**GOVERNMENT OF GUYANA MINISTRY OF HEALTH**
**NATIONAL AIDS PROGRAM**
**DRAFT**

# National Guidelines for Management of HIV-Infected and HIV-Exposed Adults and Children

**January 2009**

ONE PEOPLE ONE NATION ONE DESTINY

*A Joint Government of* Guyana - US Government Project

FXB GUYANA
François-Xavier Bagnoud Center
University of Medicine & Dentistry of New Jersey
GUYANA CARE & TREATMENT NETWORK

GUYANESE AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS


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**MINISTRY OF HEALTH, GUYANA**
**National Guidelines for Management of HIV-Infected and HIV-Exposed Adults and Children**
**January 2010/2011 Revision**

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## FOREWORD

I welcome the third publication of the *National Guidelines for Management of HIV-Infected and HIV-Exposed Adults and Children*. This 3rd edition comes at a time when Guyana reports universal access to treatment and care for people living with HIV/AIDS (PLHIV).

The availability of antiretroviral (ARV) treatment is an important part of the overall response to HIV/AIDS in Guyana. There have been major advances in ARV treatment since the advent of azidothymidine (AZT) in the early 1990s. There are now over forty different ARV drugs in seven different therapeutic categories that are available for treating PLHIV. The availability of ARV drugs has made a dramatic difference in longevity and quality of life for PLHIV. These drugs are crucial for lowering the viral load and interrupting transmission of HIV.

The Government of Guyana (GoG) is committed to providing ARV treatment as part of a comprehensive medical management programme for PLHIV. In 2002, the GoG declared universal availability of ARV treatment for PLHIV. This was a bold move, but one fraught with financial difficulties. Yet financial constraints were not the only hurdles to overcome–Guyana was also faced with a severe lack of human resources and the technical expertise to fully roll out such an enormous undertaking. With generous assistance from the United States Government, Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF), the World Health Organization (WHO)/Pan American Health Organization (PAHO), and the Global Fund to Fight AIDS, Tuberculosis and Malaria, Guyana's treatment and care programme continues to thrive. We are proud of this evolving programme, and are gradually moving towards what can be viewed as a 'model' treatment programme that provides comprehensive high quality multidisciplinary care and treatment for PLHIV.

But treatment with ARV drugs is not the only concern medical practitioners have in the overall management of PLHIV–another important aspect of the program is the differential treatment of children, adolescents, and adults. Fortunately for Guyana, not many children are born infected as a result of mother-to-child transmission of HIV. The differences in ARV drug dosing and formulation (pills vs. liquids) are important aspects of the treatment of children in comparison to the treatment of adolescents and adults. Another major concern is the co-infection of PLHIV with tuberculosis (TB). In these cases, persons must be medically managed for both HIV and TB. This is further complicated by serious interactions between anti-TB and some ARV drugs. Thus, different treatment regimens are necessary for PLHIV who are co-infected with TB.

The possibility of resistance to or diminished efficacy of ARV drugs in some PLHIV is an added concern for practitioners. It is important, therefore, that countries like Guyana establish treatment guidelines for first-line and second-line drug regimens that minimise resistance and maximise efficacy. Guyana is in a fortunate position in that, in spite of cost constraints, we are not limited in our selection of ARV drugs.

PLHIV often present at clinic with one or more opportunistic infections and with concomitant sexually transmitted infections (STIs). Practitioners must be aware of these infections and must have clear treatment guidelines to serve as a foundation for the delivery of related services to patients.

The Ministry of Health in collaboration with the United States Government (US) has revised treatment guidelines in response to the above circumstances as well as strong clinical evidence that has emerged

over the past three years. Thus this document represents the second revision of these guidelines to reflect evolving trends in the management of HIV-infected and HIV-exposed adults and children.

We are grateful for the support of the US Centers for Disease Control and Prevention (CDC) and to the partners with whom they have contracted: François-Xavier Bagnoud Center (FXBC) of the University of Medicine and Dentistry of New Jersey (UMDNJ) and AIDS Relief/Catholic Relief Services. We are also grateful to the staff of the Ministry of Health and the persons who have served on the National Steering Committee for Treatment and Care of HIV/AIDS. **The Ministry of Health has approved the treatment guidelines contained in this manual.** We are hopeful that these guidelines will be adhered to by practitioners in the public and private health sector including those who work in an NGO setting.

These revised guidelines answer central questions pertaining to many situations, including:

- Eligibility for the initiation of treatment for PLHIV who are asymptomatic
- Preferred first-line and second-line regimens
- Drugs or drug combinations that should be used or avoided
- Role of testing, including using $CD4^+$ lymphocyte counts, and viral load testing in management of HIV/AIDS
- Preferred regimens for treating adults and children
- Preferred regimens for treating HIV infected pregnant women
- Preferred regimens for post-exposure prophylaxis (PEP)
- Preferred regimens for treating persons with HIV and TB co-infection
- Treating opportunistic infections

A major shift in these guidelines is the commencement of antiretroviral therapy among persons with $CD4^+$ counts of $<350mm^3$ instead of $200mm^3$ and provision of expanded regimens for HIV-infected pregnant women instead of single dose nevirapine.
.
The guidelines are comprehensive and when used properly will enhance the ability of practitioners to provide quality service in the public and private health sectors. As Minister of Health, I recommend the *National Guidelines for Management of HIV-Infected and HIV-Exposed Adults and Children* to all practitioners caring for PLHIV and urge you to become familiar with them.

Finally, while these guidelines signify Guyana's ongoing commitment to providing standardized family centered HIV-related services, they are not meant to be rigid. This a living document that is subject to periodic reviews by the National Steering Committee for the Treatment and Care of HIV/AIDS.

Dr. Leslie Ramsammy
Minister of Health
May, 1, 2011

## MESSAGE FROM THE NATIONAL AIDS PROGRAMME MANAGER

The completion of this second revision of the *National Guidelines for Management of HIV-Infected and HIV-Exposed Adults and Children* is in keeping with the principle of staying current with the latest clinical and research developments in the field of HIV and AIDS.

This revision process continues to be comprehensive and we have again benefited from the in-country technical expertise specifically focused on the revision of these guidelines—the François-Xavier Bagnoud (FXB) Center of the University of Medicine and Dentistry of New Jersey, AIDS Relief/Catholic Relief Services and US Centers for Disease Control and Prevention (CDC). We were also fortunate to have technical support from the Institute of Human Virology at the University of Maryland, who gave unselfishly of their time to review the various drafts of revised guidelines. We have also benefited from numerous other academic and technical interested parties.

When we began using ARV preparations early in 2002, the need for treatment guidelines was recognised. Attempts at developing guidelines took into account the available ARV drugs and the laboratory support that we knew was accessible to us. This current edition of the guidelines takes into account the latest scientific evidence and the best practices and lessons learned from better endowed programmes in other regions of the world.

The revised guidelines are again based upon updates to both regional and WHO guidelines and include new information including but not limited to: viral load testing for children and adults, ART during pregnancy and for the newborns, introduction of ART post-initiation of TB treatment, first-line ART for children, monitoring pediatric growth and development, role of nutrition for adults and children, and management of co-morbid conditions including diabetes mellitus, hypertension and hyperlipidemia.

The publication of these guidelines is intended to significantly increase the number of patients on treatment as well as enhance the quality of HIV-related services provided in Guyana. In tandem with increased HIV-related laboratory capability, it is hoped that these guidelines will increase the comfort level of practitioners caring for PLHIV as well as improve HIV-related morbidity and mortality. These guidelines can also be 7tilized to train health care workers—at various levels of the health system—to know, understand and address the care and treatment needs of PLHIV.

As head of the technical working group tasked with revising the guidelines, I wish to thank all who contributed to the process and the generation of a document that continues to be relevant to its users and the eventual beneficiaries—PLHIV.

Dr. Shanti Singh Anthony, MD., MPH
Programme Manager
National AIDS Programme Secretariat,
Ministry of Health

## Abbreviation and Acronym List

| Abbreviation | Word |
|---|---|
| 3TC | Lamivudine |
| ABC | Abacavir |
| AIDS | Acquired Immunodeficiency Syndrome |
| ANC | Antenatal care |
| ART | Antiretroviral Therapy |
| ARV | Antiretroviral |
| ATV | Atazanavir |
| AZT or ZD | Azidothymidine (the chemical name) or Zidovudine, (the generic name) for the same drug |
| CDC | United States Centers for Disease Control and Prevention |
| CMV | Cytomegalovirus |
| CTX | Cotrimoxazole |
| d4T | Stavudine |
| ddI | Didanosine |
| DOT | Directly Observed Therapy |
| EFV | Efavirenz |
| ELISA | Enzyme-linked immunosorbent assay |
| FTC | Emtricitabine |
| HAART | Highly Active Antiretroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| INH | Isoniazid |
| LPV/r | Lopinavir/Ritonavir (brand names “Kaletra” and “Alluvia”) |
| MAC | Mycobacterium avium complex |
| MCH | Maternal and child health |
| MTCT | Mother-to-child transmission of HIV |
| NFV | Nelfinavir |
| NGO | Non Governmental organization |
| NRTI | Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitor |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| NVP | Nevirapine |
| OI | Opportunistic Infection |
| PCP | Pneumocystis pneumonia |
| PEP | Post-exposure prophylaxis |
| PI | Protease Inhibitor |
| PLHIV | People living with HIV |

| | |
|---|---|
| PMTCT | Prevention of Mother-To-Child Transmission of HIV |
| RTV | Ritonavir |
| sdNVP | Single-dose Nevirapine |
| TDF | Tenofovir |
| WHO | World Health Organization |
| VL | Viral Load |

## OBJECTIVES

The objectives of this document are to:

1. Provide guidelines to standardize the management of infants, children, adolescents, and adults in Guyana living with HIV.

2. Ensure that antiretroviral treatment protocols in Guyana reflect evidence-based international standards of practice.

3. Present simplified algorithms for the counselling, assessment, diagnosis, treatment, clinical and laboratory monitoring, and follow-up of adults and children living with HIV.

4. Provide streamlined information on the benefits and risks of antiretroviral therapy to facilitate a public health approach to implementing highly active antiretroviral therapy (HAART) throughout Guyana.

5. Provide recommendations on the care of pregnant mothers with HIV to prevent mother to child transmission (PMTCT) of HIV.

6. Provide recommendations on the care of individuals co-infected with tuberculosis and HIV, including strategies for the National TB Programme with the ARV programme.

7. Provide guidelines for managing post-exposure prophylaxis (PEP).

8. Provide simplified guidelines for prophylaxis and management of common opportunistic infections (OIs).

9. Strategize effective and known antiretroviral therapy models to the Guyana situation, considering the realities of challenges in human resources, health system infrastructure, socioeconomic status, and local availability of antiretrovirals.

10. Provide guidelines which integrate specialty HIV care and antiretroviral therapy into holistic, family-centered primary management of adults and children, including the management of common comorbidities.

# PART I:

# ANTIRETROVIRAL THERAPY

# FOR ADULTS AND ADOLESCENTS

# INTRODUCTION

Few scientific fields can rival the bounty of new ideas, information and technologies witnessed in the field of human immunodeficiency virus (HIV) clinical care over the last three decades. Initially a progressive and debilitating disease resulting in sickness and death, persons living with HIV may now be able to reverse the course of the disease and possibly achieve normal life expectancies. The last few years – in Guyana and internationally – have brought improved diagnostic methods, better monitoring strategies, and more effective and more tolerable antiretroviral therapies. One of the goals of these guidelines is to outline "state-of-the-art," evidence-based strategies to provide antiretroviral therapy (ART) and holistic clinical care to individuals living with HIV, while preventing the development of HIV drug resistance. Originally drafted in 2004 and later revised in 2006, this current revision of the *National Guidelines for Management of HIV-infected and HIV-exposed infants, children and adults* reflects the advancements in scientific knowledge, technology and clinical practice of HIV medicine and outlines approaches most appropriate to the current health care system in Guyana. While not all-encompassing, these guidelines also seek to provide basic information necessary to understand HIV and antiretroviral therapy. Every healthcare worker is encouraged to consult the most recent version of this document when seeking information on the management of patients who are HIV-exposed or HIV-infected.

## Transmission and Natural History of HIV-infection

Transmission of HIV-infection in adults and adolescents occurs mostly through sexual contact, though can also be acquired through the use of contaminated blood products (such as through sharing needles). Risks for transmission vary by the type of exposure and other factors, such as the presence of other concomitant sexually transmitted infections (STIs). Untreated HIV infection usually follows a predictable course. Within the first 72 hours of transmission, HIV is brought to regional lymph nodes where it uses CD4+ cells to replicate and rapidly populate all areas of the body. During these first few weeks of HIV infection, there is a rapid spike in the HIV viral load (the amount of HIV in the blood) and concurrent decrease in the CD4+ cell count (the number of circulating CD4+ T-lymphocytes in the bloodstream). The patient may feel a flu-like syndrome (the antiretroviral syndrome) or may not notice any symptoms at all. Between 6-12 weeks after infection, untreated patients experience demonstrated reductions in viral load and a modest improvement in CD4+ cell counts. This clinical recovery is followed by a prolonged asymptomatic period ("clinical latency") during which there is a very slow and gradual rise in viral load accompanied by a progressive destruction of CD4 cells. The rate of CD4 cell destruction depends on the viral load, with higher viral loads leading to more rapid CD4 cell loss. Symptomatic HIV infection (Acquired Immunodeficiency Syndrome or AIDS) results when CD4 counts have fallen below 200 cells/mm3. This is marked by weight loss, the development of opportunistic infections, and end-organ disease such as neurologic complications or renal failure. Although dependent on factors such as the HIV viral load, the average time to symptomatic HIV infection/AIDS is 8-10 years in most adults. The median survival once the CD4 count is <200 is 3.7 years; 1.6 years once an AIDS-defining complication has developed.

## Highly Active Antiretroviral Therapy (HAART)

The advent of Highly Active Antiretroviral Therapy (HAART) has revolutionized the management of HIV-infected patients and has lead to significant reductions in morbidity and mortality among HIV positive individuals. Strict adherence to HAART interrupts HIV replication, allowing the body to utilize its natural mechanisms to repair the immune system. This has, in turn, meant that HIV positive patients are living

longer and will require ongoing management of HIV, antiretroviral therapy and its complications - highlighting the need for good ongoing primary care and patient support.

The following principles guide the use of antiretroviral therapy:

- HIV is incurable using currently available antiretroviral drugs. HIV viral DNA is integrated into inactive memory T-cells; it is estimated that the natural decay of these infected memory cells takes more than 70 years.
- CD4 lymphocyte count and viral load estimations should be used to monitor the progress of HIV infection and response to treatment.
- Highly Active Antiretroviral Therapy (HAART) regimens involve an appropriate combination of three (3) or more ARV drugs given together. An effective HAART regimen should achieve optimal suppression of HIV viral load.
- The effectiveness of HAART is determined by
  a. appropriate ARV drug combination
  b. adherence to therapy
  c. management of drug toxicities and interactions
  d. the severity of immune suppression at initiation of therapy
- Although there are no randomized clinical trials that outline the optimal point at which to start antiretroviral therapy, there are multiple large cohort studies which suggest that earlier initiation and consistent HAART is associated with improved CD4 counts and lower rates of mortality – from *both* HIV and non-HIV related diseases. For this reason, lifelong continuation of HAART after initiation is recommended.
- HAART is hardly ever an emergency and life-long ARV therapy should seldom be started without assurance of adherence readiness and support, a strategic follow-up plan, and regular anaemia and psychosocial support. Patient preparation and participation are critical to success.
- Delaying the initiation of HAART may be appropriate if there are medical or non medical indications.
- As often as possible, an active opportunistic infection should be identified and managed before initiation of HAART to avoid paradoxical worsening of the patient's clinical condition.
- Insufficient adherence to therapy, inappropriate combinations or doses of ARV drugs, and drug interactions can all lead to **HIV-drug resistance**. Many HIV resistance mutations affect multiple ARVs, including entire classes of medications. Once resistance develops to given ARV medications, it lasts *lifelong*. Preventing the development and spread of HIV-drug resistance is an important part of chronic HIV disease management.
- ARV drugs, particularly protease inhibitors, can have multiple interactions with other medications and should not be prescribed without a careful review of each patient's current drug history, including herbal and traditional agents.
- Monotherapy (1 ARV) and dual therapy (2 ARVs) should NEVER BE USED in the treatment of HIV infection, due to the very rapid development of HIV-drug resistance. The use of single dose Nevirapine (or combinations of Zidovudine and Nevirapine) is only recommended in the case of a pregnant woman who is diagnosed HIV positive for the first time in labor or for an HIV exposed infant brought to hospital

within 72 hours of birth if the mother did not receive ART during pregnancy. However, optimal prevention of mother to child transmission occurs with the use of HAART during pregnancy.

- Whenever possible, protease inhibitor-based regimens should not be used as first-line regimens in resource-constrained settings because of concerns about cost, preserving future treatment options, and pill burden.
- A single drug should not be added or substituted in a failing regimen except if HIV genotypic resistance testing is available.

# ESTABLISHING DIAGNOSIS AND STAGING

## Diagnosis of HIV infection in adolescents and adults

There are several tests for diagnosing HIV infection (HIV 1 and HIV 2) in adolescents and adults. Because of the high costs associated with testing for the HIV virus itself (either through HIV DNA or HIV RNA), diagnosis is made by testing for the presence of antibodies to HIV. It is important to remember that it takes 2-6 weeks between infection and the development of a sufficient quantity of HIV-antibodies to be detected. In Guyana HIV rapid testing is used for diagnosis in adults and adolescents and are currently in use throughout Guyana at all voluntary counselling and testing (VCT) sites and at some ANC Clinic as part of the PMTCT Programme. Like Elisa testing, they are antibody tests and have reported sensitivities and specificities of over 98%. However, these tests use a sample of capillary blood and can provide results within twenty minutes. Guyana uses the parallel HIV rapid testing algorithm with the Determine$^{TM}$ and Unigold$^{TM}$ test kits. Concordant results are reported. Discordant results are verified with Statpak$^{TM}$ as the tie-breaker test. The algorithm is in Appendix 1–A.

While these are antibody tests and are used routinely to diagnose HIV infection in adults and adolescents in Guyana, HIV Deoxyribonucleic Acid polymerase chain reaction (DNA PCR) testing has recently been instituted in Guyana for infants and young children under the age of 18 months.

### Clinical Staging and Classification Systems

Two classification systems, the World Health Organization (WHO) and United States Centers for Disease Control (CDC) classification systems were developed prior to the advent of CD4 testing to help clinicians gauge the extent HIV disease progression based on purely clinical parameters. To simplify and standardize record keeping, Guyana recommends the use of the WHO Clinical Staging System for staging patients by assessing clinical symptoms. The WHO Clinical Staging system uses current and past illnesses to categorize patients into four stages, ranging from Clinical Stage 1 (mild, asymptomatic HIV infection) to Clinical Stage 4 (AIDS). The WHO Clinical staging system is located in Appendix 1-C.

# ANTIRETROVIRAL THERAPY

Advancements in pharmaceutical science over the last ten years have lead to the development of new classes of antiretrovirals. These medications are better tolerated, more effective and require a smaller daily pill burden. All antiretroviral medications work by interrupting the cycle of HIV replication at critical steps in the HIV life cycle. While ARVs cannot remove HIV virus from infected cells, they can lead to a near cessation of measurable viral activity (measured by the HIV viral load) – which is the driver of disease

progression. There are currently five major classes of ARV drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase inhibitors. Additional classes, such as viral maturation inhibitors, are currently under study. The first three of these classes – NRTIs, NNRTIs, and PIs are all available in Guyana and part of the treatment strategies for individuals living with HIV infection. While a complete overview of all ARVs is beyond the scope of this document, this section will outline some of the basic information about the most important ARVs in use in Guyana.

## Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

These drugs were the first class of antiretrovirals developed, and form the "backbone" of ARV treatment regimens. [See sections on First and Second-line regimens for appropriate combinations]. They inhibit the transcription of viral RNA into DNA, thereby interfering with viral replication (Table 1.1).

**Table 1.1: NRTIs available in Guyana: typical dosages and common side effects**

| Drug | Typical Adult Dosage | Selected Adverse Effects/Toxicities |
|---|---|---|
| Zidovudine (AZT) | 300 mg twice daily | Anaemia, neutropoenia |
| Stavudine (d4T)<br>Only used in a few children presently in Guyana | 30 mg twice daily | Lipodystrophy & metabolic complications; Peripheral neuropathy, pancreatitis |
| Lamivudine (3TC) | 150 mg twice daily | Peripheral neuropathy, lactic acidosis (rare) |
| Abacavir (ABC) | 300 mg twice daily | Hypersensitivity reaction |
| Tenofovir (TDF) | 300 mg once daily<br>(See Table 1.2 below.) | Renal toxicity |
| Emtricitabine (FTC) | 200 mg once daily | Skin discolouration |
| **Combinations:** | | |
| Truvada (TDF/FTC) | 1 tablet (300/200mg) once daily | Renal toxicity (rare) |
| Dimune (AZT/3TC) | 1 tablet (300/150mg) twice daily | Anaemia, neutropenia |

## Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

These drugs are chemically different from the NRTIs but also inhibit transcription of viral RNA into DNA in a competitive manner (Table 1.2). Together with the NRTI "backbone", they are a critical piece of the first line HAART regimens in Guyana.

**Table 1.2: NNRTIs available in Guyana: typical dosages and common side effects**

| Drug | Typical Adult Dosage | Selected Adverse Effects/Toxicities |
|---|---|---|
| Efavirenz (EFV) | 600 mg once daily, preferably at bedtime | Possibly teratogenic during the 1st trimester of pregnancy only, CNS effects (dizziness, insomnia, lethargy), Rash |
| Nevirapine (NVP) | 200 mg once daily for 14 days, then 200 mg twice daily | Stevens-Johnson Syndrome, Rash, Hepatotoxicity (potentially fatal) |

## Protease Inhibitors (PIs)

These drugs block protease, an enzyme necessary for the processing of HIV after it has been transcribed from host cell DNA. Together with an NRTI "backbone", protease inhibitors (Table 1.3) form the critical piece of the second-line HAART regimen in Guyana.

**Table 1.3: PIs available in Guyana: typical dosages and common side effects**

| Drug | Typical Adult Dosage | Dietary Rules | Selected Adverse Effects/Toxicities |
|---|---|---|---|
| Lopinavir/Ritonavir (LPV/r) 200/50mg tablets - "Alluvia" | 2 tablets twice daily | Recommended with food to decrease GI side effects | Diarrhea, Nausea, Hepatitis, Metabolic effects |

## Multiclass Fixed Dose Combinations (FDCs)

Fixed dose combinations pills have significant advantages as it reduces the pill burden both in quantity and the frequency of administration. This has shown to positively impact adherence and thus resulting in better treatment outcomes.

Atripla is the first multiclass fixed dose combination pill comprising of tenofovir 300mgs, emtricitabine 200mgs and efavirenz 600mgs and is a key recommended first line regimen in Guyana.

**Table 1.4: Fixed Dose Combination- 2NRTI and NNRTI**

| Drugs | Typical Adult Dosage | Side effects /Toxicities |
|---|---|---|
| Tenofovir 300mgs/emtricitabine 200mgs/efavirenz 600mgs- Atripla | One (1) tablet daily | Renal toxicity, CNS effects (dizziness, insomnia, lethargy), Rash |

# TREATMENT PREPARATION AND ADHERENCE

Highly Active Antiretroviral Therapy (HAART) is an effective and sustainable method to control HIV replication, slow progression to immunologic failure, and in many cases, allow for reconstitution of CD4+ cells in persons living with HIV.

