ANNEXURE V

ANNEXURE V BOTSWANA GUIDELINES

Scanned excerpts from the brochure "Botswana guidelines on antiretroviral treatment – version 2002" authored by Anabwani and Jimbo in 2002 for the Ministry of Health of Botswana that distributed the brochure free of charge to the public in 2003.

4.0 WHAT REGIMENS SHOULD BE USED IN BOTSWANA?

4.1 Guiding Principles

The question of what antiretroviral drugs should be used in Botswana is very important. There were several considerations in choosing a first line Botswana regimen. Proof of clinical efficacy as a highly active antiretroviral regimen was a prerequisite. For cost and toxicity reasons it was decided that the regimen should be non-protease inhibitor containing. Because of concerns about adherence the regimen had to have a low pill load and be simple to administer – twice daily dosing at most.

The people of Botswana (and other African countries) do not have regular eating norms. Therefore, it was important to select a regimen that could be taken independent of food. For women in the reproductive age group, it was important to include agents with proven efficacy and safety in preventing mother-to-child transmission of HIV.

Protease inhibitors were reserved as second ard third line drugs. However, nelfinavir was selected for use in the second line regimen because other protease inhibitors may still be used in the event that resistance to nelfinavir develops. With these principles in mind, the following regimens (**Table 4**) were selected:

Table 4: Recommended Regimens for Botswana

First line Regimen

Adult Patients

a) Starting regimen for **adult males** and **women in whom there is no reasonable risk of pregnancy**: *Zidovudine (ZDV) plus Lamivudine (3TC) plus Efavirenz (EFV)*
b) Starting regimen for **pregnant women** or **women in whom pregnancy is likely to occur**: *Zidovudine (ZDV) plus Lamivudine (3TC) plus Nevirapine (NVP)*

Children

a) Under 5 yrs: Zidovudine (ZDV) plus Lamivudine (3TC) plus Nevirapine (NVP)
b) Above 5 yrs: Zidovudine (ZDV) plus Lamivudine (3TC) plus Efavirenz (EFV)

Second line Regimen

Both Adult Patients and Children :_Patients who fail the first line treatment will be referred for specialist advice. If there is no contraindication to using any of the drugs, the following regimen will be used: *Didanosine (ddI) plus Stavudine (d4T) plus Nelfinavir (NFV)*

Third line Regimen

Both Adult Patients and Children :_Patients who fail the second line treatment will be referred to Specialists for advice and considered for the following third line regimen: *Ritonavir (RTV) plus Saquinavir (SQV)*

Note : ZDV plus 3TC are combined in one tablet marketed as combivir." Ddl in enteric-coated formulation is more convenient as food restrictions are less

4.2 Resistance Testing

Choices of third line, and sometimes second line drug regimen may be guided by resistance tests. With resistance testing it may be possible to recycle some of the drugs used in previous regimens.

4.3 Failure of Regimen due to Poor Adherence

Each time a patient fails a drug regimen (see below for criteria for failure) - the question of adherence to the drug regimen must be raised and carefully

enquired into. Poor adherence (poor compliance) is a common reason for treatment failure. This emphasises the need for adherence counselling and adherence monitoring at all stages of HIV treatment. If poor adherence is considered the underlying cause for treatment failure, then treatment should be stopped until the reasons for poor adherence have been addressed (**Table 5**). Nonetheless, patients whose treatment is stopped for this reason need to be followed as described in the sections on monitoring below.

