formulations available for children. All the recommended NRTIs for adults (AZT, 3TC, d4T, ddI and ABC) have formulations appropriate for young children. In the other ARV classes, only Nevirapine has a paediatric formulation. Choice of an appropriate combination of medication and dosage is highly specialized and should be discussed with a specialist experienced in the management of children with HIV.

Detailed criteria for commencement of ART, choice of medication, and monitoring of HIV infected children will appear in the future as an appendix to this document

ADHERENCE

For patients on antiretroviral (ARV) therapy, medication adherence is critically important to treatment success. Patients for whom there is concern about adherence should not be commenced on ART. Near-perfect pill taking is required to achieve viral suppression and to avoid the emergence of viral resistance. When patients skip doses and do not take their ARV medications regularly, viral resistance develops and the medicines can stop working. Missing doses is a common problem, and all patients need help to take 100 percent of their medicines as prescribed. The risks of nonadherence are so clear and so large that adherence assessment and support are integral parts of HIV care programs worldwide. Antiretroviral therapy should not be prescribed in the absence of adherence support. Ongoing counseling about the importance of adherence, recruitment of a carer in assisting with adherence, and measurement of adherence are essential components of care for all prescribing centres.

DRUG INTERACTIONS

All antiretroviral medications have the potential to interfere with other medications. Practitioners prescribing ARV's need to be aware of this potential and avoid interacting combinations, or adjust dosages where appropriate. Particularly important drug interactions include the reduction in the efficacy of the oral contraceptive pill by Nevirapine and protease inhibitors. Rifampicin significantly lowers the levels of both NNRTI's and PI's

USE OF ANTIRETROVIRAL DRUGS FOR POST EXPOSURE PROPHYLAXIS

Use of antiretroviral drugs should be considered for HIV-uninfected individuals who risk acquisition of HIV infection. Exposure to risk can be occupational or non –occupational. In general the following kinds of exposure should be considered for post exposure prophylaxis:

- Percutaneous exposure to blood from a patient infected with HIV (needlestick injury).
- Unprotected receptive anal or vaginal sex with someone infected with HIV

Antiretroviral drugs should be commenced as soon after the incident as possible, generally within 72 hours, and continued for 28 days. Health care facilities within PNG should take measures to minimise the risk for staff of occupational exposure to blood borne viruses. Rapid HIV testing of source blood and timely administration of ART to staff, exposed percutaneously to blood, are necessary components of a hospital occupational health policy.

Detailed guidelines for Post exposure prophylaxis will be issued as an appendix to this document

DATA COLLECTION

It is very important that ART use is monitored within PNG to define how improvements can be made in the management of the epidemic. It will be a requirement for prescribers to maintain a database of patients on treatment and forward specified data to NACS/NDOH when required.

DRUG DOSES

Table 4. Normal drug doses in adults

Drug class/drug	Dose
Nucleoside RTIs	
Zidovudine (AZT)	300 mg twice daily
Stavudine (d4T)	40 mg twice daily (30 mg twice daily if <60 kg)
Lamivudine (3TC)	150 mg twice daily
Didanosine (ddI)	400 mg once daily (250 mg once daily if < 60 kg)
Abacavir (ABC)	300 mg twice daily
Non-nucleoside RTIs	
Efavirenz (EFZ)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease inhibitors	
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily

LIST OF RECOMMENDED DRUGS (DOSE IN MG)

AZT/3TC/NVP (300/150/200), combination tablets
D4T/3TC/NVP (30/150/200 and 40/150/200), combination tablets
AZT/3TC (300/150), combination tablets
D4T/3TC (30/150 and 40/150), combination tablets
NVP syrup (50mg/5ml)
ABC (300)
AZT (300)
D4T (30 and 40)
DDI (EC 250 and EC 400)
EFZ (200 and 600)
SQV (200)
RTV (100)
FLUCONAZOLE (150 and 200)

APPENDIX 1. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

Clinical stage I

1. Asymptomatic
2. Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Clinical stage II

3. Weight loss, <10% of body weight
4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Herpes zoster within the last five years
6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

And/or performance scale 2: symptomatic, normal activity

Clinical stage III

7. Weight loss, >10% of body weight
8. Unexplained chronic diarrhoea, >1 month
9. Unexplained prolonged fever (intermittent or constant), >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (i.e. pneumonia, pyomyositis)

And/or performance scale 3: bedridden <50% of the day during the last month

Clinical stage IV

14. HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention[a]
15. Pneumocystis carinii pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhoea >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes
20. Herpes simplex virus infection, mucocutaneous >1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
23. Candidiasis of the oesophagus, trachea, bronchi or lungs
24. Atypical mycobacteriosis, disseminated
25. Non-typhoid Salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy, as defined by the Centers for Disease Control and Prevention[b]

And/or performance scale 4: bedridden >50% of the day during the last month

Note: both definitive and presumptive diagnoses are acceptable.

[a] HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month).

[b] HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.