Goals for the initiation of ART in adults and adolescents are to:

- Maximize HIV suppression.
- Preserve and restore immunologic function.
- Reduce HIV-related morbidity and mortality.
- Decrease the risk of HIV transmission.
- Improve quality of life.

Adherence is a fundamental component of effective ARV therapy. Successful outcomes from ART require sustained treatment adherence to complex multidrug regimens over many years. It is therefore important to ensure that patients understand the benefits of ART, risks of not taking ART, the potential side effects, and importance of adherence. Adherence is defined as the engaged and active participation of an informed patient/family to a treatment plan. Adherence rates with early ART regimens of over 95% were necessary to achieve durable and sustained viral suppression. While current regimens may be slightly more forgiving, with all regimens, lower levels of adherence correlate with virologic failure, subsequent treatment failure, and evolution of drug resistance. Achieving high rates of adherence over a long period is a challenge and is crucial for preventing drug resistance.

Although the disease course will vary among patients, it is expected that everyone will need ART at some point in their lives. Thus, assessment of readiness and treatment preparation begin with the initial patient visit. Pre-initiation clinical encounters are crucial to establishing rapport. They provide non-judgemental support and foster communication about treatment plans. Assessment of readiness and treatment support are best accomplished with a multidisciplinary team able to provide structured, individualized support. The following principles should guide adherence counselling and facilitate adherence for patients receiving HAART:

- The patient should receive adherence counselling prior to initiating HAART. It is expected that the patient will have at least three adherence counselling sessions which may include a group session. They should continue to receive additional counselling at every visit while taking HAART. All members of the health care team offer adherence counselling: nurse, physician, pharmacist, social worker and community outreach worker.
- Adherence may be monitored by self-report, pill counting, pill identification, and adherence assessment evaluation.
- Having the patient involve an adherence "partner" or "buddy" is strongly encouraged. Whenever possible, as a matter of policy, every patient should be encouraged to disclose his/her status to a person of his/her choosing, who can act as an adherence partner and accompany the patient to important clinic visits.
- An adherence support system, including a community and/or peer support system, will be established to help with medication adherence.
- Patients who miss more than two (2) successive visit appointments without justifiable reason should be considered at high-risk for treatment non-adherence and development of resistance. These patients should be flagged for rigorous interventions to support adherence – including social support mechanisms and intensive adherence counselling.

## Assessing readiness

Before initiating therapy, the clinician should make a complete assessment of eligibility and readiness to begin therapy by reviewing the following questions:

- **Does the patient have a documented diagnosis of HIV?**
  - Before starting ARV therapy an HIV positive diagnosis must be clearly documented.

- **Does the patient have an indication for antiretroviral therapy?**
  - Every HIV-infected adult or adolescent should be assessed for treatment initiation according to the recommendations contained in these guidelines.
  - While HAART may be offered to highly motivated individuals not meeting recommended criteria, those meeting eligibility criteria are at highest risk for AIDS related complications. Efforts should be particularly focused on assessing and preparing these individuals for HAART.
  - Every pregnant HIV positive woman should be offered HAART. See recommendations in the PMTCT section.

- **Is there a medical contraindication or reason to delay initiating therapy?**
  - Examples include:
    a. Renal Insufficiency (creatinine >3x normal)
    b. Hepatic Insufficiency (liver function tests >5x normal)
    c. Severe Anaemia (hemoglobin < 6.9g/dl) or Neutropenia (absolute neutrophil count < 749 cells/mm3)
    d. Severe Thrombocytopenia (platelet count <50,000)
    e. Active psychiatric illness in the patient
  - In the presence of a medical contraindication, provide a rapid and thorough evaluation to investigate the etiology and assess for the safety of starting HAART. Many of these same problems may be caused by the HIV virus and improve with HAART. Abnormally long delays in deferring HAART lead to poorer clinical outcomes.
  - When unsure of the appropriate time to initiate HAART in the presence of any of these conditions, please consult an HIV specialist.

- **Is there a current nonmedical contraindication to ARV therapy?**
  - Examples include:
    a. Denial of HIV status or ambivalence about starting lifelong therapy.
    b. Substance abuse.
    c. Severely unstable social situation (e.g. homeless, no social support, etc.).
    d. Recent history of serious medication or appointment non-adherence.
    e. Current use of herbal and traditional remedies that may interact with ARVs.
  - As with medical contraindications, it is important not to let non-medical contraindications serve as a permanent barrier to HAART for persons meeting eligibility criteria. Rapid assessment and resolution of barriers preventing good adherence (often with support from a multidisciplinary team including social workers, out reach workers, home based care providers, etc.) should be the primary goal.

- **Is there a current active opportunistic infection?**
  - Has TB been excluded? (Chest X-Ray, sputum AFB, PPD, or symptoms?)

- In patients with severe immunosuppression, are symptoms of OIs infection present?
- Active opportunistic infections are not a complete contraindication to HAART, though to simplify treatment regimens, reduce drug interactions, ascertain the causative agent of adverse drug reaction and reduce immune reconstitution inflammatory syndrome (IRIS), initial control of the opportunistic infection should be the primary goal with initiation of HAART in a matter of weeks.

- **Are adherence, clinical monitoring and follow-up possible?**
  - Is the patient motivated and does the patient understand the need for long-term medication?
  - Does the patient understand how to take the medication?
  - Does the patient have significant barriers to getting to the treatment site?
  - Is the patient willing to have an adherence partner?
  - Assess the patient using criteria that can be used to predict good adherence:
    a. Past history of adherence with anti-TB medications.
    b. Adherence with Cotrimoxazole prophylaxis.
    c. Clinic attendance at three consecutive appointments.
    d. Patient has addressed disclosure issues and has a 'treatment buddy'.

## Methods for achieving drug adherence

After having assessed the patient's readiness, there are several methods that the clinical team can use to support the patient's needs. These are:

- *Patient-related*
  a. Negotiate a regimen plan that is suitable to patient.
  b. Plan adequate time for adherence counselling
  c. Involve partner to help with adherence whenever possible.
  d. Use memory aids whenever possible—timers/alarms clocks, pill boxes.
  e. Plan ahead. Keep medications in key locations and obtain early refills.
  f. Address active substance abuse and mental illness.
- *Provider and Healthcare team-related*
  a. Provide initial and on-going information on goals of therapy, drugs, food restrictions, and side effects.
  b. Assess adherence readiness before initiating HAART and assess ongoing adherence to treatment at each visit. Identify and address any barriers to adherence.
  c. Monitor and manage side effects.
  d. Use a multidisciplinary approach. Educate volunteers, support groups and community representatives.
- *Regimen-related*
  a. Minimize adverse drug interactions.
  b. Simplify regimen as much as possible.
  c. Tell patients to anticipate some side effects and report them earliest

## WHEN TO START ANTIRETROVIRAL THERAPY (ART)

There is increasingly strong evidence showing clinical benefits of antiretroviral therapy in adults at any WHO clinical stage or CD4 count. Earlier initiation of HAART is correlated with improved CD4 counts, reductions in HIV-related morbidity and mortality, and reductions in non-HIV-related morbidity and mortality. However, the longer the exposure to HAART, the higher the chance that HIV drug resistance could develop. Choosing the optimal time to initiate antiretroviral therapy is a balancing act where the benefits of starting ART must be weighed against the risks of not starting.
Starting treatment is particularly important for adults and adolescents with lower CD4 counts. These patients have higher risk for HIV disease progression, additional complications (such as malignancies) and death. However, starting ARV therapy should not be considered an emergency. Before doing so, the clinician should discuss the diagnosis and the need for ARV therapy with the patient, addressing any questions or concerns, and perform a thorough assessment of adherence readiness as outlined in the previous section.

### Initiating HAART in Adults and Adolescents

Eligibility for ARV therapy is assessed through two methods – immunologic criteria (CD4+ cell counts) and clinical criteria (WHO clinical stage). Patients who meet either immunologic or clinical criteria to start therapy should be initiated on HAART as soon as possible after treatment preparation and readiness are addressed. Recommendations regarding the initiation of antiretroviral therapy in adults and adolescents are described in Table 1.4.

**Table 1.4: Initiation of HAART in adults and adolescents**

| Immunologic Criteria | Recommendations |
|---|---|
| CD4+ count <350 cells/mm3 | • Initiate antiretroviral therapy in patients with CD4+ cell counts <350 cells/mm3. |
| CD4+ count 351-500 cells/mm3 | • Counsel regarding the risks and benefits of antiretroviral therapy at CD4 counts between 351-500 cells/mm3. (see below)<br>• Consider initiation of antiretroviral therapy if the patient is highly motivated or there are other risk factors (e.g. Hepatitis B, renal failure, cardiovascular disease and other co morbidities, which would benefit from antiretroviral therapy) |
| CD4+ count >500 cells/mm3 | • Counsel regarding the risks and benefits of antiretroviral therapy at CD4 counts above500 cells/mm3. (see below)<br>• Antiretroviral therapy may be offered in select circumstances, though the risks may outweigh benefits for most patients unless the patient is extremely motivated to continue lifelong therapy. |
| **Clinical Criteria** | **Recommendations** |
| WHO Stage III or IV | • Initiate antiretroviral therapy in patients who meet WHO stage III or IV criteria, regardless of CD4 count. |

*Whenever antiretroviral therapy is indicated, it is important to identify and treat any active opportunistic infections, and thoroughly assess treatment preparation and readiness - before initiation of HAART.*

## Benefits and Risks of initiating HAART at different CD4 counts

The guiding principle of the Guyana's ART programme is to ensure that every person eligible for receives antiretroviral therapy. However Guyana recognizes the benefit of starting antiretrovirals early and therefore recommends that antiretroviral therapy be offered to all HIV infected persons

An outline of potential benefits and risks with earlier treatment is outlined in Table 1.5.

**Table 1.5: Benefits and risks of earlier initiation of HAART**

| Potential Benefits of Early Therapy |
|---|
| • Maintenance of higher CD4 cell counts and prevention of potentially irreversible damage to the immune system. Patients starting HAART at higher CD4 nadirs have higher CD4 plateaus on HAART.<br>• Decreased risk for HIV-associated complications that can sometimes occur at CD4 cell counts > 350 cells/mm3, such as tuberculosis, non-Hodgkin's lymphoma, peripheral neuropathy, HPV-associated malignancies (e.g. cervical cancer) and HIV-associated cognitive impairment.<br>• Decreased risk of non-HIV associated comorbidities, including cardiovascular disease, liver disease (or progression of pre-existing liver disease) and non-HIV associated malignancies.<br>• Decreased risk of HIV transmission to others.<br>• Potential decrease in the risk of some treatment related adverse events such as peripheral neuropathy, which occur when HAART is started at lower CD4 nadirs. |
| **Potential Risks of Early Therapy** |
| • Development of drug-resistance from incomplete viral suppression, resulting in loss of future treatment options.<br>• Development of treatment-related side effects and toxicities, including alterations in metabolism and cholesterol (risk of toxicities varies by medication).<br>• Less time for patient to learn about HIV and its treatment or to prepare for the need for long-term adherence.<br>• Increased total time on medication, with greater chance of treatment fatigue.<br>• Premature use of therapy before the potential development and availability of more effective, less toxic or better studied combinations of antiretroviral drugs.<br>• Transmission of drug-resistant virus in patients who do not maintain full virologic suppression. |

# FIRST LINE REGIMENS

Effective selection of appropriate ARV medications coupled with good adherence should lead to complete suppression of HIV viremia. This in turn leads to improvements in CD4 counts and the overall clinical status of the patient. "Triple therapy" using three antiretroviral drugs drawn from more than one class provides the most effective suppression of viral replication while preventing the development of resistance.

The recommended first-line ARV regimens consist of a combination of two (2) NRTIs and an NNRTI. There are alternate first-line antiretrovirals from each class for patients who may have toxicities from or contraindications to the recommended first-line combination regimen.

| Recommended First-Line Regimen | | |
|---|---|---|
| **NRTI Backbone** | | **NNRTI** |
| **Tenofovir (TDF) + Emtracitabine (FTC)**<br>Coformulated as Truvada.® | **+** | **Efavirenz (EFV)**<br>**OR**<br>**Nevirapine (NVP)** |

The NRTI backbone of Tenofovir and Emtricitabine is the first line regimen of choice because of its high potency, minimal toxicity, good resistance profile, ease of administration, dual effect on hepatitis B, and preservation of future treatment options. Efavirenz is the preferred NNRTI option over Nevirapine due to superior virologic efficacy, the convenience of once daily dosing, and fewer concerns about rare, though life-threatening, hepatotoxicity. However, there may be some scenarios where the use of alternate ARV drugs would be preferred as part of the first-line regimen.

| Alternate First-Line Regimen Options | | |
|---|---|---|
| **NRTI Backbone Options** | | **NNRTI Options** |
| **Zidovudine (AZT) + Lamivudine (3TC)**<br>Coformulated as Dimune.® | **+** | **Nevirapine (NVP)** |
| **Abacavir (ABC) + Lamivudine (3TC)** | | **OR** |
| | | **Efavirenz (EFV)** |

## Choosing alternate antiretrovirals for first-line regimens

Special considerations when alternate antiretrovirals may be preferable as part of the first line regimen:

- **Renal Insufficiency** - Although rare, Tenofovir (TDF) can exacerbate or cause renal insufficiency. The risk of TDF-induced renal insufficiency is higher in individuals with pre-existing renal insufficiency. It is important to calculate creatinine clearance to determine the appropriate dose of TDF/FTC. When Tenofovir cannot be safely used, Abacavir (ABC) or Zidovudine (AZT) in conjunction with Lamivudine is recommended as the NRTI backbone. Of note, Lamivudine and Zidovudine must also be dosed appropriately based on creatinine clearance, Creatinine clearance is calculated using the Cockcroft Gault method as per formula below.

$$\textbf{Creatinine Clearance for } \underline{\textbf{MALES}} = \frac{\textbf{Weight (kgs)x (140-age)}}{\textbf{72 x Serum Creatinine( mg/dl)}}$$

**Creatinine Clearance for <u>FEMALES</u>= Creatinine Clearance for males X 0.85**

It is also common for individuals with renal insufficiency to have anaemia due to decreased secretion of erythropoietin levels from kidney cells. While AZT use does not always exacerbate this type of anaemia, caution must be used with AZT to ensure that the anaemia does not worsen.

**Table 1.6: Antiretrovirals requiring dose adjustment for renal insufficiency**

| Antiretroviral | Estimated Creatinine Clearance (ml/min) | | |
|---|---|---|---|
| | > 50-90 | 10-50 | <10 |
| Tenofovir/Emtracitabine (Truvada) | 1 tab PO daily | 1 tab PO every 48 hours | Do Not Use |
| Lamivudine | 150mg PO twice daily | 75mg PO twice daily | 50mg PO once daily |
| Zidovudine | 300mg PO twice daily | 300mg PO twice daily | 100mg PO every 8 hrs |

- **Potential or Existing Pregnancy** – Use of Zidovudine, Lamivudine and either Nevirapine **(AZT+3TC+NVP)** or Lopinavir/Ritonavir (Alluvia) **(AZT+3TC+LPV/r) or Truvada (TDF+FTC) and Alluvia (TDF+FTC+LPV/r)** or Truvada and Nevirapine are recommended during pregnancy.

The recent guidance from WHO of 2010 indicates that Efavirenz is safe for use in pregnancy after the first trimester. *Efavirenz is not recommended in pregnant women during the first trimester of pregnancy*.

In women with CD4+ counts < 250 cells/mm3, Nevirapine is a valid option. However, the risk of serious hepatic events among women with CD4 counts >250cells/mm3 is 12-fold higher than women with CD4+ cell counts < 250. For this reason, Nevirapine use is contraindicated in women with CD4 counts >250. This creates particular challenges for pregnant women with higher CD4 cell counts. In these cases see table below that outlines the options based on CD4 counts in pregnancy.

**Table 1.7:- Antiretroviral Use in Pregnancy**

| CD4 Count | | Recommended Regimen in order of preference. | Alternative Regimen | Comments |
|---|---|---|---|---|
| First trimester | - If the patient is on ARVs- evaluate patients for appropriateness of regimen<br>- If the patient is not antiretroviral therapy, prepare patient for initiation in the second trimester ( clinical evaluation, laboratory investigations, adherence and other counselling)<br>-Begin CTX prophylaxis as needed. | | | |
| Second and third trimesters | CD4<250 | 1.TDF+FTC+EFV<br>2.TDF+FTC+NVP<br>3.AZT+3TC+EFV<br>4.AZT+3TC+NVP | AZT+3TC+LPV/r | In cases where there is a history of sdNVP exposure, PI (LPV/r) would be the preferred regimen |
| | CD4>250 | 1.TDF+FTC+EFV<br>2.AZT+3TC+EFV | AZT+3TC+LPV/r | |

In all cases in prescribing first line therapy the preservation of second line regimen remains of outmost importance.

- **Severe CNS toxicity or Mental Illness** – A significant proportion (approximately 50%) of individuals starting Efavirenz-based regimens will develop central nervous system (CNS) side effects, including dizziness, headache, sleepiness, insomnia, or depression. However, approximately 90% of patients are able to tolerate Efavirenz by the end of the first month of treatment. Thus, reassurance and symptomatic treatment of side effects is sufficient for most patients. In some cases – where destabilization of existing mental illness is a concern, or CNS side effects are intolerable – it may be advisable to change Efavirenz to Nevirapine or Lopinavir/Ritonavir (Alluvia). Due to concerns about serious hepatic adverse reactions with Nevirapine, its use is contraindicated in women with CD4 counts > 250 cells/mm3 (and in men with CD4 counts > 400 cells/mm3. In the rare event that neither Efavirenz nor Nevirapine use is possible, Lopinavir/Ritonavir or a NRTI-only regimen (see below) remain viable options.

## Use of Lopinavir/Ritonavir or Triple Nucleoside Regimens as part of First-Line Therapy

- Lopinavir/Ritonavir (LPV/r) in First-line: Use of LPV/r in first line regimens is cautioned as it may limit the efficacy of second-line regimens in the event of treatment failure. If in any case LPV/r is the only perceived first line option, consult with a specialist.
- Triple Nucleoside Regimens: Although all-NRTI regimens have the advantage of preserving future treatment options and having fewer drug interactions, several clinical trials have shown *suboptimal activity* when compared to NNRTI or PI-based regimens. However, when the use of Efavirenz, Nevirapine, and Lopinavir/ritonavir are contraindicated, there are three potential options (in recommended order):
  - Tenofovir/Emtracitabine + Zidovudine: The DART study demonstrated good efficacy of this regimen in resource limited settings and this can be particularly helpful for pregnant patients with Tuberculosis co-infection. However it has never been compared to existing NNRTI or PI based regimens.
  - Tenofovir/Emtracitabine + Zidovudine + Abacavir: This quadruple NRTI regimen has shown comparable responses to Efavirenz based regimens in small pilot studies, though there is insufficient high-quality long-term evidence to support this option.
  - Zidovudine + Lamivudine + Abacavir: This regimen has been extensively studied and shows good tolerability, though proved *inferior* to Efavirenz-based regimens.

## Additional Important Information Regarding First-Line ARVs

A more complete overview of ARV side effects (Appendix 1-D) and interactions (Appendix 1-E) is available in the appendices; however there are several important concerns to highlight in the consideration of first-line HAART regimens.

- **Zidovudine (AZT)** and **Stavudine (d4T)** should never be used together because of proven antagonism. Stavudine is rarely used in adults in Guyana.
- **Didanosine (ddI)** and **Stavudine (d4T)** should never be used together because of unacceptably high rates of pancreatitis, peripheral neuropathy and fatal lactic acidosis (particularly in pregnant women).

- **Didanosine (ddI)** and **Tenofovir (TDF)** together should be avoided due to intracellular antagonism. Use of ddI + TDF has also been linked to poor CD4 count rise. Should these two be necessary as part of an ART regimen, consultation with an HIV specialist is recommended.
- **Stavudine (d4T)** has unacceptably high rates of severe peripheral neuropathy and pancreatitis; its use is not recommended in persons with a history of either illness. Stavudine is also not recommended due to high rates of long-term mitochondrial toxicity manifesting in lipodystrophy, lipoatrophy, diabetes mellitus, and lipid disorders. Stavudine is rarely used in adults in Guyana.
- **Zidovudine** can cause a macrocytic anaemia and ideally should not be used in patients with severe anaemia or neutropoenia.
- **Efavirenz** is contraindicated during the first trimester of pregnancy due to high rates of neural tube defects in non-human primates. Counselling about family planning and contraceptive methods should be part of every visit for women on or starting Efavirenz. Women who become pregnant prior to 13 weeks on Efavirenz should be switched to a "pregnancy-friendly" regimen (see previous section) however pregnant women on Efavirenz after the first trimester should remain on same. Checking urine pregnancy tests prior to initiation of Efavirenz (and whenever indicated) is recommended.
- **Efavirenz**-related CNS side effects have been linked to hereditable differences in hepatic metabolism of the drug. Delayed rates of clearance (and hence, higher rates of adverse effects) have been observed more frequently in women, particularly of African descent.
- **Nevirapine** is contraindicated for women with CD4+ counts > 250 cells/mm3 and men with CD4counts > 400 cells/mm3 due to high rates of serious hepatotoxicity. This syndrome usually presents within the first several months of starting the drug, though can present at any time. It is manifested by abnormally high liver enzymes (> 5 times the upper limit of normal) and frequently accompanied by rash and flu-like symptoms. Nevirapine has also been linked to Stevens-Johnson Syndrome (Toxic Epidermal Necrolysis). Nevirapine should be *abruptly discontinued* whenever this syndrome is suspected and NRTIs continued for one week( See bullet below on Nevirapine and Efavirenz). ***Nevirapine should never be restarted in these patients.***
- **Nevirapine** should not be taken by patients receiving any regimen containing Rifampicin to treat TB, because Rifampicin reduces serum levels of Nevirapine. In these patients, Efavirenz is recommended.
- There is evidence to suggest that up to 25% of women who have received single dose **Nevirapine** (sdNVP) develop mutations leading to pan-NNRTI resistance, though there is some evidence to suggest that these mutations may disappear after six months. Women who have received sdNVP who are starting HAART regimens with either Efavirenz or Nevirapine should be carefully monitored for virologic, immunologic or clinical failure. There should be consideration of using a protease inhibitor LVP/r.
- Both **Nevirapine** and **Efavirenz** have longer serum half-lives than NRTI backbones. For this reason, when *stopping antiretroviral therapy*, it is recommended that the NNRTI be stopped first and the NRTI backbone be continued for 1 week to prevent prolonged exposure to NNRTI monotherapy.

## MONITORING ANTIRETROVIRAL THERAPY IN ADULTS AND ADOLESCENTS

Regular monitoring is an essential component of effective ARV treatment, permitting early detection of adverse events, ongoing reinforcement of patient adherence, and periodic assessment of treatment efficacy.

Early detection of adverse effects can reduce toxicity and prevent problems with adherence. Early detection of immunologic or clinical failure can help prevent accumulation of additional resistance mutations.

## Baseline and pre-Initiation assessment

In addition to establishing a baseline for ongoing review, the baseline assessment should serve as a means to provide counselling and support, begin discussions on secondary prevention and disclosure of HIV diagnosis, as well as to identify particular needs. It should be considered the first step in ongoing clinical monitoring. A thorough clinical and laboratory evaluation should be performed at enrollment (the baseline visit). If at the time of initiation of ART a significant amount of time has passed (or any significant clinical events have occurred) since the baseline visit, the extensive evaluation should be repeated prior to initiating HAART. Important clinical and laboratory monitoring information that should be attained at the baseline information is located in Table 1.8.