Table 5: Strategies to Improve Adherence

- Establish trust with patient and family
- Serve as educator and source of information
- Provide ongoing support and monitoring
- Intensify management in periods of low adherence by more frequent visits, recruitment of friends and family, deployment of other team members
- Utilise health team approach
- Provide training to support antiretroviral therapy team

Note: adapted from Guidelines on the Management of HIV in Adult and Adolescent Patients (http://www.hivatis.org)

4.4 Drug Interactions between TB drugs and HAART

As TB is the commonest opportunistic infection in patients with HIV in Botswana, many patients may need to be treated for both infections. However, there are some interactions between rifampicin and the drugs used to treat HIV (NNRTIs and PIs). The interaction is largely because these antiretroviral drugs are metabolised by the cytochrome P450 system of enzymes that is induced by rifampicin. The affected antiretroviral drugs are broken down at an accelerated rate, thus lowering their blood levels. PIs and NNRTI may also inhibit or reduce P450 enzymes and affect blood levels of rifampicin, the cornerstone of TB therapy. NRTIs are not metabolised by cytochrome P450.

These theoretical considerations supported by pharmacological studies in small numbers of patients indicate that serum levels of the NNRTIs (nevirapine and efavirenz) and protease inhibitors may be reduced in patients who are simultaneously treated with rifampicin (**Table 6**). It is not known whether this

interaction is serious enough to compromise the antiretroviral efficacy of NNRTIs, as there are no clinical outcomes data from controlled studies. Further, it is not known whether there are racial differences in these drug interactions. However, some recent data indicate that rifampicin can be used for treatment of active TB in patients whose antiretroviral regimen includes the NNRTI Efavirenz and two NRTIs[3] and the CDC guidelines[4] suggest that rifampicin may also be used in antiretroviral regimens that include the NNRTI nevirapine.

Nonetheless, it is an accepted principle that starting antiretroviral therapy is not an emergency and that CD4+ cell measurements should be done when the patient is not acutely ill – such as those with newly diagnosed TB. These considerations indicate that patients with newly diagnosed TB should be observed for up to four weeks and have CD4+ cell counts checked when they are stable on TB treatment before deciding whether to start antiretroviral therapy. In addition, to avoid possible adverse drug interactions, it would be better to defer starting HAART until 2 weeks after ending TB drugs, if the patient's condition allows.

Table 6: Interactions of Rifampicin with PIs, Efavirenz and Nevirapine

Drugs affected	Nevirapine NVP	Efavirenz EFV	Nelfinavir NFV	Saquinavir SQV	Ritonavir RTV
Rifampicin	NVP↓ 37%	EFV↓ 25%	NFV↓ 82%	SQV↓84%	RTV↓ 35%
	Not recommended	*No dose adjustment*	*Contraindicated*	*Contraindicated*	*No data*
Rifabutin	NVP↓16%	Rifabutin↓35%	NFV ↓32%; Rifabutin ↑2X	SQV↓40%	Rifabutin ↑4X
	No dose adjustment	↑ EFVdose; ↓ Rifabutin dose	↑NFV dose; ↓Rifabutin dose	No dose adjustment	↓Rifabutin dose

Notes: 1) Adapted from Guidelines on the Management of HIV in Adult and Adolescent Patients (http://www.hivatis.org)

2) Recommendations are italicized. Note that the recommendations (e.g. for NVP, RTV, SQV) appear inconsistent for similar margins of depression in drug levels

3) Clinical outcomes data to support these recommendations few or lacking.

The interaction between rifampicin and the protease inhibitor class of drugs (PIs) is problematic and there is strong evidence to indicate that rifampicin-induced reductions in the blood level of PIs may cause failure of the HAART regimen. In industrialised countries, it is recommended that rifampicin be

substituted with rifabutin. However, rifabutin is not part of the Botswana TB treatment guidelines, it is expensive and problems in obtaining sufficient supplies due to world shortage of this drug have been reported. Thus, substitution of rifampicin with rifabutin would be problematic and is therefore not recommended.

4.5 Overlapping Toxicities between TB drugs and HAART

There is potential for overlapping toxicities when anti-TB drugs & antiretroviral drugs are used concurrently. For example, rashes and/or hepatitis can be encountered with the use of isoniazid, pyrazinamide or rifampicin. Similarly, these toxicities could occur especially with the use of NNRTIs. Therefore, treatment of HIV using these drugs should be delayed, if the clinical condition allows, until after completion of TB treatment.