## Ongoing assessments

The majority of adverse effects with ARV medications occur within the first three months of initiation. However, some adverse effects, such as alterations in lipid profiles, may develop slowly over time. Thus, it is important to continually monitor individuals on antiretroviral therapy. The highlighted monitoring schedules [Table 1.8] are in addition to routine primary care expected for adults and adolescents.

**Table 1.8: Baseline and ongoing monitoring schedules**

| Test | Enrollment | Pre-Initiation | Ongoing Care |
|---|---|---|---|
| **Clinical** | | | |
| Complete Physical Exam | yes | yes | Continued focused physical exams based on regimens, risks, and patient concerns. |
| Weight | yes | yes | Every Visit |
| Height | yes | NA | Once per year for adults, very visit for adolescents |
| Treatment Readiness and Adherence Counselling | As needed | yes | At every clinical encounter and medication pickup. |
| **Laboratory- * If the time between enrollment and pre-initiation is less than 3 months, do not repeat test.** | | | |
| HIV Test | yes | N/A | N/A |
| *CD4 Count and CD4% | yes | yes | Every 3-6 months. Every 3 months is recommended for those recently starting HAART, clinically unstable patients, or those with CD4 <350. Once stable and adherent on HAART, can change to every 6 months. |
| HIV Viral Load | no - | no - | 6 months after beginning HAART Every 6 months thereafter |
| *CBC with Differential ( a | yes | yes | All: Recommended every 6 months or with CD4 sampling. |

| Test | Enrollment | Pre-Initiation | Ongoing Care |
|---|---|---|---|
| minimum of HgB and WBC) | | | AZT based regimen: Check 4-6 weeks after initiating AZT. Recheck at 3 and 6 months. If results are normal, can check every 6 months unless patient becomes symptomatic |
| *Creatinine (serum) | yes | yes | Every 6 months on HAART. |
| *Liver Function Test (a minimum of AST and ALT) | yes | yes | For patients on NVP based regimen, repeat at 2 weeks and at 4 weeks after initiation. For all other patients recheck at 4 weeks. For follow up of all patients repeat at 3 months and 6 months post-initiation, and every 6 months thereafter if normal. Repeat if clinically necessary |
| Serum Glucose | yes | no | Annually. |
| *Serum Cholesterol/Lipids | yes | no | Annually. Fasting lipid profile is recommended when available. More frequent monitoring if abnormal. |
| Urine Pregnancy | If indicated | yes | Repeat as indicated for missed menses, or unprotected intercourse on Efavirenz |
| PPD/Mantoux (not applicable once patient has a history of latent or active TB disease) | yes | - | Annually. If Mantoux converts to positive screen patient yearly with Chest X ray, DO NOT REPEAT PPD. Check pathway for TB assessment [outlined in Part III – Antiretroviral Therapy in Special Circumstances] |
| Chest X-Ray | - | yes | If indicated. |
| Visual Inspection with Acetic Acid (VIA) Cervical Cancer Screen (women only) | yes | - | Annually |
| Hepatitis B (HBsAg) | yes | - | Annually if sexually active or high risk. |
| RPR/VDRL | yes | - | Annually if sexually active or high risk. |

The complete physical exam that is part of the baseline assessment should include current and chronic illnesses, history of hospitalizations, history of drug allergies, current medications (including herbal medications), history of ARV therapy (including sdNVP for PMTCT), menstrual history (women only), family and social histories, and a detailed nutritional assessment. Areas of concern identified at the baseline visit should be explored at subsequent ongoing visits. It is also recommended that patients receive a thorough physical exam once yearly.

## Notes on CD4 cell count testing

CD4 lymphocyte counts are useful for assessing immunologic function, determining need to initiate opportunistic infection prophylaxis, determining eligibility for HAART, assessing the effectiveness of HAART, and diagnosing immunologic failure. *An increase in the CD4 lymphocyte count is expected in an ARV-naïve patient who is adhering to the treatment regimen.* CD4 counts should be monitored no less than every 3-6 months. For individuals not yet eligible for HAART, bigger changes in CD4 values over time is correlated with higher viral loads and may be an indication for more frequent (i.e. every 3 months) monitoring. For individuals on ART, viral load testing provides the first evidence for treatment failure, though as HIV replication continues, the CD4 count begins to plateau or drop. Routine CD4 absolute cell count and percentage monitoring for indications of immunologic failure while on HAART. Because intercurrent illnesses or immunizations can temporarily distort true CD4 values, it is recommend that CD4 testing be performed 1-2 weeks after an acute illness or immunization.

## Viral load testing

Effective antiretroviral therapy results in suppression of viral replication in the blood to levels below the threshold of detection ["undetectable viral loads"]. Changes in viral load precede changes in CD4+ counts and can identify treatment failure earlier than CD4 monitoring alone
Because intercurrent illnesses or immunizations can temporarily distort true viral load values, it is recommended that viral load testing be performed 4 weeks after an acute illness, surgery, hospitalization or immunization. In Guyana viral load testing began in 2009 and for adults is indicated at six months post initiation of HAART and thereafter every six months.

The National Public Health Reference Laboratory defines viral suppression as <400 copies per milliliter. Blips in viral load testing can occur up to 2000 copies per milliliter.

Reasons for viral load testing in Guyana are:

- Routine treatment monitoring for patients on ART
- Suspicion of treatment failure and or consideration of second line
- Repeat follow-up of prior high VL

Viral load testing is not recommended for the following reasons until after one month:

1. Immunization within the last month
2. Severe viral infections or hospitalizations
3. Recent surgery
4. Recent infections including malaria, TB disease, pneumonia

## Additional information on monitoring for specific ARV regimens

- ***TDF:*** Although rare, patients should be monitored for the development of renal insufficiency while on TDF-containing regimens. TDF-related renal insufficiency is usually manifested by increases in serum creatinine, though can also be manifest by glycosuria, hypophosphatemia, or rarely proteinuria. Monitoring of urinalysis every 6-12 months can be considered in high-risk patients (patients with borderline creatinine clearance, history of diabetes, etc.)
- ***AZT:*** All patients starting AZT should be monitored for potential development of anaemia. This includes clinical assessment of pallor in addition to CBC screening outlined above. Much anaemia on AZT may be due to other nutritional factors or HIV disease itself. It is therefore important to investigate these causes before ascribing anaemia to AZT. The anaemia from AZT is macrocytic and may improve with folate supplementation.
- ***ABC:*** Patients started on ABC containing regimens should be evaluated at 2 weeks, 4 weeks and 6 weeks following initiation of ABC for hypersensitivity reaction (HSR). Though rare (2-9%), abacavir HSR can be fatal with re-challenge. Abacavir HSR typically presents with fever, rash, and abdominal pain. Any patient identified as developing HSR to Abacavir should ***never*** be rechallenged with Abacavir. Abacavir HSR only develops within the first 6 weeks of starting ABC.
- ***d4T:*** As part of the routine clinical examination, any patient on d4T based regimens should be regularly evaluated for the presence of peripheral neuropathy or lipodystrophy. This drug is rarely used in adults in Guyana.
- ***NVP:*** The three most common and serious adverse effects from Nevirapine therapy are hepatitis, rash, and toxic epidermal necrolysis (TEN)/Stevens-Johnson Syndrome (SJS). Both drug induced NVP hepatitis and SJS/TEN can be potentially fatal. Screening for jaundice should be combined with liver function testing at 2 and at 4 weeks after starting NVP. TEN/SJS is a very rare, but potentially fatal, skin rash that involves sloughing of the epidermal layer and usually involves mucous membranes. Both TEN/SJS and hepatitis are much more common within the first 3 months of starting HAART. NVP can also cause a more benign rash without epidermal sloughing or mucous membrane involvement. This can be treated conservatively with anti-histamines and/or low doses of prednisone in most cases.
- ***EFV:*** The most common adverse effects from Efavirenz therapy are central nervous system side effects (dizziness, sleepiness, lethargy, vivid dreams, depression, etc.). These frequently (~95%) improve after the first month of therapy and can usually be managed conservatively. Additionally, Efavirenz can have a drug-related hepatitis, rash, and chance for SJS/TEN similar to NVP though these are less common and less serious than with NVP.
- ***LPV/r:*** Patients starting Lopinavir/ritonavir should be assessed for gastrointestinal side effects such as diarrhea and nausea. These side effects usually improve within the first 4 weeks of therapy and can usually be managed conservatively using anti-motility agents and dietary management. Additionally, long-term use of protease inhibitor therapy has been linked to insulin resistance and changes in cholesterol. It is recommended that an annual screen for blood sugar and cholesterol be part of the routine evaluation for patients on LPV/r.

## Recommended clinic visit schedules on HAART

- Pre-initiation: to assess support for and readiness to begin therapy, to provide for intensive education for patient and adherence partner*.
- Initiation.
- Two weeks post-initiation to assess short term toxicity.
- Four weeks post-initiation.
- Monthly until compliance/adherence is established.
- Subsequent visits should be scheduled based on treatment response, adherence assessment, signs and symptoms of disease, and adverse events. Longer intervals (2–3 months) can be given for patients who are stable and have a history of excellent adherence.

*An adherence partner is anyone selected by the index patient to assist him or her with drug adherence and social support. Ideally, it should be the partner or a member of the immediate family but could also be a friend, a coworker, etc. Whoever is chosen must be aware of the index patient's diagnosis, and be willing to come for some clinic visits with the patient and to help support the patient with adherence to the medication.

## Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is the paradoxical clinical deterioration after starting HAART that results when the improving immune system interacts with organisms that have colonized the body during early stages of HIV infection.
It is a pathogen specific cellular and humoral response to multiple opportunistic pathogens including mycobacteria, fungi and viruses. The most common cases of IRIS reported in Guyana are with tuberculosis, pneumocystis jiroveci (PCP), toxoplasma, Cryptococcus , herpes but also could occur with MAC, CMV, JC virus, cryptosporidiosis, microsporidiosis, HPV or any other opportunistic organism.
IRIS could present two scenarios:

1. Patient has begun treatment for an OI (an example pulmonary TB) and begins HAART. IRIS may develop complicating the response to treatment with paradoxical worsening of a treated OI (significant lymphadenopathy, fever and lethargy).
2. Clinically stable patient initiated on HAART who develop signs and symptoms of a dormant and previously unrecognized OI.

Whenever possible, all active OIs should be excluded or treated before initiating HAART to reduce the chance of developing IRIS. It is recommended to delay initiation with HAART for at least 2 weeks to 28 days or more, depending on the pathogen, pill burden, drug interaction and adverse effects. The symptoms of IRIS usually occur after 2-12 weeks after beginning HAART. Reassure and prepare the patient preferably at the time of initiation that this is temporary complication of their immune system improving with the assistance of HAART. IRIS commonly occurs in patients with a CD4 count <200.

**Treatment of IRIS:** Continue HAART and continue or start treatment for the relevant OI.
In few cases with severe inflammatory reaction the use of corticosteroids may be necessary. Recommended is prednisone 20 to 80 mg daily with tapering based on symptoms and should be prolonged for two to five weeks. Only in life threatening IRIS, HAART should be discontinued.

## ANTIRETROVIRAL SUBSTITUTION FOR TOXICITY OR INTOLERANCE

Some side effects to antiretrovirals are mild and/or transient, while others may require supportive therapy, more frequent monitoring, or even drug withdrawal. When significant adverse events are present, a drug is considered *toxic*. Symptoms and laboratory investigations help determine when the effects of an ARV are toxic. It is the clinician's responsibility to monitor for adverse effects based on the regimen being used. While the majority of patients on HAART experience no adverse effects, or experience mild and/or transient symptoms, some may require supportive therapy (e.g. antiemetics) or more frequent clinical monitoring. Rarely, symptoms may be severe enough to require changing the drug regimen.

Managing adverse events is an integral part of ARV therapy. If the adverse events are severe or disruptive, they will be a barrier to adherence to the ARV drug regimen. The clinician should explain to the patient in simple terms the risks and signs for common adverse events for each medication. Emphasis should be placed on the immediate reporting of the occurrence of any such adverse reaction. Unfortunately, in many instances, it is difficult to differentiate between the complications of HIV infection, a concurrent illness and adverse events secondary to ARV drugs. A grading system has been developed to assist the clinician with classifying the seriousness of adverse events. Ultimately, the clinician will determine the severity and whether the drug regimen needs to be changed.

- Treatment options for ARV side effects: **Mild or Moderate reactions**: Continue ARV therapy as long as feasible while providing reassurance and supportive therapy. Stress maintaining adherence despite current side effect. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.
- **Severe reactions**: Substitute the offending drug without stopping ARV therapy.
- **Severe life-threatening reactions**: Immediately discontinue all ARV drugs and manage the medical event (symptomatic and supportive therapy). Reintroduce ARV drugs using a modified regimen (i.e. substituting for the offending ARV) when the patient is stabilized.

If the adverse event can be linked to a drug in the regimen, it is advisable to replace the drug with one from the same class that is not associated with the same toxicities and does not interact with other drugs in the regimen. Common examples are listed in table 1.9.

**Table 1.9: Management of severe first-line antiretroviral drug toxicities**

| First-line Drug | Most Frequent Significant Toxicity | Suggested Management/Substitution Strategies |
|---|---|---|
| **TDF** | Fanconi Syndrome Nephrotoxicity | Change to ABC/3TC or AZT/3TC. |
| | Progressive renal insufficiency (not presenting with Fanconi syndrome or related to TDF) | Continue monitoring creatinine and dose of TDF/FTC. Switch therapy to ABC or AZT if CrCL < 10ml/min. Add an Angiotensin Coverting Enzyme Inhibitor (ACEI). |
| **ABC** | Hypersensitivity reaction | Discontinue ABC immediately. Substitute TDF or AZT if possible. |
| **AZT** | Anaemia or neutropoenia | Rule out malaria in endemic areas. Start with folic acid supplementation and frequent monitoring for mild cases. If meets severe criteria (Appendix 1-G), switch to TDF, ABC or d4T (in that order of preference) if possible. |

| | | |
|---|---|---|
| | Gastrointestinal intolerance | Manage mild cases with antiemetics and antimotility agents. If meets criteria for severe GI intolerance (Appendix 1-G), or intolerance is refractory or prevents ingestion of ARV regimen, switch to TDF, ABC, or d4T (in that order of preference) if possible. |
| **d4T** | Lactic Acidosis | Stop HAART immediately; once stabilized change regimen to TDF/FTC or ABC/3TC. |
| | Lipodystrophy, Insulin Resistance or Metabolic Complications | Use of d4T is rarely recommended due to high rates of metabolic side effects. Change therapy to TDF/FTC or ABC/3TC (in that order of preference). |
| | Peripheral Neuropathy | Use of d4T is rarely recommended due to high rates of metabolic side effects. Change therapy to TDF/FTC or ABC/3TC (in that order of preference). |
| | Pancreatitis | Stop drug immediately and change therapy to TDF/FTC or ABC/3TC (in that order of preference). |
| | Lactic Acidosis | Stop HAART immediately; once stabilized change regimen to TDF/FTC or ABC/3TC. |
| **EFV** | CNS Toxicity (including exacerbation of pre-existing mental illness) | Manage CNS toxicity through counselling and symptomatic management. When CNS toxicity becomes severe (Appendix 1-G), change to NVP when CD4<250 (women) or <400 (men). If unable to use NVP, change to LPV/r or NRTI-only regimen. |
| | Rash | Manage conservatively, using antihistamines and corticosteroids if necessary. If evidence of Stevens-Johnson Syndrome[a], stop therapy and weigh the advantages of following alternatives:<br>• Substitute EFV with third NRTI (usually AZT/FTC/TDF)[c]<br>• Substitute EFV with LPV/r[d] |
| | Hepatitis | Assess the severity of hepatitis (Appendix 1-G). For mild to moderate hepatitis, continue treatment with more intensive monitoring and review of medication regimen and alcohol intake. For persistent severe hepatitis, weight the advantages of substituting EFV with a third NRTI[c] or LPV/r. [d] |
| | New or anticipated pregnancy | Change to NVP if CD4 < 250. Otherwise, change to LPV/r during pregnancy and return to EFV after delivery. |
| **NVP** | Mild Hepatitis | Assess the severity of hepatitis (Appendix 1-G). For mild to moderate hepatitis, delay dose intensification and monitor closely. For severe hepatitis, follow the guidance below. |
| | Severe Hepatitis with Hypersensitivity reaction | Discontinue NVP. Continue NRTI backbone for 2 weeks then cautiously start EFV with intensive monitoring of LFTs. If there is no improvement, or EFV causes similar hepatotoxicity, weigh the advantages of substituting NVP/EFV with a third NRTI[c] or LPV/r.[d] |
| | Severe or life-threatening rash (Stevens-Johnson Syndrome[a]) | Discontinue NVP immediately; Start antihistamines and coritcosteroids as necessary. Weigh advantages of following alternatives based on the severity of the reaction: |

| | | |
|---|---|---|
| | | • Substitute EFV[b]<br>• Substitute NVP with third NRTI (usually AZT/FTC/TDF)[c]<br>• LPV/r[d] |
| **3TC** | Lactic acidosis-rare<br>Hepatomegaly with steatosis | Stop drug immediately. Once stable change to TDF/FTC<br>Monitor LFTs |
| **FTC** | Lactic acidosis-rare<br>Hepatomegaly with steatosis | Stop drug immediately. Once stable change to AZT/3TC<br>Monitor LFTs |

a) Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis; Stevens - Johnson syndrome can be life-threatening.
b) For life-threatening rash, most clinicians would not substitute EFV because of the potential for NNRTI-class specific toxicity.
c) Studies suggest triple NRTI are less potent than combination NRTI/NNRTI therapy.
d) The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure.

**For the guiding principle for the management of adverse effects please see appendix 1-F**

## TREATMENT FAILURE AND SECOND-LINE REGIMENS

### Treatment Failure and Resistance

Several factors play a role in treatment failure: poor adherence, sub-therapeutic drug levels, inadequate drug potency, and/or genetic differences in drug metabolism. All of these factors result in insufficient ARV drug levels which, in turn leads to HIV viral replication. Viral replication in the setting of insufficient drug levels provides selective pressure to promote the development of **drug resistance**. Drug resistance occurs when the HIV virus develops specific mutations that allow it to continue replication despite antiretroviral therapy. The drug resistant virus capable of replicating rapidly becomes the majority population of HIV virus in an affected patient, and these viral strains are archived in inactive CD4 cells and other viral reservoirs. Thus, once a patient has developed resistance to specific ARVs, this resistance is likely to remain throughout a patient's life, meaning that the affected ARVs will no longer be effective in suppressing HIV.

Suppression of HIV replication is best achieved when a minimum of three active antiretroviral agents are used. When a drug resistance mutation affecting one component of a triple-drug regimen develops, the patient only has two active agents remaining. Continuation of this regimen then makes the development of additional drug resistance to the remaining active agents even more likely. Continuations of failing regimens eventually lead to the gradual accumulation of additional drug resistance mutations. Drug resistance mutations not only permanently affect the current antiretroviral regimen but can seriously limit the efficacy of future treatment options. Thus it is ***very important to diagnose treatment failure early***. It is the clinician's responsibility, based on clinical and laboratory assessments, to determine when a drug regimen is failing, determine the reason why, and intervene appropriately.

## Definition of Treatment Failure

Treatment failure can be defined through virologic, immunologic and or clinical criteria. When antiretroviral regimens begin to fail, HIV replication can first be detected by measurement of detectable viral loads in the bloodstream (virologic failure). Continued viral replication results in the depletion or lack of an appropriate increase of CD4+ cells (immunologic failure). Finally, continued immunologic failure leads to the development of opportunistic infections (clinical failure).

**It is important to note the following**

-Virologic failure can be identified at varying viral loads depending on the current patient regimen. See table below

-Always correlate virologic failure with the CD4 and clinical pictures.

- Confirm failure with repeat VL.

| First-line Regimen | Failure at VL |
|---|---|
| TDF + FTC + EFV/NVP | Consider with VL >1000 and correlate with clinical and immunological findings |
| AZT/d4T + 3TC + EFV/NVP | >1000 copies /ml |
| ABC + 3TC + EFV/NVP | >1000/ copies/ml |

**WHO 2010 definition for clinical, immunologic and virologic failure in an adherent patient who has been on HAART for at least 24 weeks is as follows in table 1.10 below:**

**Table 1.10: Definition of treatment failure**

| Failure | Definition | Comments |
|---|---|---|
| Clinical Failure | New or recurrent WHO stage 4<br>and<br>Certain WHO stage 3 conditions including pulmonary TB (PTB) and severe bacterial infections may be an indication of treatment failure. | Condition must be differentiated from Immune Reconstitution Inflammatory Syndrome (IRIS)<br><br>Note-PTB may not necessarily indicate treatment failure and may not require evaluating whether a second line regimen is necessary. |
| Immunologic Failure | Fall of CD4 count to baseline or below<br>Or<br>50% fall from on- treatment peak value<br>Or<br>Persistant CD4 values <100 cells/mm3 | Without concomitant infection to cause transient CD4 count decrease |

| | | |
|---|---|---|
| Virologic Failure | Plasma viral load > 1000 copies/ml | A repeat viral load measurement is recommended before definitively diagnosing treatment failure |

***To confirm treatment failure an elevated viral load test is required prior to beginning second line regimens.***

## Assessing Treatment Failure

While other factors such as inappropriate ARV dosing, intercurrent infections or genetic differences in drug metabolism may also lead to treatment failure, the most frequent cause of treatment failure in adults is poor adherence. *Therefore, it is necessary to insure that adherence to therapy has been assessed and any challenges addressed before switching to a second-line regimen.* When patients are poorly adherent, it is frequently difficult to determine whether treatment failure results from negligible drug levels with active drugs or from drug resistance. Studies suggest that patients with moderate levels of adherence (50-92%) are at highest risk for drug resistance. In patients with very poor adherence (<50%), antiretroviral medication levels may not even be sufficient to generate selective pressure favoring resistance. Thus, it may be reasonable to intervene to support adherence and reassess shortly thereafter before switching to second-line therapy. ***Once treatment failure is diagnosed and suspected due to drug resistance, it is important to support adherence and switch to an appropriate second-line regimen***.

If adherence cannot be assured, treatment should be suspended while the patient receives ongoing counselling, and is continued on Cotrimoxazole until adherence can be assured. Continuing first-line therapy in the face of obvious therapeutic failure is not recommended as additional mutations can accumulate lowering the efficacy of second-line therapy. In rare instances, continuing Lamivudine (3TC) monotherapy [see section in 2nd Line Regimens] may be beneficial until adherence can be assured and second-line started; this should only be attempted after consultation with an HIV specialist.

## Second line regimen in the event of treatment failure

When treatment failure is confirmed, it is necessary to switch to a second-line ARV regimen. The most effective second-line therapy would involve including three antiretrovirals that would be expected to be active given the patient's ARV history. Without the ability to perform resistance testing, clinicians should consider the patient's antiretroviral history when selecting a second-line regimen. In patients who have been exposed to several first line regimens, it should be assumed that drug resistance has occurred to the components of the regimen the patient was taking when treatment failure was diagnosed. Although prior agents (e.g. discontinued due to intolerance) may still be active, it may be important to consider them in selecting a second-line regimen. Since patients are not (usually) exposed to protease inhibitors as part of first-line therapy, they remain the lynchpin of second-line HAART.

**Table 1.11: Selection of appropriate Second-Line regimens based on First-Line therapy**

| First-line Regimen at Failure | Appropriate Second-Line Options(s) |
|---|---|
| TDF + FTC + EFV/NVP | TDF + FTC + AZT + LPV/r[a] |

| | |
|---|---|
| AZT/d4T + 3TC + EFV/NVP | TDF + FTC + AZT + LPV/r[a] |
| ABC + 3TC + EFV/NVP | AZT + 3TC + LPV/r |
| Any NRTI-only Regimen | TDF + FTC + AZT + EFV/NVP[b]<br>TDF + FTC + LPV/r |
| Any Protease Inhibitor Regimen[c] | TDF + FTC + AZT + LPV/r |

a) Given the limited efficacy of NRTI options after failure of thymidine analogue containing regimens, a triple nucleoside backbone is recommended.
b) Use of an NNRTI (if possible) could be considered in patients without presumed resistance to NNRTI. This strategy has the advantage of saving lopinavir/ritonavir for future use.
c) Use of Protease inhibitors as part of a first-line regimen is not recommended. However, in cases of severe NNRTI toxicity, PI-regimens may be used as part of first line. Please see the following information on salvage regimens.

**Principles behind selection of agents in First-Line treatment failure**

Although there is some individual variability, antiretroviral medications tend to develop resistance in predictable patterns. Multiple studies on the development of resistance mutations and the efficacy of ARV drugs in the presence of common drug mutations have allowed us to learn important lessons for creating ARV regimens in the absence of resistance testing:

- The most common early mutations that occur in first line regimens are mutations to the NNRTI (EFV or NVP) component and a mutation (M184V) that affects 3TC/FTC.
- No NNRTI can be used among the second-line drugs once an NNRTI was used as first-line because the most common type of resistance—K103N resistant mutation—confers cross-class resistance to all NNRTIs.
- While the M184V mutation confers high-level resistance to both 3TC and FTC, there is some efficacy in retaining 3TC/FTC as part of the second-line regimen. The M184V mutations decrease the viral replicative capacity and make the HIV virus hyper-susceptible to both TDF and AZT.
- Patients taking thymidine analogues (AZT or d4T) as part of the first line regimen have a propensity to develop thymidine analogue mutations "TAMs". These are a group of mutations which affect all medications in the NRT I class, and may even reduce the efficacy of other classes of ARVs. The efficacy of other ARVs is reduced the more TAMs accumulate.
- Resistance to TDF develops through a K65R mutation. While this mutation affects the efficacy of all-NRTIs, TDF and AZT both retain partial efficacy. Since TDF has a high threshold of resistance, it is frequently uncertain if the K65R has developed in addition to other mutations. Here again, AZT use my help delay the emergence of the K65R. ddI may also retain some efficacy, though the combination of TDF + ddI is no longer recommended because of intracellular drug interactions and concerns about persistent CD4 lymphocyte count decline.
- ABC retains very little efficacy in the setting of TAMs (in the case of failure on AZT/d4T) or the K65R mutation (in the case of failure on TDF).
- LPV/r should retain full efficacy in adherent patients who have not been exposed to protease inhibitors. Resistance to ritonavir-boosted PIs occurs through the slow accumulation of PI-associated mutations.

Because of the high genetic barrier to resistance, several PI-associated mutations are required before LPV/r will begin to lose efficacy. Even in the setting of PI resistance, there is usually some reduction in viral replicative capacity.

## Salvage regimen

When the second-line (or first-line PI regimen) regimen fails, there is likely resistance to many of the ARVs in the regimen. It is recommended that clinicians contact an experienced HIV treatment specialist. The use of certain antiretrovirals, even in the setting of resistance, can reduce morbidity and mortality due to HIV infection, by reducing viral fitness and the rate at which HIV replicates (the replicative capacity). Lamivudine or Emtracitabine (3TC or FTC), Tenofovir (TDF) and Lopinavir/Ritonavir (LPV/r) have this effect. Thus it is recommended that clinicians continue the use of second-line regimens while contacting the National Care & Treatment Center (NCTC) in the setting of treatment failure to second-line regimens. The National AIDS Programme Secretariat is investigating the possibility of procurement of small stocks of newer antiretrovirals that may work in the setting of second-line failure. These medications would be carefully monitored and prescribed by the NCTC.

## The use of "Holding Regimens" (3TC Monotherapy)

While continued use of failing NNRTI or PI antiretrovirals leads to the continued accumulation of resistance mutations, continued exposure to 3TC/FTC in the setting of M184V does *not* lead to the additional accumulation of resistance mutations. 3TC/FTC has also been shown to reduce the replicative capacity of the virus even in the presence of M184V. For patients with multiclass resistance, the use of 3TC monotherapy has been shown to reduce CD4 decline and overall mortality compared to complete cessation of ARVs. Thus, in situations where 3TC resistance is highly likely, 3TC monotherapy may be considered as a bridge to a new regimen. However, this is only recommended when potential new therapies (with suspected efficacy against HIV) are expected in the near future *and* the use of other ARVs (TDF and LPV/r especially) may impact the efficacy of the anticipated regimen. Consultation with an experienced clinician is recommended before using 3TC monotherapy.

## Rechallenging with ARVs.

For patients who have stopped their ARV and require re initiation, it is important that a detailed and clear history be obtained.
The following should be considered in the decision to rechallenge on original ARV regimen:
1. Patients during treatment with ARVS had good virologic suppression.
2. Patient has a good history of adherence
3. Patient stopped all ARVS at one time.

Under these circumstances it is recommended that the patient be re-challenged on the original regimen

# MANAGEMENT OF CHRONIC DISEASE AND COMORBIDITIES

## Life Expectancy and Comorbidities in the era of HAART

Since the advent of highly active antiretroviral therapy, the life expectancy of persons living with HIV has been raised dramatically. Prognostic models, developed from longitudinal cohort studies of PLHIV have

suggested that the life expectancies of PLHIV can match, or nearly match, those of their HIV-negative peers. This has lead to a shift in the management of HIV infection away from an acute care model to more of a chronic disease model. As PLHIV are living longer, they will have more time exposed to HIV, antiretroviral therapy, and the psychosocial consequences of living with a potentially stigmatizing chronic disease. As such, to maximize both the life expectancy and quality of life, the astute clinician must also have a solid understanding of the interplay of HIV and HAART on chronic disease, as well as the best management strategies for common comorbidities.

*The Role of HAART:* Antiretroviral medications alter the ability of the HIV virus to replicate using host cell machinery in conjunction with several prepackaged enzymes. Naturally, it is not unexpected that long-term use of antiretrovirals may have unintended consequences for host physiology. Several ARVs have been linked to metabolic abnormalities, including alterations in fat metabolism, cholesterol levels and insulin resistance. Although these effects are minor in comparison to their ability to reduce HIV replication, they are important to monitor, especially in patients with pre-existing comorbidities. One challenge in trying to asses the role of ARVs in the development of comorbidites is differentiating the role of specific ARVs apart from the role of the combination of medications (some of which may have synergistic properties). In addition, because many physiologic changes may be subtle (e.g. insulin resistance), significant time can pass before clinical disease (e.g. diabetes) becomes apparent. During this time, patients may have changed HAART regimens, providing further challenges to researchers trying to determine the effect of different ARVs on the development of comorbidites. Despite these challenges, there is some consensus that specific ARV medications are concerning for the development of medical comorbidites. A brief overview is outlined in Table 1.11.

**Table 1.11. Overview of Medical comorbidities and HAART**

| ARV Class | Concerns |
|---|---|
| NRTIs | • Most NRTIs (particularly thymidine analogues) except TDF and ABC have been linked to the development of lipodystrophy.<br>• Stavudine, a potent mitochondrial toxin, has been linked strongly to the development of lipodystrophy and the development of dyslipidemias.<br>• The mitochondrial toxicity of Stavudine is enhanced by co-administration of Didanosine; these two should never be used together.<br>• There is evidence to suggest that changing a thymidine analogue (d4T or AZT) based regimen to either a TDF or ABC containing regimen may lead to improvement in lipid parameters and lipodystrophy.<br>• There is a very small, but increasing, body of evidence to suggest that ABC and ddI may be linked to higher risks of myocardial infarction (MI). It is still not entirely clear whether this effect is due to the medication or selection bias (e.g. patients at risk for MIs are placed on ABC) |
| NNRTIs | • Efavirenz is associated with higher levels of triglycerides. |
| PIs | • Ritonavir-boosted protease inhibitors, including LPV/r, are associated with the development of insulin resistance through the blocking of the glut-4 glucose transporter on some cell membranes.<br>• The insulin-resistance from protease inhibitors seems to increase with increasing doses of ritonavir.<br>• LPV/r, in addition to other PIs, is also associated with higher LDL levels. One exception |

| ARV Class | Concerns |
|---|---|
| | is ATV. |

*The Role of HIV Infection:* While early research focused more on the role of ART in the development of metabolic complications, recent randomized clinical trials and prospective cohort studies have provided evidence that time *off* antiretroviral therapy (and thus more time exposed to HIV viral replication) is associated with increases in the severity and incidence of several comorbidities, including cardiovascular disease, renal disease, liver disease, and non-HIV associated malignancies. Ongoing HIV replication leads to continued production of inflammatory mediators which in turn may have significant consequences on human physiology – perhaps even more significant than the consequences of HAART. As the role of the immune system in the prevention of "non-infectious" complications (such as malignancies) is increasingly recognized, it follows that immunosuppression can be an important risk factor in the development of "non-infectious" chronic disease.

In truth, it can be very difficult to tease apart the role of HIV infection, HAART, pre-existing genetic tendencies and social, environmental and dietary factors in the development of chronic medical comorbidities. However, there are some best practices for common comorbidities outlined below.

## Management of Common Comorbidities

**Cardiovascular Disease and Dyslipidemias**
Traditional risk factors associated with the development of Coronary Artery Disease (CAD) have been well defined. They include age, gender, tobacco use, family history of CAD, and the presence of diabetes, hypertension, or dyslipidemias. PLHIV tend to have higher rates of tobacco use and are at risk for dyslipidemias from HAART. Still, PLHIV have *higher* observed rates of CAD than what would be expected based on predictive models with known risk factors, suggesting that HIV infection may also serve as a risk factor for the development of CAD.

Asymptomatic HIV-infected patients should be screened regularly for CAD risks as outlined in the "Monitoring Antiretroviral Therapy" section. Screening should take place more frequently for those identified as higher-risk. Screening includes evaluation for the presence of hypertension (blood pressure monitoring), diabetes (glucose screening), obesity (weight and body mass index monitoring), tobacco use (performed while taking the history) and dyslipidemias (cholesterol screening).

HIV infection and HAART are both associated with changes in serum cholesterol. Cohort studies suggest that HIV-infection leads to a global decrease in levels of circulating cholesterol (LDL, HDL and total), though leads to increased levels of triglycerides. Most antiretroviral medications (with TDF, ABC, and ATV the most noteworthy exceptions) are associated with increases in circulating cholesterol and triglycerides. While HAART may play a role in the development of dyslipidemias, in the absence of a suitable alternative for substitution (e.g. substituting TDF for d4T), continuing HAART while intervening to reduce the lipid abnormality is the recommended course of action.

**Approach to lipid disorders for patients living with HIV**

- Obtain fasting lipid profile (where available), prior to initiating antiretrovirals and within 3-6 months of starting new regimens.
- Assess overall cardiac risk factors (below) to determine the optimal level of lipid control.
- Recommend low-fat, low-cholesterol diets for patients with elevated lipid levels.
- When lifestyle interventions alone are insufficient consider pharmacotherapy:
  - For elevated LDL levels, an HMG-coA Reductase inhibitor ("statin") is the most effective medication strategy. *Be careful of the use of statins with protease inhibitors. Simvastatin is contraindicated due to drug-drug interactions* (Appendix 1-F). Atorvastatin can be used with caution at low levels (10mg once daily).
  - There are few options in Guyana for low levels of HDL cholesterol. Nicotinic acids have the greatest effect; however it is poorly tolerated by patients.. Exercise also produces modest benefit.
  - For elevated triglycerides, fish oil and fibrates have both shown efficacy in reducing serum triglycerides.
- Recommend a fibrate (Gemfibrozil or Fenofibrate) if serum triglycerides > 500 mg/dL.

There are several validated 'calculators' available which can estimate the chance of having a myocardial infarction in the next ten years based on pre-existing risk factors. An interactive calculator is available online at http://hin.nhlbi.nih.gov/atpiii/calculator.asp.

**Management Strategies for Patients with suspected or confirmed CAD**

- ECG testing may help in the diagnosis of past MI in patients with suspected CAD or identify symptomatic patients at high risk for imminent MI.
- Aspirin therapy (81-325mg) daily reduces the risk of MI in individuals with CAD.
- ACE-inhibitors (unless contraindicated) also reduce the risk of subsequent MI in individuals with a previous history of MI.
- Maintain glycemic control – fasting glucose levels below 100 mg/dl.
- Maintain LDL levels below 100mg/dl, preferably below 70mg/dl; goal HDL levels are > 45mg/dl, and maintain triglyceride levels below 150mg/dl
- Low-dose statins compatible with HAART regimens have lead to further reductions in morbidity and mortality in patients even with acceptable LDL levels.
- Blood pressure control: systolic below 130, and diastolic below 80.
- Well balanced diet (high fiber, low fat).
- Regular exercise consisting of a minimum of thirty minutes exercise, five times per week.
- Smoking cessation – may be the *single most important* modifiable risk factor in the development of CAD.

## Lipodystrophy

Several antiretrovirals – particularly thymidine analogues from the NRTI class have been associated with "lipodystrophy" syndromes. Lipodystrophy refers to changes in the normal metabolism and storage of adipose (fat) tissue in the human body. A subset, lipoatrophy, refers specifically to the *loss* of fat tissue from areas where it is normal stored. Many patients with lipodystrophy may have both abnormal fat accumulation (e.g. buffalo hump, visceral adiposity) and abnormal fat loss (e.g. facial wasting). Lipodystrophy can be very disfiguring and stigmatizing for PLHIV, and the development of lipodystrophy has been associated with subsequent poorer treatment adherence. The best intervention studies for lipodystrophy involve changing

thymidine analogue medications (d4T and AZT) to either TDF or ABC. Both decrease the development of lipoatrophy and may result in slow redistribution of fat to more normal distributions. However, the process is very slow and patients should be counseled that benefits (if they arrive) may take significant time to appear. The effect of other pharmacotherapies (e.g. Metformin, growth hormones) for the treatment of lipodystrophy have been studied, though to date remain entirely experimental; frequently adverse effects outweigh any potential benefit and these measure are *not* recommended.

**Lipodystrophy Summary**

- Avoid the use of thymidine analogue NRTIs (particularly stavudine) whenever possible.
- In patients on thymidine analogues who develop lipodystrophy and can be safely switched, replace d4T or AZT with TDF or ABC.
- Counsel patients that recovery from lipodystrophy may be possible, though will be a long process.

## Diabetes Mellitus

Increased insulin resistance has been linked to protease inhibitors (particularly Ritonavir-boosted protease inhibitors such as LPV/r) and to a lesser extent Stavudine and other NRTIs. PI related insulin resistance is hypothesized to occur through blocking of a glucose transporting channel (which transports glucose into the cell in response to insulin secretion) on cell membranes. Hence, it is particularly important to monitor for the development of diabetes in patients on second-line (or first line LPV/r) therapy. Fasting (FBS) or random (RBS) glucose screening (at least annually) is recommended for HIV positive patients, or sooner if symptoms of diabetes are present. A schematic for diagnosis based on glucose results is located in Table 1.12. Appropriate glycemic control has been shown to reduce the incidence of renal, ophthmalogic and neurologic complications due to diabetes.

**Table 1.12 Follow-up of fasting plasma glucose screening for diabetes mellitus**

| First FBS, mg/dL | Repeat FBS, mg/dl | Diagnosis | Treatment |
|---|---|---|---|
| >125 | >125 | DM | Treat for DM |
| >125 | 101-125 | Indeterminate | Treat AS IFG (Impaired Fasting Glucose) |
| >125 | <100 | Indeterminate | Repeat; if >125 treat as DM; if 101-125 treat as IFG; <100 consider normal |
| 101-125 | >125 | Indeterminate | Treat as IFG |
| 101-125 | 101-125 | IFP | Treat as IFG |
| 101-125 | <100 | Indeterminate | Repeat; if >125 treat as DM; if 101-125 treat as IFG; <100 consider normal |
| **First RBS, mg/dL** | **Repeat FBS, mg/dl** | **Diagnosis** | **Treatment** |
| ≥220 | >125 | DM | Treat for DM |
| ≥220 | 101-125 | Indeterminate | TREAT AS IFG |
| ≥220 | <100 | Indeterminate | Treat as IFG |
| 120-200 | >125 | Indeterminate | Repeat; if >125 treat as DM; if 110-125 treat as IFG; <110 consider normal |
| 120-200 | 101-125 | Indeterminate | Repeat; if >125 treat as DM; otherwise treat as IFG |

| | | | |
|---|---|---|---|
| 120-200 | <100 | Normal | Recommend Annual screening |
| FBS: Fasting Blood Sugar; RBS: Random Blood Sugar; DM: Diabetes Mellitus; IFG: Impaired Fasting Glucose | | | |

*Adapted from UpToDate*

Diet and exercise is the first step in the management of Diabetes Mellitus (DM). Dietary modification as well has regular daily exercise has been shown to improve insulin sensitivity and reduce complications of diabetes. Additionally, available pharmacologic agents in Guyana have proven efficacy in the treatment of diabetes. Metformin is the initial choice for the treatment of type 2 noninsulin DM. In addition to glycemic control, Metformin can contribute to weight reduction and stabilization. However Metfomin can lead to lactic acidosis and should be avoided in patients with renal insufficiency (creatinine>1.4 in women and >1.5 in men), congestive heart failure, chronic severe liver disease or in cases of severe tissue hypoperfusion (acute sepsis). Sulfonylureas are also available in Guyana, and can moderately decrease glucose levels by increasing pancreatic insulin output. Sulfonylureas are recommended as an adjuvant to Metformin or for use as a first line anti-diabetes agent when Metformin is contraindicated or unavailable. Insulin therapy, where available, can be used for patients in whom glycemic control is unachievable using oral agents. Insulin can be utilized in combination with oral agents.

## Nephropathy

The management of Chronic Renal Disease (CRD) in the setting of HIV disease is important to slow the progression to End Stage Renal disease. Patients with persistently abnormal renal function should be worked up for all possible treatable causes.

Recommendations for management of CRD are as follows:

- Strict control of DM and HTN.
- Addition of Angiotensin Converting Enzyme Inhibitor.
- Renal diet.
- Renal dosing of all potentially nephrotoxic medications.

## Cervical Cancer Screening

The risk of developing cervical cancer in HIV-positive women is ten times greater than that of their HIV-negative peers. In addition the rate of progression of the disease is inversely related to CD4 counts. Cervical cancer screening via visual inspection with acetic acid (VIA) is recommended annually. Screening via Papanicolaou (PAP) smear is also acceptable, though it is more expensive. Initial referral for screening is recommended within the first 1 to 3 months of the primary visit. VIA is a proven methodology with high sensitivity and specificity and has the advantage of a single visit approach.

## Family Planning.

Women living with HIV should be given realistic, accurate and appropriate counselling regarding family planning. It is important to explore a woman's desire for children, the status of her partner, the presence of outside support, and issues with disclosure of HIV infection before providing thoughtful, non-judgemental counselling regarding the advantages and disadvantages to different methods of family planning and risks of mother to child transmission of HIV infection. An overview of family planning options is located in Table 1.13.

**Table 1.13: Overview of family planning options**

| Method | Notes for the HIV-positive Woman |
|---|---|
| **Condoms (male & female)** | Recommended whenever the patient is not actively trying to conceive; has the additional benefit of protection against other STIs and HPV infection. Patients require adequate training in the application, storage and removal of condoms. |
| **Intrauterine device** (copper-bearing or hormonal IUDs) | A woman with HIV can have an IUD inserted, however women with clinical AIDS should not have an IUD inserted unless she is clinically well on ARV therapy. (A woman who develops AIDS while using an IUD can safely continue using the IUD.) |
| **Female sterilization** | Women who are infected with HIV, have AIDS, or are on antiretroviral therapy can safely undergo female sterilization with proper informed consent. Special arrangements are needed to perform female sterilization on a woman with AIDS to prevent sepsis. Delay the procedure if she is currently ill with AIDS-related illness. |
| **Vasectomy** | Men who are infected with HIV, have AIDS, or are on antiretroviral therapy can safely undergo vasectomy. Special arrangements are needed to perform vasectomy on a man with clinical AIDS. Delay the procedure if he is currently ill with AIDS-related illness. |
| **Spermicides** (including when used with diaphragm or cervical cap) | Should not use spermicides when an uninfected woman is at risk of HIV; spermicides can irritate the vaginal mucosa leading to increased transmission of HIV (or drug-resistant HIV virus to an HIV-positive woman with an HIV-positive partner on HAART). |
| **Hormonal methods** (combined oral contraceptives, progestin-only pills, progestin-only injectables, monthly injectables, patches, rings, implants) | Can safely use any hormonal method unless she is on ARV therapy that includes a Ritonavir-boosted protease inhibitor. For patients taking Ritonavir-boosted protease inhibitors (e.g. LPV/r), she generally should not use combined (estrogen-progesterone) oral contraceptives or progestin-only pills, as they may be less effective. She can use progestin-only injectables or implants. Women whose ARV therapy does not include a ritonavir-boosted protease inhibitor can use any hormonal method. |

## Smoking and the HIV infected patient

The prevalence of smoking in the HIV population is markedly elevated as compared to their non HIV infected counter parts. Like HIV, smoking is a risk factor for diabetes , cancer, Chronic Obstructive Pulmonary Disease, Erectile Dysfunction and Coronary Heart Disease (CAD) and when combined presents an increased risk for associated morbidity and mortality

### *Smoking Screening*

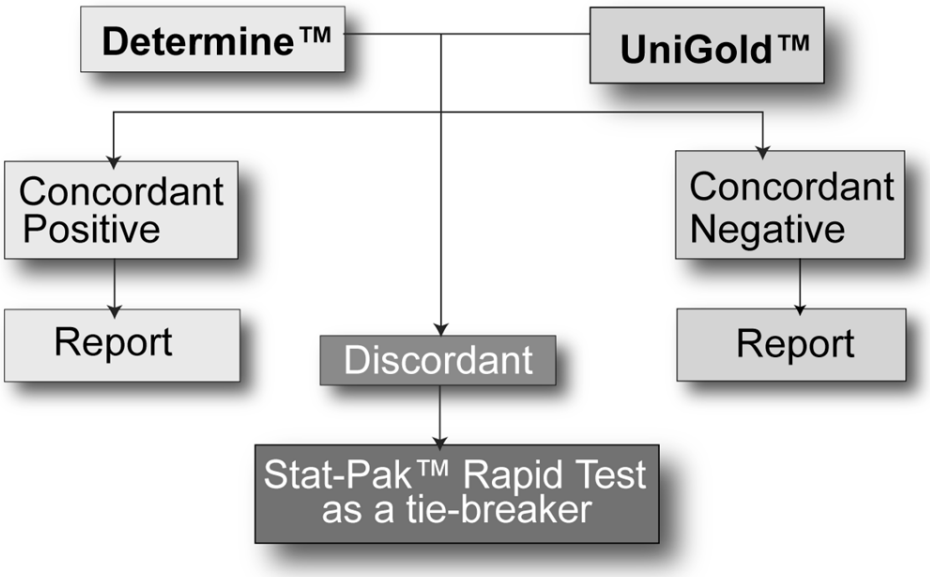
For all HIV patients' particularly non smokers it is essential that there be ongoing education on the benefits of not smoking. Patients who smoke should be offered smoking cessation counselling on every visit. Recommendations on smoking cessations counselling

- Recommend 5 to 15 minute interactive discussion between patient and health care provider.
- Provide printed materials on the benefits of smoking cessation
- Identify health benefits and financial gains from smoking cessations
- Encourage defaulters to reattempt cessation efforts despite their multiple previous failed attempt

# APPENDICES

## Appendix 1–A

### Guyana HIV Testing Algorithm HIV Rapid Test



## Appendix 1–B
## Revised WHO Clinical Staging System of HIV Infection and Disease in Adolescents and Adults

| **Clinical Stage 1**[a] |
|---|
| ▪ Asymptomatic<br>▪ Persistent generalized lymphadenopathy |
| **Clinical Stage 2**[a] |
| ▪ Unexplained persistent hepatosplenomegaly<br>▪ Papular pruritic eruptions<br>▪ Extensive wart virus infection<br>▪ Extensive molluscum contagiosum<br>▪ Recurrent oral ulcerations<br>▪ Unexplained persistent parotid enlargement<br>▪ Lineal gingival erythema<br>▪ Herpes zoster<br>▪ Recurrent or chronic URTI (otitis media, otorrhea, sinusitis, tonsillitis)<br>▪ Fungal nail infections |
| **Clinical Stage 3**[a] |
| ▪ Unexplained moderate malnutrition not adequately responding standard therapy<br>▪ Unexplained persistent diarrhea (≥14 days)<br>▪ Unexplained persistent fever (>37.5intermittent or constant >1 month)<br>▪ Persistent oral Candida (outside of first 6-8 weeks of life)<br>▪ Oral hairy leukoplakia<br>▪ Acute necrotizing ulcerative gingivitis /periodontitis<br>▪ Symptomatic lymphoid interstitial pneumonitis<br>▪ Lymph node TB<br>▪ Pulmonary tuberculosis<br>▪ Severe recurrent presumed bacterial pneumonia<br>▪ Chronic HIV associated lung disease including bronchiectasis<br>▪ Unexplained anaemia (<8g/dl), neutropenia (<500/mm3) or chronic thrombocytopenia (<50,000/mm3)<br>▪ HIV associated cardiomyopathy or HIV associated nephropathy |
| **Clinical Stage 4**[a] |
| ▪ Unexplained severe wasting , stunting or severe malnutrition not responding to standard therapy<br>▪ *Pneumocystis* pneumonia (PCP)<br>▪ Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonias<br>▪ Chronic herpes simplex infection>1 month<br>▪ Kaposi's sarcoma<br>▪ Extrapulmonary tuberculosis<br>▪ Toxoplasmosis on the brain<br>▪ Oesophageal candidiasis<br>▪ CNS toxoplasmosis outside of neonatal period<br>▪ Cryptococcal meningitis |

- HIV encephalopathy

**Clinical Stage 4**[a]

- Cryptosporidiosis with diarrhea>1 month
- Isosporiasis with diarrhea>1 month Progressive multifocal encephalopathy
- Cytomegalovirus infection (retinitis)
- Acquired HIV associated fistula
- Cerebral or B cell non Hodgkin lymphoma
- Disseminated endemic mycosis
- Chronic cryptosporidiosis
- Chronic Isosporiasis
  Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
  Progressive multifocal leukoencephalopathy
  Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a: Unexplained refers to when the condition is not explained by other causes.