4.6 Management of TB and HIV Co-infection

Considering the above, the following are recommended regarding TB and the Botswana treatment regimens:

- Patients with newly diagnosed TB should be treated for TB first before starting HIV treatment
- However, in patients with newly diagnosed TB who are considered to be too ill, HAART should be delayed by at least two weeks after starting TB treatment
- Patients who develop TB while on the first line regimen (ZDV+3TC+EFV or NVP) should be treated for TB and HIV concurrently without drug modification
- Patients who develop TB while on the second line regimen (ddI+d4T+NFV) will need to be referred to specialists who will consider either boosting NFV with RTV or substituting NFV with the RTV/SQV combination
- Patients who develop TB while on the third line regimen (RTV/SQV) should be treated for TB without drug modification.
- There is no contraindication to the use of isoniazid preventive therapy (IPT) in patients receiving antiretroviral therapy.

5.0 ADULT PATIENTS

5.1 Criteria for Selecting Patients for Treatment

In contrast to the early days when the dictum "start early, hit hard" was the norm, long-term toxicity, problems with adherence and the risk of viral resistance argue for greater caution. Today, the guiding principle is to start therapy when it is most likely to be needed, and when patients are either having AIDS-related illnesses or they are at high risk of developing them due to their low levels of CD4+ lymphocyte cell counts. Most international guidelines and most HIV experts agree that the following two categories of HIV-infected patients should be treated:

a) Patients with severe, recurrent HIV-related disease or tumour (AIDS) irrespective of CD4+ cell count as they are already symptomatic
b) Asymptomatic patients with CD4+ cell counts that are consistently <200/ml as they are at increased risk of developing AIDS-related disease within a few months

These guidelines recommend using the above two categories to select adult patients for treatment. In asymptomatic patients with CD4+ cell counts that are consistently >200 and <350/ml, few data support starting therapy. Moreover, in Botswana where more than 300,000 people are estimated to be living with HIV/AIDS, selecting higher CD4+ cell cut-off points could lead to unmanageable numbers and demand. Children and HIV-infected pregnant women constitute special categories that are dealt with in subsequent sections.

Adult patients with major opportunistic conditions related to advanced immune suppression include TB, chronic diarrhoea, encephalopathy, and recurrent severe bacterial infections. They do not include an episode of herpes zoster or persistent generalised lymphadenopathy, conditions in which the CD4+ count may be well preserved. Also HIV-infected patients previously treated for TB will not automatically qualify for treatment but will be considered for treatment on the basis of their CD4+ cell levels.

5.2 Asymptomatic Adult Patients with CD4+ Count >200/ml

Asymptomatic adult patients not fulfilling the treatment criteria above will be followed up and monitored as outlined below. Those with high viral load (>55,000 copies/ml) or CD4+ cell counts 200-400/ml will be monitored more closely.

Periodic contact with these patients will provide an important opportunity for continued counselling with emphasis on positive living with HIV: safer sex, maintenance of good nutrition and physical exercise.

6.0 MONITORING ADULT PATIENTS

6.1 Patients not receiving Antiretroviral Treatment

These patients will be monitored periodically to assess disease progression using only the CD4+ count, as follows:

1) If CD4+ count 201-400/ml - Check CD4+ count every 3 month
2) If CD4+ count > 400/ml - Check CD4+ count every 6 months

6.2 Patients on Treatment

The ideal intervals for monitoring patients on treatment have not been determined. Because the cost of patient monitoring could be higher than the cost of purchasing HAART regimens, determination of the minimum schedule that could be used without compromising patient care, especially in our setting, remains an important area of study.

Taking into consideration the timing of expected toxicities and changes in measures of treatment efficacy, the schedules below are considered pragmatic while awaiting clinical trial data. Monitoring therapy will be done using viral load and CD4+ cell counts (to assess treatment efficacy), by clinical examination (to assess toxicity, adherence, clinical outcomes) and by blood chemistry and haematology (to assess drug toxicity). The recommended schedule for monitoring is shown in **Table 7**.