World Health Organization (WHO) *WHO Case Definitions of HIV for Surveillance, and Revised Clinical Staging and Immunological Classification of HIV Related Disease in Adults and Children, May 2006.*

## Appendix 1–C
## ARV Adverse Reactions

| Type | Drug | Comment |
|---|---|---|
| **Potentially fatal** | | |
| Pancreatitis | ddI, d4T | Stop drug immediately. Substitute the causative drug. |
| Hypersensitivity reactions | ABC | Stop drug immediately. Do not re-challenge. Substitute the causative drug |
| Toxic epidermal necrolysis Stevens-Johnson Syndrome | NVP | Stop drug immediately. Substitute the causative drug |
| Lactic acidosis | All NRTIs | Stop drug immediately. Substitute the causative drug |
| Psychosis, major depression | EFV | Stop drug immediately. Substitute the causative drug |
| Acute hepatotoxicity | NVP | Manage according to criteria below. |
| Haematologic toxicity | AZT | |
| **Disabling** | | |
| Peripheral neuropathy | ddI, d4T | Stop drug immediately. Substitute the causative drug. |
| Hepatotoxicity | NNRTIs, PIs | Manage according to criteria below. |
| **Long-term** | | |
| Lipoatrophy | NRTIs | Patient needs to be referred to an experienced HIV clinician. |
| Lipodystrophy | PIs, all NRTIs | |
| Hyperlipidaemia | PIs, all NRTIs, EFV | |
| Insulin resistance | D4T and PIs | |
| Lactic acidosis | All NRTIs mainly d4T, ddI | Stop drug immediately and manage accordingly. |
| ddI = didanosine, d4T = stavudine, ABC = abacavir, NVP = nevirapine, NRTI = nucleoside reverse transcriptase inhibitor, EFV = efavirenz, AZT = zidovudine, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor | | |

*Source:* Adapted from Rabkin M, W El-Sadr, and E Abrams. 2003 *The MTCT-Plus Clinical Manual.* Mailman School of Public Health, Columbia University. Retrieved 20 November 2004, from http://www.mtctplus.org/pdf/ClinicalManual.pdf.

## Appendix 1–D
## Drug Interactions

| Drug category | Calcium channel blocker | Cardiac | Lipid lowering agents | Anti-mycobacterial | Anti-histamine | Gastro-intestinal drugs | Neuro-leptic | Psyco-tropic | Ergot Alkaloids | Herbs | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Indinavir (IDV) | none | amiodarone | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | Cisapride | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | atazanavir |
| Ritonavir (RTV) | bepridil | amiodarone flecainide propafenone quinidine | simvastatin lovastatin | rifapentine | astemizole terfenadine | Cisapride | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | voriconazole (with RTV ≥400 mg bid fluticasone |
| Saquinavir (SQV) | none | None | simvastatin lovastatin | rifampin rifabutin rifapentine | astemizole terfenadine | Cisapride | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | |
| Nelfinavir (NFV) | none | None | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadi | cisapride | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) | St John's | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ne | | | | ergotamine (various forms) ergonovine methylergovonine | Wort | |
| Lopinavir + Ritonavir (LPV + RTV) | none | flecainide propafenone | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | Cisapride | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | |
| Atazanavir (ATV) | bepridil | None | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | cisapride proton pump inhibition | pimozide | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | indinivair irinotecan |
| Efavirenz | none | None | none | rifapentine | astemizole terfenadine | Cisapride | none | midozolam triazolam | dihydroergotamine (DHE 45) ergotamine (various forms) ergonovine methylergovonine | St John's Wort | Voriconazole |

## Appendix 1–E
## Laboratory Monitoring Schedule and Follow-up Visits for Antiretroviral Therapy

| Test | Frequency |
|---|---|
| HIV test | Baseline |
| CD4 lymphocyte count* | Baseline and every 3–6 months |
| Viral Load | 6 months after HAART initiation |
| CBC and differential* | Baseline, and every 3-6 months with CD4<br>If on AZT-2-6wks,3 months and then every 6 months |
| VDRL | Baseline and annually |
| HBsAg | Baseline, when clinically indicated |
| Pregnancy* | Baseline (as indicated) |
| Chest X-ray | Baseline (as indicated) |
| Liver function test* | Baseline, 2 weeks after initiation, 4 weeks after initiation and subsequently every six months. |
| Renal function test | Baseline and every 6 months |
| Cervical Cancer Screening(VIA) | Baseline and annually |
| PPD* | Baseline and annually until positive, if never had INH prophylaxis/TB disease treatment. Then monitor with yearly chest x-rays |
| Toxoplasmosis immunoglobulin (IgG) | Baseline and repeat if<br>CD4 lymphocyte count <100 cells/$mm^3$ |
| Serum amylase, lipase | Baseline and if symptomatic |
| Serum glucose | Baseline and every 6–9 months for patients taking PIs and if otherwise indicated |
| Serum lipids | Baseline and every six months for patients with abnormal baseline values or taking PIs, d4T, or Efavirenz |
| **Optional tests** | |
| Serum lactate | When lactic acidosis is suspected |
| *Minimum required test<br>VDRL = Venereal Disease Research Lab test, HBsAg = hepatitis B surface antigen, ALT = alanine aminotransferase, AST = aspartate aminotransferase, bil = bilirubin, PPD = purified protein derivate, IgG = immunoglobulin G, ARV = antiretroviral | |

## Appendix 1–F
## Guiding Principles for the Management of Antiretroviral Drug Toxicity

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug or drugs or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g. viral hepatitis in an individual on ARV drugs who develops jaundice) because not all problems that arise during treatment are caused by ARV drugs.
4. Manage the adverse event according to severity. In general:
   - **Grade 4 (severe life-threatening reactions):** Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized.[a]
   - **Grade 3 (severe reactions):** Substitute the offending drug without stopping ART.[a]
   - **Grade 2 (moderate reactions):** Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.[a]
   - **Grade1 (mild reactions)** are bothersome but do not require changes in therapy.
5. Stress the maintenance of adherence despite toxicity for mild and moderate reactions.
6. If there is a need to discontinue ART because of life-threatening toxicity, all ARV drugs should be stopped until the patient is stabilized.

# PART II:

# ANTIRETROVIRAL THERAPY

# IN CHILDREN

# INTRODUCTION

In the past decade, clinicians have made considerable progress preventing mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) around the world. Unfortunately, some women do not receive the benefits of participating in a PMTCT program and their infants become HIV-infected. HIV disease progresses faster in children infected with HIV through perinatal transmission, underscoring the need for early diagnosis and treatment. Recent introduction of deoxyribonucleic acid polymerase chain reaction (DNA PCR) testing in Guyana through dried blood spot (DBS) collection allows for earlier diagnosis of HIV-exposed children. Simplification of HAART regimens through the introduction of specially dosed pediatric formulations and appropriate sequencing of antiretroviral agents should allow for easier adherence, less toxicity and long-term durability of antiretroviral therapy for HIV positive children.

**Natural History of Peadiatric HIV Infection**

Transmission from mother to infant is the main source of HIV infection in infants and children. The infant is at risk of becoming infected in utero, during labour, delivery, and during breastfeeding. Current data suggest that in the absence of intervention, approximately 25-30% of infants born to HIV infected mothers will acquire HIV. Data suggest that the bulk of this transmission occurs during labour and delivery because as the infant passes through the genital tract, the infant's skin and mucous membranes are exposed to the mother's blood and secretions. Breastfeeding is another important source of exposure to HIV. The risk of transmitting HIV during breastfeeding is between 10% and 20% and the longer the mother breastfeeds, the higher the risk is. When compared to exclusive breastfeeding, mixed breastfeeding increases mother-to-infant HIV transmission nearly four-fold after six months and is associated with a three-fold greater risk of death by age six months. Sexual abuse and behaviorally-acquired HIV should be considered modes of HIV transmission, particularly in younger children at high risk for abuse, and in adolescents.

After infection, HIV rapidly populates all areas of the body within a matter of days, using CD4+ T-lymphocytes to replicate. HIV destroys CD4 cells, weakening the entire immune system, and leaves the infant or child vulnerable to opportunistic infections. As children – particularly infants and younger children – do not yet have fully developed immune systems, they are at particularly high risk for morbidity and mortality due to HIV and opportunistic infections. Of children infected with HIV perinatally, approximately 10-25% rapidly develops profound immunosuppression and few of these children will survive past age two in the absence of HAART. Another 70-85% may progress slower; though still have a more rapid progression to clinical AIDS than adults. Overall, perinatally infected children tend to have a faster progression of HIV disease to clinical AIDS. This more rapid clinical course emphasizes the importance of early identification, diagnosis and appropriate treatment for children potentially infected with HIV

## ESTABLISHING DIAGNOSIS AND STAGING

In resource limited settings, the diagnosis of HIV infection in the pediatric population can be challenging. Passively transmitted maternal HIV antibodies persist for 12-18 months after birth, rendering antibody tests unreliable. Currently, there are three general types of diagnostic tests to establish HIV infection in Guyana:

- **HIV Elisa** – These tests are performed on a venous blood sample and measure the presence of HIV antibodies. Elisa testing has a sensitivity of greater than 99%. This test takes several days for the return of a result and is currently in use only at the Blood Bank and the National Public Health Reference Laboratory in Georgetown. The DNA PCR test is used to diagnose HIV in children less than 18 months. The HIV rapid tests are used to diagnose HIV in children older than 18 months and not breastfeeding.
- **HIV Rapid Tests** – HIV Rapid tests are currently in use throughout Guyana at all sites where voluntary counselling and testing (VCT) is available. Like Elisa testing, they are antibody tests and have reported sensitivities and specificities of over 99%. However, these tests use a sample of capillary blood and can provide results within twenty minutes. Currently an algorithm of two different rapid tests (using a third rapid test as a tie-breaker) is used to confirm infection in all persons over 18 months old. The Guyana HIV Testing algorithm is located in
- **DNA PCR testing** – Deoxyribonucleic Acid polymerase chain reaction (DNA PCR) testing was instituted in Guyana in 2007 for infants and young children under the age of 18 months. For infants and children <18 months of age, dried blood spot (DBS) testing for DNA PCR has proved robust and reliable. This assay can determine whether an infant is HIV infected by measuring proviral DNA, the DNA created when the HIV virus enters a cell. It is performed by obtaining capillary blood from a finger stick or heel stick. Since this test measures viral particles (DNA) instead of antibodies, it provides a more accurate diagnosis for children less than 18 months. Sensitivity and Specificity are both > 99%.

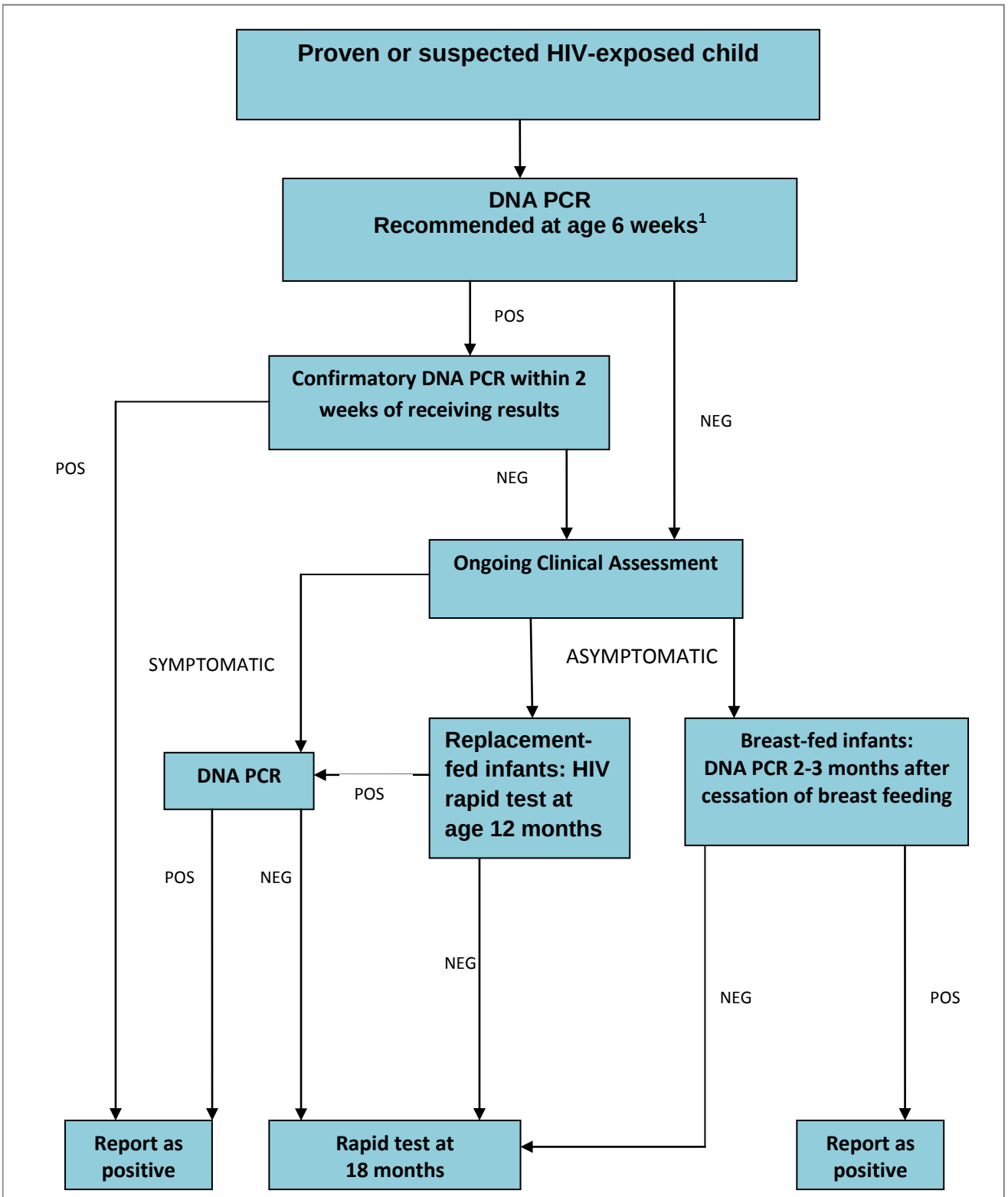
The National Public Health Reference Laboratory provides DBS testing and the results are returned within four weeks. Infants during the first year of life are particularly vulnerable to rapid progression of HIV disease. Therefore, it is important to provide regular follow-up and monitor signs and symptoms of an HIV-exposed infant.

**National testing algorithm for children under 18 months**

The definitive laboratory diagnosis of HIV infection in children younger than 18 months can only be made with virologic testing. The HIV diagnostic algorithm for children less than eighteen months of age is located in Figure 2.1. Beginning at age 6 weeks, all HIV-exposed children less than 12 months should receive a DNA PCR test. Children who are positive will receive a repeat confirmatory test, but *should be treated as an HIV-positive child*. Children testing negative will be presumed HIV-negative, but should have a confirmatory rapid test at age 12 months (or 3 months after cessation of breastfeeding) and 18 months. During breastfeeding, an infant or child born to an HIV-infected mother remains at risk of acquiring HIV infection. As a result, in an infant who is breastfeeding, a negative virologic test does not rule-out HIV infection.

If a child is determined to be HIV-infected, siblings and the mother's partner may be infected. For this reason, the clinician should ask the mother to bring the siblings for HIV testing and to speak with her partner about being tested as well.

**Figure 2.1: Algorithm for testing children 6 weeks to 18 months**




[1] **Any child between 6 weeks and 18 months is offered HIV DNA PCR testing at the initial visit if exposure to HIV is suspected or proven.**

**HIV testing for children older than 18 months**

By 18 months of age, most all HIV-exposed children who are not HIV-infected have lost maternal antibodies. Therefore, testing HIV-positive with an antibody test at 18 months or older is indicative of HIV infection. HIV testing for children older than 18 months follows the same algorithm outlined in the adult section of the national guidelines. The one exception for making a definitive diagnosis is the rare case when an HIV-positive mother continues to breastfeed past 18 months. HIV can be passed through breast milk, and thus an HIV-exposed child should receive a confirmatory rapid test three months after breastfeeding has ceased. DBS testing can be used to confirm the presence of HIV infection in an exposed infant that is breastfeeding.

**Presumptive diagnosis of severe HIV disease in children <18 months of age**

Where DBS testing is not available, or for symptomatic children less than 18 months of age still awaiting a DBS result, a presumptive diagnosis using clinical criteria is recommended:

**A presumptive diagnosis of severe HIV disease should be made if:**

- The infant is confirmed as being HIV antibody-positive or has a positive DNA PCR test

*AND*

- The clinician can make a diagnosis of any AIDS-indicator condition(s)[a]

*OR*

- The infant is symptomatic with two or more of the following:
  - Oral thrush[b]
  - Severe pneumonia[b]
  - Severe sepsis[b]

Other factors that support the diagnosis of severe HIV disease in an HIV-positive infant include:

- Recent HIV-related maternal death or advanced HIV disease in mother
- CD4<20%[c]

Children not meeting these criteria may be considered for treatment, but consult a pediatric HIV specialist. Confirm the diagnosis of HIV as soon as possible.

a) AIDS indicator conditions include some but not all HIV clinical stage 4 conditions such as *Pneumocystis* pneumonia, esophageal candidiasis, cryptococcal meningitis, cerebral toxoplasmosis, HIV wasting, Kaposi sarcoma, TB.

b) As per IMCI definition:
   - Oral thrush: Creamy white soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
   - Severe pneumonia: Cough or difficult breathing in a child with chest wall retractions, stridor, or any of the IMCI general danger signs, ie lethargic or unconscious, inability to drink or breastfeed, vomiting, and presence or history of convulsions during current illness.
   - Severe sepsis: Fever or low body temperature in a young infant with any severe sign, e.g. fast breathing, chest wall retractions, bulging fontanelle, lethargy, , not feeding or sucking breast milk, convulsions.

c) It is unclear how often CD4 count is lowered in the above conditions in HIV-uninfected children.

Adapted from: World Health Organization (WHO). *Antiretroviral therapy in infants and children towards Universal Access, 2010*

## CLINICAL CARE OF THE HIV-EXPOSED AND HIV-POSITIVE CHILD

With the successful implementation of antiretroviral therapy programs, the prognosis for HIV-exposed and HIV-infected children has improved considerably. It becomes increasingly important to provide holistic supportive pediatric primary care to ensure the best outcomes possible for every child. This section provides an overview of the routine pediatric care necessary to maximize the child's health by thorough screening for problems and effective interventions to address them.

**Exposed Infants**

In addition to screening and the clinical assessments necessary for every infant, HIV-exposed infants need extra attention paid to their growth, development, and history of past illness. Approximately 10-25% of children infected with HIV perinatally develop rapid and profound immunosuppression within the first year of life. A minority of these children will survive past age two in the absence of HAART. A particular challenge in the care of HIV-exposed children is being able to recognize the signs and symptoms of immunosuppression and intervene quickly and effectively, even in the absence of HIV test results.

The post-delivery care described here includes:

- The physical assessment of mothers and infant.
- Infant Cotrimoxazole prophylaxis.
- Infant HIV testing.
- Infant feeding information.
- Counselling and support.
- Family planning services.
- Appropriate referrals for HIV treatment, care and support.
- Monitoring growth and development
- Appropriate immunizations
- Diagnosis of HIV by DNA PCR
- Appropriate management and treatment of common infections including opportunistic infections
- Prompt Referral and /or assessment for ARV therapy if DNA PCR is positive

Knowing when and how to make referrals for HIV care and treatment is a critical part of post-delivery care for HIV-infected mothers and their infants. Healthcare workers (HCWs) should ensure that mothers who are HIV-infected - whether they have given birth in a healthcare facility or at home - attend post-delivery care with their infants. It may be especially difficult to coordinate post-delivery appointments for mothers who have given birth at home. Whenever possible, HCWs should utilize community-based support (such as home-based care) to facilitate this important follow-up care.

PMTCT interventions reduce, but do not eliminate, the risk of HIV transmission from mother-to-child. Regardless of whether ARV prophylaxis for PMTCT is administered to mother and/or infant, regular follow-up care is critical for all HIV-exposed infants. Follow-up care facilitates early diagnosis by providing opportunities for clinical screening and laboratory screening. These early interventions allow HIV infected

infants to be recognized and started on ARV therapy as soon as possible. This reduces the significant risk of morbidity and mortality that HIV-infected children face in the years of life.

**Timing of follow-up visits**

HIV infection increases an infant's risk of illness and failure to thrive. The infant and mother should be seen in the healthcare facility within two weeks of delivery or sooner to monitor feeding progress. It is recommended that subsequent visits are scheduled monthly until age twelve months, when less frequent (e.g. every 2-3 month visits) may be reasonable for the healthy children. To encourage the mother to attend care, it is recommended that her post-delivery and ongoing follow-up appointments coincide with her infant's visits when possible.

**Clinical Care and Assessment for HIV-exposed and HIV-infected Children**

Close clinical follow-up is critical for HIV-exposed and HIV-infected infants. Growth, nutritional and developmental assessments should be conducted at each follow-up visit. Table 2.1 provides an outline of the clinical care that comprises each follow-up visit.

**Table 2.1: Overview of clinical care for HIV-exposed and HIV-infected children**

| | |
|---|---|
| **Infant & Child Diagnosis (previous section)** | ▪ Provide HIV virologic testing / DNA PCR at 4–6 weeks of age.<br>▪ HIV Rapid testing can be initiated starting at 12 months. If still breastfeeding, repeat test 3 months after cessation of breastfeeding.<br>▪ Information and protocols for testing is described in the previous section. |
| **Prevention of Infections: Cotrimoxazole Prophylaxis** | ▪ Provide Cotrimoxazole (CTX) prophylaxis starting at age 6 weeks or at the first encounter with the healthcare system thereafter.<br>a. Assess for side effects or adverse events of Cotrimoxazole.<br>b. Appropriate dosing changes based on age or weight.<br>c. Provide Cotrimoxazole refills until 5 years old.<br>d. Routinely re-assess HIV-positive children for eligibility for CTX prophylaxis after age 5.<br>e. Can stop CTX prophylaxis once an exposed infant is diagnosed HIV-negative.<br>. |
| **Management of Childhood Illness: IMCI** | ▪ Assess for common illnesses of childhood and manage appropriately as directed by the *Integrated Management of Childhood Illness* (IMCI)/MoH guidelines. |
| **Growth & Development Monitoring** | ▪ Perform standard developmental assessment including height, weight, head circumference and assessment of developmental milestones.<br>▪ Infants who fail to grow require special attention. At every visit, the weight and height of the infant should be done and plotted on their growth chart. If the child is not growing well, assess feeding and potential medical causes. |
| **Nutritional Assessment** | ▪ Infant feeding assessment: Assess and support the mother's infant feeding choice. Discussions about infant feeding are especially important in the early months of life. HCWs should continue to assess feeding practices and diet for infants older than 6 months and provide appropriate anaemia that considers locally available food, family circumstances and feeding customs.<br>▪ Counsel the mother and other caregivers on nutrition for mother and infant |

| | |
|---|---|
| | ▪ Provide infants/children who are anaemic, or at risk of iron deficiency, iron and folic acid supplementation. |
| **Immunizations** | ▪ Immunise according to MoH/MCH guidelines. |
| **Tuberculosis** | ▪ Screen for TB and refer for treatment if indicated.<br>▪ Follow national guidelines for initiating preventive therapy. |

**Cotrimoxazole Prophylaxis**

Cotrimoxazole is an antimicrobial medication that can prevent bacterial infections and malaria as well as two very important opportunistic infections, *Pneumocystis* pneumonia (PCP) and toxoplasmosis. ***PCP is a leading cause of death in HIV-infected infants***. PCP often strikes infants between the ages of 3–6 months. Long-term Cotrimoxazole prophylaxis has resulted in fewer opportunistic infections, improvements in quality of life and increased survival in patients with HIV. The benefits of providing Cotrimoxazole prophylaxis to ***all*** exposed infants far outweighs the risks associated with taking the medicine.

Cotrimoxazole contains two medications: Trimethoprim and Sulphamethoxazole (sometimes referred to as TMP-SMX, Septrin or CTX). CTX suspension formulation is Trimethoprim 200mg and Sulphamethoxazole 40mg in 5ml. The dose of Cotrimoxazole for infants is **4mg/kg** and the required dose should be calculated at each monthly visit. Cotrimoxazole is generally well-tolerated by most patients. Cotrimoxazole prophylaxis is recommended to begin for all HIV-exposed infants starting at 6 weeks of age (or as soon as possible thereafter) until breastfeeding has stopped and the infant has been diagnosed as HIV-negative. Table 2.2 provides a quick reference for guiding CTX prophylaxis dosing in young children.

**Table 2.2: Cotrimoxazole dosing by weight for HIV-exposed and HIV-infected infants and children**

| Child's weight in kilograms(kg) | Amount of 8 mg (TMP)/ml suspension |
|---|---|
| 3.0–4.9 kg | 2 ml daily OD |
| 5.0–6.9 kg | 3 ml daily OD |
| 7.0–9.9 kg | 4 ml daily OD |
| 10.0–11.9 kg | 5 ml daily OD |
| 12.0–14.9 kg | 7 ml daily OD |
| 15.0 kg and above | Use adult dosing. |

Once an HIV-exposed infant has a definitive HIV diagnosis (and there has been no history of feeds utilizing breast milk for >3 months) Cotrimoxazole prophylaxis can safely be discontinued. If an HIV-exposed infant tests positive, Cotrimoxazole prophylaxis should be continued until a child is age 5. After age 5 years the child needs to be reassessed clinically and immunologically to determine CTX prophylaxis needs including the possibility of discontinuation.

**Assessment and Monitoring of Growth, Nutrition and Neurodevelopment**

Studies have suggested that even with adequate HAART, HIV infected children do not grow as well as the non-infected HIV child. While HIV-exposed infants have not yet received a diagnosis of HIV-infection and may not have HIV infection, it is important that they are monitored just as rigorously. Growth and nutrition

status is a strong predictor of morbidity and mortality; thus it is of grave importance that we continually assess and support the proper growth and development of both HIV-exposed and HIV-infected children.

**Growth**

The assessment of growth, nutrition and neurodevelopment of the HIV-infected child should parallel that of the HIV-negative child. At each child follow-up visit, the child's growth parameters (i.e. weight, height, and head circumference) should be assessed and plotted on the growth chart. A typical full-term infant will lose 10% of its birth weight within the first few days of life; by age 7-10 days that infant should regain the weight. Thereafter, a typical infant will gain an average of 25 to 35 grams of weight per day. By the age of 4-5 months the child should have doubled its birth weight; by 1 year the child should be three times the birth weight and by age 4 years the child should be four times its birth weight.

**Table 2.3:Expected weight gain in Infants and children**

| AGE | WEIGHT |
|---|---|
| Birth | ≈2500gms |
| 1-5days | Birth weight – ( 10%x birth weight) |
| 7-10days | Birth weight |
| 1- 4 months | Birth weight + ( 25gms x age in days) |
| 4-5 months | Birth weight x 2 |
| 12 months | Birth weight x 3 |
| 48 months | Birth weight x 4 |

The child's length should be measured in recumbent position until age two. After age two the height should be measured using the same instrument at each visit. The child should be measured standing against an immobile structure such as a wall and without any shoes or socks on. When ever possible the care provider performing these measurements should remain constant. The child's length should have increased by 50% by the first birthday. By age two years the length should be twice the birth length and by age thirteen the length should be three times the birth length.

**Table 2.4:Expected height velocity in infants and children**

| AGE | HEIGHT |
|---|---|
| Birth | ≈51 cm |
| 12months | Birth height +( Birth height x 0.5) |
| 48months | Birth height x 2 |
| 13 years | Birth height x 3 |

The measurement of the child's head circumference is an essential tool in the assessment of cerebral growth within the first two years of life. As the first two years are critical to CNS development and HIV disease can have irreversible effects on the neurological development of the child, it is important to assess head circumference at each clinical visit. Head circumference should increase by 0.25cm per week until the age of 3 months - approximately 2cm per month. From age 4-6 months the head circumference will increase by one cm per month and thereafter increase by 0.5cm per month until age one year. The posterior fontanel closes by approximately two months of age and the anterior fontanel closes by age 18months.

**Table 2.5: Expected head circumference growth in Infants and Children**

| AGE | HEAD CIRCUMFERENCE (HC) |
|---|---|
| Birth | ≈ 32cm |
| 0-3months | Birth HC + (0.25cm x age in weeks) |
| 4-6 months | Estimated 3mth HC + (1cm x (Current age - 3month)) |
| 6-12months | Estimated 6mth HC + (0.5cm x ( current age – 6months)) |
| 2 months | Closure of Posterior Fontanel |
| 18 months | Closure of Anterior Fontanel |

The correct use of growth curves will provide the health care worker with a reliable tool for assessing the child's physical development over time. Clinicians should monitor the weight and height for age in addition to the head circumference. The weight/height for age can be a useful tool to detect chronic malnutrition and failure to thrive. Plotting weight for height can be a useful measure of acute malnutrition.

Growth failure is defined as a persistent decline in growth velocity. The growth failure and malnutrition observed in children who are HIV-infected are attributable to several factors:

- Decreased intake due to oral and gastrointestinal pathology or caregiver factors.
- Impaired absorption due to oral and gastrointestinal pathology.
- Increased metabolic requirements secondary to HIV and/or other infections.

When growth failure is present in a child, the child should have a thorough nutritional assessment, assessment for concurrent infections, and assessment for the antiretroviral therapy if indicated.

**Nutrition**

Good nutrition is vital to the development of any child. A nutritional assessment should be done at every visit beginning at birth or soon there after. The main goal is to prevent malnutrition and failure to thrive. The health care provider should provide to the caregivers a clear understanding of the nutritional requirements for HIV-infected children. The energy requirements for the well HIV infected child equals the normal daily requirements for HIV-negative children. The gross estimated caloric requirement of the normal child is:

- 100kcal/kg for the first 10kg of body weight,
- 50kcal/kg for the second 10kg of body weight
- 20kcal/kg for each kg over 20kg of body weight.

In times of stress (e.g. acute infection), a child's caloric requirements may increase up to 150% of the estimated normal daily requirements. Caloric needs are increased by 12% for every degree rise in centigrade above normal body temperature, 25% for acute diarrheal episodes, and 60% for sepsis. As proteins provide the essential substrates for proper growth & development, protein intake is particularly important for children. Typical energy and protein requirements for children are illustrated in Table 2.6.

**Table 2.6: Recommended daily energy and protein intake by age**

| Age(years) | Kcal/kg | Protein/kg(grams) |
|---|---|---|
| 0-0.5 | 108 | 2.2 |
| 0.5-1 | 98 | 1.6 |
| 1-3 | 102 | 1.2 |
| 4-6 | 90 | 1.2 |
| 7-10 | 70 | 1.0 |
| 11-14 (males) | 55 | 1.0 |
| 11-14 (females) | 47 | 1.0 |
| 15-18 (males) | 45 | 0.8 |
| 15-18 (females) | 40 | 0.8 |

*Adapted from handbook of Pediatric HIV care*

**Neurodevelopmental assessments**

Throughout childhood, the central nervous system undergoes a period of rapid growth and development. By age 2 the human body has the total number of neurons it will have throughout life.The development and maturation of the nervous system is supported by an array of helper cells, such as glial cells and astrocytes. Since HIV can penetrate the blood-brain barrier and supportive cells in the CNS can become infected with the HIV virus, the CNS serves as a reservoir for HIV infection. In many children, *the first manifestation of symptomatic HIV infection maybe slowed neurodevelopment*. Monitoring of head circumference (described above) and the acquisition of typical developmental milestones is integral in the care of the HIV-infected and HIV-exposed child. Developmental assessment can allow for early detection and intervention in cases of HIV-related CNS dysfunction, which can present as cognitive, linguistic, motor or behavioral impairments. A developmental milestones checklist (placed in **Appendix 2-B**) should be completed at each routine follow-up visit. When deficiencies are noted, appropriate investigation into the cause should be initiated. *Significant neurodevelopmental delay is an indication to start HAART in the HIV-infected child*.

**Routine immunizations of the HIV-exposed and HIV-infected child**

All HIV-infected and HIV-exposed children should received the same immunisations for HIV-negative children as outlined in the Maternal and Child Health (MCH) guidelines., HIV-infected children should not be given live virus vaccines with the exception of MMR.. See table 2.7 for the recommended vaccine schedule.

**Table 2.7: Immunisation Guidelines for HIV-exposed and HIV-infected children**

| **INFANTS BORN TO MOTHERS WHO ARE HIV-EXPOSED/ POSITIVE** | |
|---|---|
| **Age group** | **Vaccine** |
| At birth or by 2 months | **Do not give BCG at birth , until HIV status is known**<br>**If the child is <u>HIV positive do not</u> give BCG**<br>**If the child is HIV negative give BCG** |
| 2 months or 8 weeks | 1st **Dose of Inactivated Polio Vaccine (IPV)**<br>1st Dose of Pentavalent Vaccine (Hepatitis B + DPT + Hib)<br>1st Dose Pneumococcal -7 Valent conjugate vaccine) |

| INFANTS BORN TO MOTHERS WHO ARE HIV-EXPOSED/ POSITIVE | |
|---|---|
| **Age group** | **Vaccine** |
| 4 months or 16 weeks | 2nd Dose of **Inactivated Polio Vaccine (IPV)**<br>2nd Dose of Pentavalent Vaccine (Hepatitis B + DPT + Hib)<br>2nd Dose of Pneumococcal -7 Valent conjugate vaccine |
| 6 months or 24 weeks | 3rd Dose **of Inactivated Polio Vaccine (IPV)**<br>3rd Dose of Pentavalent Vaccine (Hepatitis B + DPT + Hib)<br>3rd dose of Pneumococcal -7 Valent conjugate vaccine |
| 12 months or 1 year | • **G**ive Measles Mumps and Rubella (MMR) only to children with WHO stage 1 and 2<br>4th dose of Pneumococcal -7 Valent conjugate vaccine<br>• **Do not give Yellow Fever (YF) vaccines if the child is HIV positive** |
| 18 months or 1 year 6 months | Booster IPV and DPT vaccines |
| 45 months or 3 years 9months | 2nd Booster IPV, DPT, MMR |

## Additional Elements of HIV Paediatric Care

**Assessment and support of the family and social structure of the HIV-infected child**
The stigma and discrimination surrounding HIV disease has an enormous impact on the socialization of the HIV infected child. The health care provider is tasked with building a support network of parents, caretakers, school workers and community organizations to promote the understanding of HIV disease. This structure will allow for improvements in the health and well being of the HIV infected child. Past experiences have shown that children who have chosen to disclose the HIV status and attend school with the full support of all involved community organizations and care providers have benefited significantly from their educational experiences.

In addition, health providers need to ensure that the network of care providers understands and will follow the child's scheduled medical follow up appointments. Coordinating a child's medical and educational needs requires ongoing communication among the family, healthcare providers and school health staff. The child should also be involved with the ongoing process of managing their disease. Once it is determined that the child is emotionally equipped to handle his or her medical diagnosis, the care giver should be encouraged to disclose the child's HIV status. From there on the child should be involved in all discussions relating to the medical management of his or her case.

# TREATMENT PREPARATION AND ADHERENCE

Highly Active Antiretroviral Therapy (HAART) is an effective and sustainable method to control HIV replication, slow progression to immunologic failure, and in many cases, allow for reconstitution of CD4+ cells in children. Goals for the initiation of ART in children are to:

- Reduce HIV-related morbidity and mortality
- Improve quality of life
- Restore and preserve immunologic function
- Maximally and durably suppress viral load
- Promote or restore normal growth and development.

However, successful outcomes from ART require sustained treatment adherence to complex multidrug regimens over many years. It is therefore important to ensure that patients understand the benefits of ART, risks of not taking ART, the potential side effects, and importance of adherence. Adherence is defined as the engaged and active participation of an informed patient/family to a treatment plan. Assessment of readiness and adherence in children is particularly challenging as children may lack the ability to understand their illness or prepare and administer their medicines. Treating a child with HIV infection successfully is dependent on the child having a dedicated caregiver. Before starting ARV therapy in children, it is imperative that the clinician explain to the caregiver how to give the ARVs. The caregiver must make a commitment to be vigilant about following the regimen: administering the right amount, at the correct time of day, with the recommended frequency.

Although the disease course will vary among children, it is expected that every child will need ART at some point in their lives. Thus, assessment of readiness and treatment preparation begin with the first visit with the patient. Pre-initiation clinical encounters are crucial to establishing rapport with the child and family. They provide non-judgemental support and foster communication about treatment plans. Assessment of readiness and treatment support are best accomplished with a multidisciplinary team able to provide structured, individualized support.

## Assessing readiness

Before initiating therapy, the clinician should make a complete assessment of eligibility and readiness to begin therapy by focusing on the following questions:

1. **Does the patient have a documented diagnosis of HIV?**
   - Before starting ARV therapy, all HIV-infected infants, children, and adolescents, should have their diagnosis confirmed with antibody or virologic testing.
   - When testing is not available or receipt of test results will delay ARV therapy in children meeting clinical criteria, this should not be an absolute contraindication to HAART. However, efforts to verify the serostatus of a child should continue while the child's WHO clinical stage and eligibility for HAART are assessed.

2. **Is the child receiving Cotrimoxazole (CTX) prophylaxis?**
   - Unless the child has a reason to defer or stop Cotrimoxazole (CTX) prophylaxis, treatment initiation can serve as a good reminder to provide CTX prophylaxis.
   - CTX prophylaxis provides an opportunity to assess medication adherence.

**3. Does the child have an indication for antiretroviral therapy?**

- Every HIV-infected infant or child should be assessed according to the recommendations contained in these guidelines.

**4. Is there a medical contraindication or reason to delay initiating therapy?**

- Examples include:
  a. Renal Insufficiency (creatinine >3x normal)
  b. Hepatic Insufficiency (liver function tests >5x normal)
  c. Severe Anaemia (hemoglobin < 6.9g/dl) or Neutropenia (absolute neutrophil count < 749 cells/mm3)
  d. Severe Thrombocytopenia (platelet count <50,000)
  e. Active psychiatric illness in the patient
- In the presence of a medical contraindication, provide a rapid and thorough evaluation to investigate the etiology and assess for the safety of starting HAART. Many of these same problems may be caused by the HIV virus and improve with HAART. Abnormally long delays in deferring HAART lead to poorer clinical outcomes.
- When unsure when to initiate HAART in the presence of any of these conditions, please consult an HIV specialist.

**5. Is there a current non medical contraindication to ARV therapy?**

- Examples include:
  a. Psychiatric illness in the caregiver.
  b. Substance abuse in the caregiver.
  c. Severely unstable social situation.
  d. Recent history of serious medication or appointment non-adherence.
  e. Current use of herbal and traditional remedies.
- As with medical contraindications, it is important not to let non-medical contraindications serve as a permanent barrier to HAART for children meeting eligibility criteria. Rapid assessment and resolution (often with support from multidisciplinary team members, including social workers, home based care providers, etc.) should be the primary goal. Plans to address these issues may involve other support persons, support agencies, and in extreme cases referral to Human Services for alternative placement.

**6. Is there a current active opportunistic infection?**

- Has TB been excluded? (Chest X-Ray, sputum AFB, PPD, or symptoms?)
- In patients with severe immunosuppression, are symptoms of OI present?
- Active opportunistic infections are not a complete contraindication to HAART, though to simplify treatment regimens, reduce drug interactions, ascertain the causative agent of adverse drug reaction and reduce immune reconstitution inflammatory syndrome (IRIS), initial control of the opportunistic infection should be the primary goal with initiation of HAART in a matter of weeks.

**7. Is there a high probability of adherence?**

- Criteria that can be used to predict good adherence:
  a. Completion of the child's immunization card
  b. Past history of adherence with anti-TB medications where applicable
  c. Adherence with Cotrimoxazole prophylaxis and treatment
  d. Clinic attendance at three consecutive appointments.

**8. Are adherence follow-up and clinical monitoring follow-up possible with the family or caregivers?**
- Is there a responsible caregiver to administer medications to the child?
- Is there an adherence partner who knows and understands the child's health problems in case the primary caregiver is ill or unavailable?

**Special adherence issues with children**

Focusing on adherence is critical for maximizing the effectiveness of ARV therapy and preventing drug resistance. High pill burdens, frequent dosing, poor taste or lack of availability of easy to administer pediatric ARV formulations can make adherence a major challenge. In addition, the child's developmental level and the severity of the disease affect the child's ability to take the medications and the caregiver's ability to administer them.

**Adherence counselling**

Before initiating ARV therapy, the clinician and multidisciplinary team members should:
- Meet the caregiver and explain that she or he will be responsible for making sure the child receives the ARVs throughout the day and every day.
- Establish trust among the caregiver and child and the clinicians providing care.
- Discuss the importance of having an alternate caregiver in case he or she is unavailable.
- Educate the caregiver and the family about the importance of good adherence and the implications of incomplete adherence.
- Explain the treatment plan and the ARV regimen.
- Select the drug formulation appropriate for the child's age, while minimizing the volume of liquid or number of pills, limiting the dosing frequency (bid vs. tid vs. qd), and taking into account the palatability of the ARVs to be administered.
- Identify obstacles to adherence (eg, unstable social situation)
- Schedule a home visit by a field worker, if possible, to confirm the family's address. An alternate address and contact person should be requested.

**Monitoring and maximising adherence**

Adherence during the first days and weeks of therapy is critical, which is why it is recommended that all programs have a support system in place before initiating ARV therapy. Assessing adherence weekly during the first two weeks of therapy, then monthly going forward, is an essential component of effective treatment. It is important to have the caregivers explain how they give medications to ensure that children are receiving the correct dose. Support and anaemia for families with children receiving ARV therapy must be a multidisciplinary effort, including the clinicians, the nurse, the social worker, and outreach workers. At each clinic visit, adherence should be assessed by at least one member of the HIV care team. If there is a suspicion of non-adherence, have a field worker schedule home visits to assess adherence, if possible, with the caregiver's agreement. If any issue arises, adequate support should be provided.

Non-adherence to the ARV regimen is the most common cause of therapeutic failure. Caregivers play a critical role in facilitating adherence.
- If possible, before initiating therapy make a home visit to assess whether there is sufficient readiness and support to maximize adherence.
- Education and empowerment of the family, including participating in a support group of families with HIV-infected children, may help families cope with life-long therapy and maximize medication adherence.

- All children with unresolved issues about adherence should have initiation of ARV therapy delayed until adherence readiness is assured.
- The reluctance of families to disclose the child's HIV diagnosis may interfere with adherence during day care and school hours.
- If therapeutic failure occurs, consider a period of hospitalization to assess adherence and reinforce that adherence to the regimen is fundamental to effective antiretroviral therapy.

If adherence is a problem, in some instances it may be recommended to stop ARV therapy to prevent the development of drug resistance, especially in settings where drug availability is limited. If this is a concern please contact a paediatrics HIV specialist.

## WHEN TO START ANTIRETROVIRAL THERAPY (ART)

There is very strong evidence for the clinical benefits of ARV therapy in the pediatric population with HIV disease. Starting treatment is particularly important for infants < 12 months of age; the probability of death is high: researchers have reported mortality rates of up to 40% in this age group. For this reason, clinicians should have much lower thresholds for starting children on HAART compared with adults.
Starting ARV therapy should not be considered an emergency**.** Before doing so, the clinician should discuss the diagnosis and the need for ARV therapy with the appropriate caregiver(s), addressing any questions or concerns, and perform a thorough assessment of adherence readiness as outlined in the previous section.

**Initiating ARV Therapy in Infants and Children**
Eligibility for ARV therapy can be assessed through two methods – immunologic criteria (CD4+ cell counts) and clinical criteria (WHO clinical stage). Infants and Children with HIV infection are eligible for ARV therapy when either immunologic ***or*** clinical criteria are met. There is a natural decline in the total amount of circulating CD4+ lymphocytes in the peripheral blood in young children with continued development of the immune system. As a result, the eligibility criteria for children are based on age. Recommended thresholds for initiating ARV therapy for children are located in Table 2.8.