6.3 Criteria for Success

The goals for HIV therapy are to effect maximal and durable suppression of viral load, restore or preserve immune function, improve quality of life and reduce HIV-related diseases and deaths. Clinically, patients who were symptomatic should improve steadily on treatment and be free of serious drug-related toxicities. In addition, the following surrogate measures of efficacy should change as indicated:

- Viral load should fall by 1 log by 3 months after starting therapy
- Undetectable viral load by 6 months after starting therapy
- A steady rise in the CD4+ cell count

The earliest test for efficacy of the chosen regimen is the viral load determination 6-8 weeks after the start of therapy. However, for convenience, the first viral load determination for Botswana will be done at 12 weeks. Viral load values are expressed in raw numbers and as $\log_{10}$. A fall of 1 log therefore

APPENDIX – III

LIST OF ANTIRETROVIRAL DRUGS CURRENTLY REGISTERED IN BOTSWANA

BRAND NAME	GENERIC NAME	FORM & STRENGTH	Company Name	SHELF LIFE
Crixivan	Indinavir	200 mg Capsules	MSD Pty Ltd SA	2 Yrs
Norvir	Ritonavir	150 mg Tablets	Abbott Laboratories SA	2 Yrs
Norvir	Ritonavir	80 mg/ml Solution	Abbott Laboratories SA	2 Yrs
3TC	Lamivudine	10 mg/ml oral Solution	GlaxoWellcome SA	2 Yrs
3TC	Lamivudine	150mg Tablets	GlaxoWellcome SA	2 Yrs
Zerit	Stavudine	30 mg Capsules	Bristol Myers Squibb SA	2 Yrs
Zerit	Stavudine	15 mg Capsules	Bristol Myers Squibb SA	2 Yrs
Zerit	Stavudine	1 mg/ml powder for oral Solution	Bristol Myers Squibb SA	2 Yrs
Zerit	Stavudine	40 mg Capsules	Bristol Myers Squibb SA	2 Yrs
Zerit	Stavudine	20 mg Capsules	Bristol Myers Squibb SA	2 Yrs
Videx	Didanosine	100 mg Tablets	Bristol Myers Squibb SA	3 Yrs
Videx	Didanosine	150 mg Tablets	Bristol Myers Squibb SA	3 Yrs
Videx	Didanosine	2 gms paed powder for oral Solution	Bristol Myers Squibb SA	3 Yrs
Videx	Didanosine	4 gms paed powder for oral Solution	Bristol Myers Squibb SA	3 Yrs
Videx	Didanosine	25 mg Tablets	Bristol Myers Squibb SA	3 Yrs

Videx	Didanosine	50 mg Tablets	Bristol Myers Squibb SA	3 Yrs
Combivir	Lamivudine + Zidovudine	150mg + 300 mg Tablets	Glaxo Wellcome SA	4 Yrs
Viramune	Nevirapine	200 mg Tablets	Ingelheim Pharmaceuticals Ltd	2 Yrs
Viramune	Nevirapine	50 mg / 5 ml oral suspension	Ingelheim Pharmaceuticals Ltd	2 Yrs
Stocrin	Efavirenz	200mg Capsules	MSD Pty Ltd SA	2 Yrs
Kaletra	Ritonavir * Lopinavir	33.3mg and 133.3mg Caps	Abbott Laboratories SA	1.5 Yrs
Norvir SE	Ritonavir	100mg Capsules	Abbott Laboratories SA	2 Yrs
Retrovir	Zidovudine	100 mg Capsules	GlaxoWellcome SA	5 Yrs
Retrovir	Zidovudine	250 mg Capsules	GlaxoWellcome SA	2 Yrs
Hivid	Zalcitabine	0.75 mg Tablets	Roche Pharmaceuticals Ltd	2 Yrs
Hivid	Zalcitabine	0.375 mg Tablets	Roche Pharmaceuticals Ltd	2Yrs