**Table 2.8:Criteria for Initiating ART in Children**

| Age | Eligible for ARV Therapy at either of following thresholds | | |
|---|---|---|---|
| | **WHO Clinical Stage** | | **CD4+ Cell Count** |
| Less than 24 Months | All | OR | All |
| | | | |
| 2 year – 5 years | III or IV | | CD4% < 25%<br>Absolute CD4+ Count <750 |
| Greater than 5 years | III or IV | | CD4% < 20% or<br>Absolute CD4+ Count < 350 |
| ** Can offer antiretroviral therapy to all children above initiation thresholds after conducting a thorough adherence assessment.* | | | |

Additionally, recent studies have suggested that there are improved immunological outcomes and reductions in the development of comorbidities in adults starting HAART at CD4+ levels above treatment initiation thresholds. Although similar studies have not specifically looked at these benefits in children, it is expected that with good adherence similar benefits will be observed.

# FIRST LINE REGIMENS

**Prescribing ART for Children: General Principles**

There is a substantial difference between the pharmacokinetics of drugs in adults and in children. Children and adults differ with respect to body composition, renal excretion, liver metabolism, and gastrointestinal function. These differences are reflected in potential variations in distribution, metabolism, and clearance. As the child grows, dosage adjustment is necessary to avoid under dosing, which can lead to drug resistance. Many experts recommend adjustment when the weight increases ≥10% of the baseline. For detailed information on ARV formulations for children and appropriate weight-based dosing, please turn to **Appendix 2-C**.

Effective selection of appropriate ARV medications coupled with good adherence should lead to complete suppression of HIV viremia. This in turn leads to improvements in CD4 counts and the overall clinical status of the child. As with adults, to aggressively control viral replication and arrest the progression of HIV infection, "triple therapy" using three antiretroviral drugs is the current standard of treatment for HIV infection. There is strong evidence based on published data that combination therapy with at least three drugs from more than one class may prevent, delay, or reverse resistance. Selecting a drug regimen that has been proven to be effective and safe, maximizes the child's ability to adhere to the regimen, and allows for appropriate sequencing of future second-line regimens will lead to the best possible outcome for the child.

**First-Line Regimens: Selecting an Appropriate Regimen**

There are several factors that must be considered when selecting an ARV regimen:

- **Potency:** Has the drug regimen been proven effective in children?
- Drug Interactions: Would any medications in the ARV regimen interact with other medications being taken?
- **Adverse Effects Profile**: Would the patient be at high risk for unacceptable adverse effects from a particular medicine in the ARV regimen?
- **Ability to Adhere to Treatment**: ARV Regimens must be acceptable to the patient and the caregiver. Are the patient and caregiver likely to be able to understand and adhere to specific doses, timing of doses, and the number of doses per day?
- **Availability of medication** or appropriate laboratory monitoring
- **Sequencing:** Would there be an acceptable option to optimize second-line therapy should the first line fail?
- **Previous ART Exposure**: Did the child contract HIV despite a documented history of single-dose Nevirapine in labor?

**Recommended First-Line Regimens for Children**

The preferred option when choosing a first-line regimen for infants and children includes two nucleoside reverse transcriptase inhibitors (NRTIs) (the "backbone") plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), unless transmission occurred despite a documented history of single-dose NVP in labor (see below).

**Preferred First-Line Regimen**

| Non-Nucleoside (NRTI) Backbone | | | | NNRTI |
|---|---|---|---|---|
| **ABC** | + | **3TC[b]** | + | **NVP[c]** *-or-* **EFV[d]** |

When the preferred first line regimen would not be optimal for a child for medical reasons or concerns about adherence, an alternative first-line regimen can be used.

**Alternative First-Line Regimens**

| Non-Nucleoside (NRTI) Backbone | | | | NNRTI |
|---|---|---|---|---|
| **d4T [a]** *-or-* **AZT [a]** | + | **3TC[b]** | + | **NVP[c]** *-or-* **EFV[d]** |

**Notes on Selection of First-Line Triple Therapy Regimen**

a) Do not give AZT in combination with d4T.
b) Nevirapine should be avoided in postpubertal adolescent girls (considered adults for treatment purposes) with baseline CD4 absolute cell counts >250/mm$^3$. And boys with a baseline CD4 count >400.
c) Efavirenz is not currently recommended for children under 3 years of age or <10 kg and should be avoided in postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.

Adapted from World Health Organization (WHO). *Antiretroviral drugs for the treatment of HIV infection in infants and children in resource-limited settings. Recommendations for a public health approach* (2006).

**Advantages and disadvantages to recommended First-Line regimens**
The advantages and disadvantages of common NRTI backbone and NNRTI medications are summarized in Tables 2.9 and 2.10.

**Table 2.9: Advantages and disadvantages of NRTI backbones**

| NRTI Backbone | Advantages | Disadvantages |
|---|---|---|
| **ABC+3TC+NNRTI** | ▪ Relatively little long-term toxicity documented<br>▪ Clinical failure or resistance to an ABC/3TC based regimen will usually result from the L74R mutation instead of TAMs. This should allow for full efficacy of AZT or d4T in future second-line regimens | ▪ Although rare, ABC has a possibility of a potentially fatal hypersensitivity reaction<br>▪ Requires three medicines which may come in different forms or doses, complicating adherence<br>▪ Can be costly<br>▪ The expected first initial resistance mutation, M184V, while impacting 3TC, may also reduce the efficacy of ABC |
| **D4T+3TC+NNRTI** | ▪ d4T/3TC/NVP comes as a fixed-drug combination which simplifies dosing and reduces pill burden<br>▪ Can safely be used after development of AZT related anaemia | ▪ Continued poor adherence to a d4T-based regimen will result in the accumulation of Thymidine Analogue Mutations (TAMs). This can result in diminished efficacy of the NRTI backbone for a second-line regimen<br>▪ d4T has been linked to long-term metabolic alterations including lipodystrophy and hyperlipidemia<br>▪ Fixed dose combination are only available in tablet form which may not be appropriate for young infants |
| **AZT+3TC+NNRTI** | ▪ AZT/3TC/NVP can come as a fixed-drug combination, though there are concerns about the relative weights of doses in the combination.<br>▪ Less long-term toxicity than d4T-based regimens<br>▪ The expected first initial resistance mutations, M184V, may slightly enhance the efficacy of AZT. | ▪ Continued poor adherence to an AZT-based regimen will result in the accumulation of Thymidine Analogue Mutations (TAMs). This can result in diminished efficacy of the NRTI backbone for a second-line regimen<br>▪ AZT can cause or exacerbate anaemia<br>▪ May require high volumes of liquid, especially in older children |

**Table 2.10:Advantages and disadvantages of NNRTI options**

| NNRTI | Advantages | Disadvantages |
|---|---|---|
| NVP | ▪ Inexpensive in liquid form<br>▪ Comes in fixed drug combinations with AZT/3TC and d4T/3TC | ▪ Twice daily<br>▪ NVP is not recommended for postpubertal girls with CD4>250 or postpubertal boys with CD4>400 due to unacceptably high rates of severe (possibly fatal) drug-induced hepatitis<br>▪ Have more serious side effects (Stevens-Johnson Syndrome and hepatic necrosis) than EFV<br>▪ Requires lead-in dosing for the initial two weeks |
| EFV | ▪ In adults, EFV has consistently outperformed NVP in ARV-naïve patients<br>▪ Has fewer serious adverse effects than NVP<br>▪ Once daily dosing | ▪ More expensive<br>▪ May have more troubling, albeit less serious side effects (particularly CNS side effects) than NVP<br>▪ Possible teratogenicity in pregnant patients during the first trimester only (consider with adolescents and women of child bearing age)<br>▪ In the absence of liquid preparations, may be difficult to accurately dose in young children<br>▪ There is a paucity of safety or efficacy data for EFV in young (<3 years) children |

Consultation with an HIV specialist is recommended if clinical circumstances prevent use of the combinations outlined above for first-line therapy. In these very rare circumstances, use of tenofovir (TDF), triple nucleoside regimens of AZT/3TC/ABC or AZT/3TC/TDF or a PI-containing regimen may be appropriate as part of first-line therapy. These combinations, however, are either less potent, have concerning adverse effects, or limit future options when compared to currently recommended first-line regimens.

**Table 2.11: NRTI drug combinations to avoid**

| **NRTI drug combinations to avoid**[a] | |
|---|---|
| d4T+AZT | Both drugs work through a common metabolic pathway, so no extra benefit is obtained. |
| d4T+ddl[b] | These drugs have overlapping toxicities. |

a) Based on data from studies performed in adults.

b) Didanosine (ddI) is an adenosine analogue NRTI, which is generally reserved for second-line regimens.

Adapted from *World Health Organization (WHO) Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach*. P 32. May 2006.

**ARV therapy in infants with a history of ARV exposure during PMTCT or breastfeeding**
Infants who were infected with HIV despite the documented use of single-dose NVP have very high rates of documented NNRTI resistance and failure when started on NVP-containing regimens. ***For this reason, HIV positive infants whose mothers received single dose NVP for PMTCT should receive ABC + 3TC + LPV/r***. alternatively; the NRTI backbone could be changed to AZT/3TC or d4T/3TC if there are serious concerns about the use of Abacavir.

There is also a small possibility that a breastfeeding infant could contract HIV infection from a mother taking antiretrovirals. In cases where the transmission of HIV can be documented to have occurred during breastfeeding (e.g. an infant with an initially negative DNA-PCR HIV test that later tests positive), it is important to consider the mother's antiretroviral regimen when selecting treatment for the child. In this case, it is recommended that you consult a pediatric HIV specialist.

**Triple therapy in adolescents older than 15 years of age**
Adolescents in Tanner stage IV or V are considered adults and the same recommendations and special considerations apply, including the use of WHO clinical and immunologic classifications for adults. Please refer to *The National Guidelines for Adults with HIV Infection.*

**Adolescents adherent to a HAART regimen do not have to change to an adult regimen**
For children already taking a highly active antiretroviral therapy regimen, it is recommended that you **continue the child on their *current* regimen** unless there is evidence of clinical failure or an overwhelming benefit (in adherence or toxicity profile) is expected after changing the regimen. The rationale for this is to reduce the number of antiretroviral agents the child will be exposed to, which increases the number of potential agents available for second-line therapy. Naturally, when toxicity or anticipated benefit is present, switching therapy remains a viable option.

## MONITORING ANTIRETROVIRAL THERAPY IN CHILDREN

In addition to the routine clinical monitoring and medical care required for HIV+ children [outlined in "Clinical Care of the HIV+ Child", additional vigilance and support is required for children taking ART. The purpose of this monitoring is to detect adverse effects of medications or evidence of immunologic or clinical failure. Early detection of adverse effects can reduce toxicity and prevent problems with adherence. Early detection of immunologic or clinical failure can help prevent accumulation of additional resistance mutations.

**Baseline and pre-Initiation assessment**
The baseline assessment should serve as a means to provide counselling and support for children and/or caregivers concerning secondary prevention and disclosure of HIV diagnosis to others, as well as to identify particular needs. It should be considered the first step in ongoing clinical monitoring. A thorough clinical and laboratory evaluation of the child's health should be performed at enrollment (the baseline visit). If at the time of initiation of ART a significant amount of time has passed (or any significant clinical events have occurred) since the baseline visit, the evaluation should be repeated prior to initiating HAART. Important clinical and laboratory monitoring information should be attained as the baseline information. See table 2.12.

**Ongoing assessments**

The majority of adverse effects with ARV medications occur within the first three months of initiation. However, as children continue on HAART their bodies continue to develop and grow, which creates risk for under and over-dosing of ARV medications. This highlights the need to rigorously monitor children on ARV therapy. As with baseline assessments, HIV+ children should receive the same attention to regular health conditions as HIV- children. The highlighted monitoring schedules [Table 2.12] are in addition to routine clinical care.

**Table 2.12: Baseline and ongoing monitoring schedules**

| Test | Enrollment | Pre-Initiation | Ongoing Care |
|---|---|---|---|
| **Clinical** | | | |
| Complete Physical Exam | yes | yes | Continued focused physical exams based on regimens, risks, and patient concerns. |
| Weight | yes | yes | Every Visit |
| Height | yes | yes | Every Visit |
| Head Circumference | yes | yes | Every Visit until age 2. |
| Developmental Milestones Assessment | yes | yes | At a minimum every 3 months during clinical encounters. |
| Treatment Readiness and Adherence Counselling | As needed | yes | At every clinical encounter and medication pickup. |
| **Laboratory** | | | |
| HIV Test (DBS confirmed by another DBS and or rapid test after 18 months) | yes | - | - |
| CD4 Count and CD4% | yes | yes | Every 3-6 months. Every 3 months is recommended for those recently starting HAART, clinically unstable patients, or those with CD4 <350 (CD4 %< 25%). Every 6 months once stable and adherent on HAART. |
| Viral Load | No | yes | 6 months after beginning HAART and every 6 months afterward. |
| CBC with Differential (Minimum of Hb and WBC) | yes | yes | Recommended every 6 months or with CD4 sampling. AZT based regimen: Check 4-6 weeks after initiating AZT. Recheck at 3 and 6 months. If results are normal, can check every 6 months unless patient becomes symptomatic. |
| Creatinine (serum) | yes | yes | Not necessary unless symptomatic or on a TDF-based regimen. Adolescents taking TDF should monitor creatinine every 6 months. |
| Liver Function Test | yes | yes | 2-4 weeks after initiation, thereafter every 6 |

| Test | Enrollment | Pre-Initiation | Ongoing Care |
|---|---|---|---|
| (Minimum of ALT and AST) | | | months<br>NVP-based regimen: Check at 2 weeks and 4 weeks after starting a NVP based regimen. Recheck at 3 and 6 months. If results are normal, can check every 6 months thereafter unless patient becomes symptomatic. |
| PPD/Mantoux (not applicable once child has a history of latent or active TB disease) | yes | If > 12mos since last PPD | Annually until positive. If Mantoux converts to positive, follow pathway for TB assessment [outlined in Special Issues pp.__] |
| Hepatitis B (HBsAg) | yes | - | Annually if sexually active or high risk |
| RPR/VDRL | yes | - | Annually if sexually active or high risk |

Important signs indicating a response to ARV therapy include the following:

- Improvement in growth, especially in children who were severely malnourished and diagnosed with growth failure.
- Improvement in developmental milestones in children with neurodevelopmental delay.
- Improvement in CD4+ cell counts, viral load testing and the absence of infection.

Once a child is on ARV therapy, clinical assessment should consider the child's and caregiver understands of the therapy as well as anticipated support and adherence to therapy. Observation of the child's responses to therapy should also include symptoms of potential drug toxicities or treatment failure. Positive laboratory or clinical findings may necessitate more frequent screening or additional testing (e.g. a Chest X-Ray following a positive Mantoux screen).

**Additional Information on monitoring for specific ARV regimens**

- ***ABC:*** Children started on ABC containing regimens should be evaluated at 2 weeks, 4 weeks and 6 weeks following initiation of ABC. Abacavir hypersensitivity reaction (HSR) typically presents with fever, rash, and abdominal pain. Please see section on Adverse Effects of ARV Medications for more information. Children identified as developing HSR to Abacavir should ***never*** be rechallenged with Abacavir. Abacavir HSR develops within the first 6 weeks of starting ABC.
- ***AZT:*** All children starting AZT should be monitored for potential development of anaemia. This includes clinical assessment of pallor in addition to CBC screening outlined above. Anaemia on AZT may be due to other nutritional factors or HIV disease itself. It is therefore important to investigate these causes before ascribing anaemia to AZT. The anaemia from AZT is macrocytic and may improve with Folate supplementation.
- ***d4T:*** As part of the routine clinical examination, children on d4T based regimens should be regularly evaluated for the presence of peripheral neuropathy or lipodystrophy.
- ***NVP:*** The three most common and serious adverse effects from Nevirapine therapy are hepatitis, rash, and toxic epidermal necrolysis (TEN)/Stevens-Johnson Syndrome (SJS). Although rarer in children, drug induced NVP hepatitis can be potentially fatal. Screening for jaundice should be combined with liver

function testing within 2-4 weeks after starting NVP. TEN/SJS is a very rare, but potentially fatal, skin rash that involves sloughing of the epidermal layer and usually involves mucous membranes. Both TEN/SJS and hepatitis are much more common within the first 3 months of starting HAART. NVP can also cause a more benign rash without epidermal sloughing or mucous membrane involvement. This can be treated conservatively with anti-histamines and/or low doses of prednisone in most cases.

- ***EFV:*** The most common adverse effects from Efavirenz therapy are central nervous system side effects (dizziness, sleepiness, lethargy, vivid dreams, depression, etc.). These frequently (~95%) improve after the first month of therapy and can usually be managed conservatively. Additionally, Efavirenz can have a drug-related hepatitis, rash, and chance for SJS/TEN similar to NVP though these are less common and less serious than with NVP.
- ***LPV/r:*** Children starting Lopinavir/ritonavir should be assessed for gastrointestinal side effects such as diarrhea and nausea. These side effects usually improve within the first 4 weeks of therapy and can usually be managed conservatively. Additionally, long-term use of protease inhibitor therapy has been linked to insulin resistance and changes in cholesterol. It is recommended that an annual screen for blood sugar be part of the routine evaluation for children on LPV/r and that cholesterol screening be incorporated in late adolescence.

Viral load testing

Effective antiretroviral therapy results in suppression of viral replication in the blood to levels below the threshold of detection ["undetectable viral loads"]. Changes in viral load precede changes in CD4+ counts and can identify treatment failure earlier than through CD4 monitoring alone. Now available in Guyana, Viral load testing has become part of the routine clinical care of children living with HIV soon. Viral load testing will monitor for treatment failure. Viral load testing is done on children prior to initiation and 6 months post initiation. Viral load testing is then performed every six months thereafter. If there is suspicion of treatment failure or need to begin second line ART, viral load testing should be performed.

## SUBSTITUTION FOR TOXICITY OR INTOLERANCE

It is the clinician's responsibility to monitor the adverse events based on the regimen being used. Children or caregivers may report some signs and symptoms and other adverse events may be detected by laboratory testing. Most symptoms are mild and/or transient, while others may require supportive therapy, (e.g. antiemetics) or more frequent clinical monitoring. Rarely, symptoms may be severe enough to require changing the drug regimen.

Managing adverse events is an integral part of ARV therapy. If the adverse events are severe or disruptive, they will be a barrier to adherence to the ARV drug regimen. The clinician should explain to the caregiver in simple terms the major adverse events for each medication in the regimen, and emphasize that those adverse events should be reported to the clinician as soon as possible if they occur. Unfortunately, in many instances, it is difficult to differentiate between the complications of HIV infection, a concurrent childhood illness, and adverse events secondary to ARV drugs. If adverse events do occur, they should be managed according to severity:

- **Mild or Moderate reactions**: Continue ARV therapy as long as feasible while providing reassurance and supportive therapy. Stress maintaining adherence despite toxicity. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.
- **Severe reactions**: Substitute the offending drug without stopping ARV therapy.

- **Severe life-threatening reactions**: Immediately discontinue all ARV drugs and manage the medical event (symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. substituting for the offending ARV) when the patient is stabilized.

If the adverse event can be linked to a drug in the regimen, it is advisable to replace the drug with one from the same class that is not associated with the same toxicities and does not interact with other drugs in the regimen. Common examples are listed in table 2.13.

**Table 2.13: Severe toxicities in infants and children associated with specific first-line antiretroviral drugs: potential first-line drug substitutions**

| First-line ARV drug | Most frequent significant toxicity | Suggested first-line ARV drug substitution |
|---|---|---|
| **ABC** | Hypersensitivity reaction | Discontinue ABC immediately<br>Substitute d4T or AZT for ABC |
| **AZT** | Severe anaemia[a] or neutropoenia | d4T or ABC |
| | Severe gastrointestinal intolerance[b] | d4T or ABC |
| | Lactic acidosis | ABC |
| **D4T** | Lactic acidosis | ABC |
| | Peripheral neuropathy | |
| | Pancreatitis | |
| | Lipoatrophy/metabolic syndrome | |
| **EFV** | Persistent and severe central nervous system toxicity | NVP |
| | Potential teratogenicity (WHO recommends EFV use after 13 weeks of pregnancy Therefore all sexually active adolescents girls and women should avoid EFV during first trimester of pregnancy | |
| **NVP** | Acute symptomatic hepatitis | EFV |
| | Hypersensitivity reaction | Discontinue NVP immediately<br>Start antihistamines and/or corticosteroids as necessary.<br>Weigh advantages of following alternatives based on the severity of the reaction:<br>• Substitute EFV[d]<br>• Substitute NVP with a third NRTI (usually AZT/3TC/ABC)[e]. Consider restarting EFV after symptoms resolve.<br>• LPV/r[f] |
| | Severe or life-threatening rash (Stevens-Johnson Syndrome)[c] | |

Note: 3TC/FTC-associated pancreatitis has been described in adults but is considered very rare in children.

e) Rule out malaria in areas of endemic malaria.

f) Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

| First-line ARV drug | Most frequent significant toxicity | Suggested first-line ARV drug substitution |
|---|---|---|

g) Severe rash is defined as extensive rash with desquamation, angioedeoma, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis; Stevens - Johnson syndrome can be life-threatening.
h) For life-threatening rash, most clinicians would not substitute EFV because of the potential for NNRTI-class specific toxicity.
i) Studies suggest triple NRTI are less potent than combination NRTI/NNRTI therapy.
j) The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure.

## TREATMENT FAILURE AND SECOND-LINE REGIMENS

### Treatment Failure and Resistance

Several factors may play a role in treatment failure in children: poor adherence, insufficient drug doses, inadequate drug potency, and/or genetic differences in drug metabolism. All of these factors result in insufficient ARV drug levels which, in turn leads to HIV viral replication. Viral replication in the setting of insufficient drug levels provides selective pressure to promote the development of **drug resistance**. Drug resistance occurs when the HIV virus develops specific mutations that allow it to continue replication despite antiretroviral therapy. The drug resistant virus capable of replicating rapidly becomes the majority population of HIV virus in an affected patient, and these viral strains are archived in inactive CD4 cells and other viral reservoirs. Thus, once a patient has developed resistance to specific ARVs, this resistance is likely to remain throughout a patient's life, meaning that the affected ARVs will no longer be effective in suppressing HIV.

Suppression of HIV replication is best achieved when a minimum of three active antiretroviral agents are used. When a drug resistance mutation affecting one component of a triple-drug regimen develops, the patient only has two active agents remaining. Continuation of this regimen then makes the development of additional drug resistance to the remaining active agents even more likely. Continuation of failing regimens eventually leads to the gradual accumulation of additional drug resistance mutations. Drug resistance mutations not only permanently affect the current antiretroviral regimen but can seriously limit the efficacy of future treatment options. Thus it is ***very important to diagnose treatment failure early***. It is the clinician's responsibility, based on clinical and laboratory assessments, to determine when a drug regimen is failing, determine the reason why, and intervene appropriately.

### Definition of Treatment Failure in Children

Treatment failure can be defined through virologic, immunologic or clinical criteria. When antiretroviral regimens begin to fail, HIV replication can first be detected by measurement of detectable viral loads in the bloodstream (virologic failure). Continued viral replication results in depletion or lack of an appropriate increase of CD4+ cells (immunologic failure). Finally, continued immunologic failure leads to the development of opportunistic infections (clinical failure).

A switch to second line ARV's is recognized if there is one of the following

- Virologic failure and or
- Immunologic failure and or
- Clinical Failure

**Virologic definition of treatment failure**
Virologic failure is defined as a persistent viral load of >400 copies /milliliter after at least 6 months of ARV's in an adherent child.

Viral load testing should not be performed until after one month if a child has had the following:

- Immunizations within the last month
- Severe viral infections or hospitalizations
- Other recently diagnosed infections; malaria. Pulmonary TB, pneumonia
- Recent surgery

**Immunologic definition of treatment failure**

**Definition of Immunologic Failure in Children**

- Rapid decrease of CD4% of >30% in less than six months.
- Overall decrease of CD4% [or overall CD4+ cell count for children > 5years] by >50% from peak level on antiretroviral therapy.
- CD4% at or below pre-treatment baseline levels in the absence of concurrent infection

Note: Treatment failure cannot be determined until the child has had a reasonable trial on the ARV regimen – at least 24 weeks

Immunological failure is recognized as developing or returning to the following age related immunological thresholds after at least 24 weeks on ART, in a treatment adherent child:≥2 years to <5 years of age CD4 count of <200 cells/mm3 or %CD4+ <10 ≥5 years of age CD4 count of <100 cells/mm3

**Clinical definition of treatment failure**
Clinical failure is defined as the appearance or reappearance of WHO stages 3 or 4 events after 6 months on HAART in a treatment adherent child.

***It is also important to note that pulmonary TB alone, while a stage 3 condition, may not necessarily indicate treatment failure and may not require evaluating whether a second-line regimen is necessary.***

**Definition of Clinical Failure in Children**

- Growth failure: a persistent and unexplained decline in weight-growth velocity despite adequate nutritional support and in the absence of other concomitant diseases that may explain the weight loss.
- Neurodevelopmental deterioration as evidenced by loss of developmental milestones or progression/development of HIV encephalopathy (indicative of WHO paediatric clinical stage 4).
- Disease progression as defined by the development of a new WHO paediatric Stage 3 or 4 opportunistic infection or malignancy.
- Recurrence of infections such as oral or esophageal candidiasis that is refractory to treatment.

**Assessing Treatment Failure**
While other factors such as inappropriate ARV dosing, intercurrent infections, or genetic differences in drug metabolism may also lead to treatment failure, it is important to note that poor adherence to the drug regimen is the most common cause of treatment failure. Therefore, it is necessary to ensure that adherence to therapy has been assessed and any challenges addressed before switching to a second-line regimen. When patients are poorly adherent, it is frequently difficult to determine whether treatment failure results from negligible

drug levels with active drugs or from drug resistance. Studies suggest that patients with moderate levels of adherence (50-92%) are at highest risk for drug resistance. In patients with very poor adherence (<50%), antiretroviral medication levels may not even be sufficient to generate selective pressure favoring resistance. Thus, it may be reasonable to intervene to support adherence and reassess shortly thereafter before switching to second-line therapy. Although most children will show an immunologic and clinical response quickly to HAART, it is important to ensure that the child receives a reasonable trial of the ARV regimen (at least 24 weeks) before diagnosing treatment failure. ***Once treatment failure is diagnosed and suspected due to potential drug resistance, it is important to support adherence and switch to an appropriate second-line regimen***.

**Differentiating clinical failure from the Immune Reconstitution Inflammatory Syndrome**

Clinical treatment failure must be differentiated from the immune reconstitution inflammatory syndrome (IRIS), which is infrequent (<30%) but may occur in the first 3 months following initiation of ARV therapy. IRIS has been observed in adults and less frequently in children starting ARV therapy, particularly those with low CD4 values.

With IRIS, the signs and symptoms of an OI may appear a few weeks after the start of ARV therapy in a patient who is severely immunocompromised. IRIS is a paradoxical inflammatory response to a previously subclinical infection that has been reactivated after immune reconstitution with HAART. The symptoms of IRIS are manifestations of opportunistic infections; however IRIS is accompanied by a rapid rise in CD4 values. Because some opportunistic infections (e.g. latent tuberculosis) may be undiagnosed when starting HAART, they may sometimes appear as the development of a new opportunistic infection. The most common precipitating infections are Mycobacterial infections (MAI and M.Tb) and Cryptococcal meningitis. IRIS does *not* signal treatment failure. The OI should be treated as recommended, and ARV therapy should be continued with the same regimen.

**Second- Line Regimens in the event of treatment failure**

When treatment failure is confirmed, it is necessary to switch to a second-line ARV regimen. The most effective second-line therapy would involve including three antiretrovirals that would be expected to be active given the patient's ARV history. Without the ability to perform resistance testing, clinicians should consider the patients antiretroviral history when selecting a second-line regimen. In patients who have been exposed to several first line regimens, it should be assumed that drug resistance has occurred to the components of the regimen the patient was taking when treatment failure was diagnosed. Although prior agents (e.g. discontinued due to intolerance) may still be active, it may be important to consider them in selecting a second-line regimen. Since patients are not exposed to protease inhibitors as part of first-line therapy, they remain the lynchpin of second-line HAART. Prior to switching to second line HAART, get a viral load to confirm treatment failure.

**Table 2.14: Selection of appropriate Second-Line regimens based on First-Line therapy**

| First Line Regimen | Appropriate second line | Alternative second line options |
|---|---|---|
| ABC + 3TC + EFV/NVP | AZT + 3TC + LPV/r | - |
| AZT + 3TC + EFV/NVP | Truvada ( Tenofovir)+3TC + LPV/r | TDF + FTC + LPV/r[b] (Children at least Tanner 3 or greater or weigh at least 35 kg. |
| D4T + 3TC + EFV/NVP | Truvada ( Tenofovir)3TC + LPV/r | |

| | | |
|---|---|---|
| AZT + 3TC + ABC (Triple NRTI) | TDF + FTC + EFV/NVP<br>TDF + FTC + LPV/r | |
| Protease Inhibitor Regimen | Switch Nucleoside Backbone and Continue PI[e] | |

**Use of Tenofovir in Children.**
Tenofovir (TDF) is a nucleotide reverse transcriptase inhibitor commonly used in adult regimens. It has a different resistance profile than other commonly used nucleoside reverse transcriptase inhibitors and frequently retains efficacy in the setting of resistance to other NRTIs. Tenofovir is not recommended in children under 3 years old unless it is the only alternative. However, in the setting of severe immunosuppression and treatment failure to first-line regimens, it may offer improved chances of immune reconstitution and survival. Recommended dosing of Tenofovir should not exceed **210-240 mg/m$^2$**. Where coformulated TDF/FTC 300/200mg fixed-dose combinations are available, this limits use to children weighing roughly 35kg or more. Clinicians should carefully weigh any potential risks with benefits when contemplating the use of TDF in a second-line regimen. It is recommended that you consult an experienced HIV specialist when starting TDF in children who have not yet reached Tanner Stage III development.

**Salvage regimens**
When the second-line regimen fails, it is recommended that clinicians contact an experienced HIV treatment specialist. The use of certain antiretrovirals, even in the setting of resistance, can reduce morbidity and mortality due to HIV infection, by reducing viral fitness and the rate at which HIV replicates (the replicative capacity). Lamivudine or Emtracitabine (3TC or FTC), Tenofovir (TDF) and Lopinavir/Ritonavir (LPV/r) have this effect. Thus it is recommended that clinicians continue the use of second-line regimens while contacting the National Care & Treatment Center (NCTC) in the setting of treatment failure to second-line regimens. The National AIDS Programme Secretariat is investigating the possibility of procurement of small stocks of expensive newer antiretrovirals that may work in the setting of second-line failure. These medications would be carefully monitored and prescribed by the NCTC.

## SPECIAL CONSIDERATIONS FOR CHILDREN

**Tuberculosis and HIV Infection: Special Considerations for Children**
TB is considered the most common opportunistic infection and the leading cause of death in people infected with HIV in resource-constrained countries. Screening and treatment for TB in the setting of HIV infection is detailed in Section 3 “Antiretroviral Therapy in Special Circumstances”

Screening for tuberculosis is an important part of the management of an HIV positive child, as immunosuppression makes primary infections and reactivation of latent TB infection more likely. In addition, in the later stages of HIV infection, children are more likely than adults to develop miliary TB and other severe complications, including tuberculous meningitis and/or tuberculous lymphadenopathy. ***It is essential that clinicians, based on the prevalence of TB in the community, maintain a high level of suspicion for TB-HIV co-infection in children, diagnose children with TB-HIV co-infection without delay, and provide prompt and appropriate treatment.*** Diagnosing TB in children may be difficult because of a broader range of nonpulmonary and pulmonary manifestations. The use of sputum microscopy and tuberculin testing as outlined in Section 3 can help in making an appropriate diagnosis. In many cases, the diagnosis is presumptive and is based on a constellation of clinical signs and symptoms, known contact with a household member with TB disease, and the child’s response to empirical TB therapy.

As outlined, recommended antiretroviral regimens usually avoid the use of Nevirapine or protease inhibitors such as Lopinavir/Ritonavir due to drug interactions with Rifampicin. An NRTI backbone in combination with Efavirenz is recommended. Given the lack of safety data in children and possible concerns for toxicity, Tenofovir-based regimens should be avoided. Use Abacavir (ABC) with Lamivudine (3TC) and Efavirenz (EFV) using appropriate weight-based doses. Zidovudine (AZT) or Stavudine (d4T) can be substituted for ABC depending on other clinical factors. In children under the age of two or weighing <10kg, Efavirenz has not been well studied though could be used at a 300mg once daily dose with careful monitoring. In cases of EFV toxicity, an appropriately dosed triple NRTI regimen of Zidovudine (AZT) + Lamivudine (3TC) + Abacavir (ABC) is recommended. Stavudine (d4T) can be substituted for AZT in the setting of severe anaemia. The timing of initiation and monitoring of antiretroviral therapy after starting therapy for TB is similar to that of adults and is detailed in Section 3.

For children already on HAART who are diagnosed with active TB infection, continuation of the HAART regimen is recommended while starting anti-TB therapy, with careful attention paid to appropriately modifying the HAART therapy to avoid drug-drug interactions. Efavirenz should be substituted for Nevirapine. Although the development of new TB disease may not necessarily constitute treatment failure, it is important to closely monitor for antiretroviral failure through CD4 testing. For children already taking second-line PI-based therapy, please contact the National TB Programme for use of Rifabutin (three times weekly) in the place of Rifampicin.

**Disclosure and Psychosocial Issues**

Diagnosing and caring for infants and children who are HIV-exposed and HIV-infected is a partnership among the clinician, the child, and the caregiver(s). Recognizing the importance of this alliance and building a trusting relationship among all who participate in the child's care, is central to providing the best possible long-term care for children with HIV infection. One of the first steps in this process is discussing the child's diagnosis with the caregiver(s).

**Talking to caregivers about paediatrics diagnosis**

Parents and caretakers of HIV-exposed infants are understandably anxious about the health of their children. Most are worried that their child has or will have HIV infection. Given the complexity of the subject, it can be very difficult to explain the issues around infant diagnosis to parents and caretakers. However, a number of steps can be taken to help them better understand the situation.

- Mothers who have participated in a PMTCT program have the benefit of an early education about HIV transmission.
- For those who have not participated in a PMTCT program, it is recommended to begin talking about infant diagnosis as early as possible, preferably during the first pediatric appointment.
- Discuss with the parent or caregiver that the infant or child can have a blood test (either DNA-PCR dried blood spot test or HIV rapid test) to determine if the child is infected with HIV. It is important to stress the benefits of knowing one's HIV status early and the possibility of effective management with ARV therapy.
- If the infant or child fulfills the criteria for initiation of ARV therapy, reassure families that although there is no cure to date, there are treatments available that HIV-infected infants and children can receive to prolong survival and improve their quality of life.
- Speaking openly with parents at each visit can be very helpful. Eliciting and addressing their questions and concerns can decrease their anxiety. Telling them about the infant or child's progress and highlighting positive findings (good growth, normal examination) can also be reassuring.

- Reassure caregivers that HIV cannot be transmitted by casual contact such as playing with other children. However, toothbrushes should not be shared and Universal Precautions should be applied if exposure is to blood, tissue, or other body fluids containing visible blood.

It is important to always be open and honest about the child's health, to use simple language, and to include the caregivers in the treatment decision-making process at each stage of HIV infection. It is to be expected that caregivers will have fears and anxieties about caring for a child who is HIV-infected and about the long-term prognosis. Making time to discuss their concerns at each clinic visit will build trust, support adherence, and maximize the likelihood that treatment will be successful.

When an infant or child is diagnosed with HIV, it may be the first indication that one or both parents is/are infected as well. Parental feelings of guilt or anger may surface, resulting in additional disruption of the family unit. Counselling and psychosocial support at this juncture can help parents and guardian cope more effectively with the diagnosis of HIV and the ongoing care of the affected infant or child.

Addressing any psychosocial issues in a timely, sensitive, and direct manner will increase the likelihood that the family will obtain the best possible care for their infant or child. Providing the support that will enable the caregiver to return to the clinic with the child for follow-up visits is central to maximizing adherence. The family should be referred to community-based organizations where they can receive support and be educated about the disease.

**Talking to HIV-positive children about their diagnosis**

Disclosure of an HIV-positive diagnosis to an infected child must be done at the appropriate time. Young children may not have enough knowledge of what HIV is or about confidentiality. This can lead to a children telling others of their HIV diagnosis inappropriately, which may lead to unintended stigma and discrimination. Yet it is important to tell children about their diagnosis as early as they are capable of understanding the consequences. Although the appropriate age at which to disclose to a child is different for each child, clinicians and family members can use the child's questions as a guide to knowing when a child is capable of understanding.

Disclosure can be handled by the clinician, the caregiver, or a family member in the clinical setting. In some situations, the caregiver or family member may want to disclose at home. Follow-up discussion should be made at the next clinic visit to insure that proper information was provided to the child or adolescent and that unanswered questions are addressed.

Caregivers also may choose to disclose on a need-to-know basis to siblings of the infected child, other family members, friends, school nurses, teachers, and administrators. If the caregiver decides to disclose the child's HIV diagnosis, psychosocial support should be provided as needed. Often, they will need assistance with disclosing the diagnosis to the child and siblings in a way that is age-appropriate. It is important for the clinician to explain to the caregivers that it is likely to be less stressful for the child and siblings to know the diagnosis than to know the child is affected by an unnamed but obvious illness.

**HIV and School Issues**

Schools are an important part of a child's growth and development and should provide a supportive, caring environment for all children. The children who are HIV-infected and their siblings have the same right to learn in an environment free of stigma and discrimination as do their classmates.

**Confidentiality and disclosure**
The parents or legal guardians have the right to decide whether they will inform the school staff that a child is HIV-infected. If they decide to disclose, they should restrict giving the information to the people directly involved with the child's education. The parents or guardians should ask that the information be held in the strictest confidence. Once the staff is aware of the child's HIV status, they should consider what additional support may be necessary for the child and the family during school hours. It is essential that teachers, administrators, and clinicians maintain confidentiality at all times.

**Administering HIV medications**
Most schools do not have a nurse or clinician who can provide medications as part of the school staff. Therefore, to avoid compromising confidentiality, we strongly recommend children be placed on a regimen that requires taking ARV drugs once or twice a day. In that way, the drugs can be administered at home in the morning and evening, and not during school hours.

**Training**
It will be very important to offer training for the entire school system about HIV prevention, about dispelling myths concerning HIV transmission, and about ethical issues including disclosure and confidentiality. Regardless of whether students with HIV infection are known to be in attendance, teachers, administrators, custodians, and all other school employees at all schools should be trained in Universal Precautions to prevent transmission of any infection, including HIV. Management of wound care, nosebleeds, and bite care, and disposal of sanitary napkins should be discussed. It is imperative to refer for appropriate care and management when the risk of exposure to HIV is considered high.

**Adolescents and HIV**
During adolescence (ages 10-19), there are multiple developmental stages – physical, psychological, and sexual – that all adolescents must complete and that have implications for providing appropriate care and treatment. All children progress through these stages at different times and at different rates. Moving from a pediatric to an adult care model occurs in the context of these stages, and is challenging and complex not only for adolescents but also for HIV care providers. Taking this into consideration, it is recommended that clinicians who care for adolescents:

- Inform them of their HIV status.
- Educate them about their disease and treatment regimen.
- Stress the importance of adherence.
- Assist them with disclosing their HIV status to those whom they want to know about it.
- Help them identify and build a support system, so they know whom they can request help and advice from when they need it.

**Regimen considerations**
It is recommended that the choice of regimen and dosages for adolescents newly starting HAART be based on Tanner staging. Those who begin therapy on a pediatric regimen should be monitored closely, because they may experience a growth spurt that necessitates changes in ARV dosing and, eventually switching to an adult regimen. Adolescents in Tanner stage 4 or higher should begin therapy on an adult regimen.

**Adolescents with behaviorally acquired HIV infection**
Adolescents may acquire HIV through unprotected sex, sexual abuse, or as sex workers. That constitutes a different cohort whose needs and social issues are not similar to those with perinatally-acquired HIV

infection. More often than not, adolescents do not want a parent or guardian to be aware that they are been tested for HIV, nor do they want results disclosed. Most adolescents in Guyana live with a parent or guardian who usually accompanies the adolescent to clinic visits. This may be a principal barrier to adolescents accessing HIV counselling and testing services.

***When a clinician knows or suspects an adolescent is sexually active, or has been sexually assaulted or has a sexually-transmitted infection, it is critical that the clinician offer confidential HIV counselling and testing.***

**Adolescents and adherence issues**

Caring for any adolescent with a chronic disease entails addressing barriers directed to the developmental tasks of adolescence: becoming independent from parents or guardians and wanting to be liked by their peers. Having to disclose to a parent or guardian, who probably will need to remind them to take medication, thwarts the adolescent's desire for independence, and taking medication daily is a constant reminder that they are different from their peers. Before treatment is initiated, it is recommended that clinicians conduct a comprehensive assessment of factors influencing adherence. For most adolescents, the factors influencing adherence include: denial, misinformation, cultural and religious beliefs, distrust of clinicians, and suspicion about the effectiveness of ARV drugs, low self-esteem, unstructured and chaotic lifestyles, and lack of family and social support. The clinician also needs to balance the aim of prescribing a potent and effective regimen with realistic considerations (e.g. does the adolescent have a support system that can facilitate adherence?). When possible, the clinician should select a regimen with minimal pill burden; this strategy may help maximize adherence.

**Adolescents and sexual activity**

Counselling adolescents about their sexual activity involves a delicate balance of emphasizing the need for secondary prevention (e.g. always using condoms) while also emphasizing that they are just like their peers. Lecturing HIV positive adolescents in manners which suggest that they are treated different because of HIV infection risks alienating them at a time when they are increasingly seeking acceptance from peer groups. Adolescents who are HIV-infected should be encouraged to use condoms and to disclose their status to their sex partners to prevent transmission and re-infection. It is also important to discuss the possibility of having children in the future, how this can be handled most appropriately, and answering questions in a forthright and honest manner.

# APPENDICES

## Appendix 2-A
## WHO Clinical Staging of HIV and AIDS for Infants and Children with Established HIV Infection

| **Clinical Stage 1**[a] |
|---|
| ▪ Asymptomatic<br>▪ Persistent generalized lymphadenopathy |
| **Clinical Stage 2**[a] |
| ▪ Unexplained persistent hepatosplenomegaly<br>▪ Papular pruritic eruptions<br>▪ Extensive wart virus infection<br>▪ Extensive molluscum contagiosum<br>▪ Recurrent oral ulcerations<br>▪ Unexplained persistent parotid enlargement<br>▪ Lineal gingival erythema<br>▪ Herpes zoster<br>▪ Recurrent or chronic URTI (otitis media, otorrhea, sinusitis, tonsillitis)<br>▪ Fungal nail infections |
| **Clinical Stage 3**[a] |
| ▪ Unexplained moderate malnutrition not adequately responding standard therapy<br>▪ Unexplained persistent diarrhea (≥14 days)<br>▪ Unexplained persistent fever (>37.5intermittent or constant >1 month)<br>▪ Persistent oral Candida (outside of first 6-8 weeks of life)<br>▪ Oral hairy leukoplakia<br>▪ Acute necrotizing ulcerative gingivitis /periodontitis<br>▪ Symptomatic lymphoid interstitial pneumonitis<br>▪ Lymph node TB<br>▪ Pulmonary tuberculosis<br>▪ Severe recurrent presumed bacterial pneumonia<br>▪ Chronic HIV associated lung disease including bronchiectasis<br>▪ Unexplained anaemia (<8g/dl), neutropenia (<500/$mm^3$) or chronic thrombocytopenia (<50,000/$mm^3$)<br>▪ HIV associated cardiomyopathy or HIV associated nephropathy |
| **Clinical Stage 4**[a] |
| ▪ Unexplained severe wasting , stunting or severe malnutrition not responding to standard therapy<br>▪ *Pneumocystis* pneumonia (PCP)<br>▪ Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonias<br>▪ Chronic herpes simplex infection>1 month<br>▪ Kaposi's sarcoma |

- Extrapulmonary tuberculosis
- Toxoplasmosis on the brain

**Clinical Stage 4**[a]

- Oesophageal candidiasis
- CNS toxoplasmosis outside of neonatal period
- Cryptococcal meningitis HIV encephalopathy
- Cryptosporidiosis with diarrhea>1 month
- Isosporiasis with diarrhea>1 month
- Progressive multifocal encephalopathy
- Cytomegalovirus infection (retinitis)
- Acquired HIV associated fistula
- Cerebral or B cell non Hodgkin lymphoma
- Disseminated endemic mycosis
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a) Unexplained refers to when the condition is not explained by other causes.

Source: World Health Organization (WHO) *WHO Case Definitions of HIV for Surveillance, and Revised Clinical Staging and Immunological Classification of HIV Related Disease in Adults and Children, May 2006.*

# APPENDIX 2-B
## Mini Developmental Milestone Check List

### Pediatrics Developmental Milestones

**1 – Month**

- ☐ Head lag
- ☐ Moro
- ☐ Tight fist
- ☐ Prefers human face
- ☐ Tonic neck
- ☐ Follows pass midline
- ☐ 45" Chin lift

**6 – 7 Months**

- ☐ Absent Tonic neck
- ☐ Assist when been pulled to sit
- ☐ Stands with hands held
- ☐ Unilateral grasp
- ☐ Sits without support
- ☐ Transfer toys from 1 hand to the next
- ☐ Says syllables
- ☐ Says mama & dada
- ☐ Looks down for dropped object
- ☐ Creeps army style

**18 – 21 Months**

- ☐ Runs stiffly
- ☐ Climbs stairs step by step one hand on rail
- ☐ Climbs on chair
- ☐ Scribbles
- ☐ 10-20 words vocab
- ☐ Points to 1-2 body parts
- ☐ Put 9-10 object in cup
- ☐ Build tower of 3 objects
- ☐ Uncovers hidden objective without visible displacement

**48 – 50 Months**

- ☐ Complex sentences
- ☐ Tell stories
- ☐ Knows adjectives
- ☐ Knows 4-5 colours
- ☐ Hop few steps
- ☐ Balances on 1 foot for few seconds
- ☐ Draws cross, square
- ☐ Draws persons with 3 body parts
- ☐ Dresses self
- ☐ Buttons clothes
- ☐ Tandem walk backwards
- ☐ Tell stories

**2 – Months**

- ☐ Head lag
- ☐ Moro
- ☐ Regards hand
- ☐ Social Smile
- ☐ Make vowel sounds
- ☐ Keeps head up for few seconds
- ☐ Head in midline

**9-10 Months**

- ☐ Sits well without support
- ☐ Stands, cruises
- ☐ Pincer grasp
- ☐ Bangs & waves toys
- ☐ Gets into sitting position
- ☐ Plays games (peek-a-boo)
- ☐ Stranger & separation anxiety
- ☐ Creeps & pull to stand
- ☐ Waves bye-bye

**24-30 Months**

- ☐ Follows 2 step command
- ☐ 50 word vocab
- ☐ 2-3 word sentences
- ☐ Build tower of 6-8 cubes
- ☐ Kick/throws ball
- ☐ Walk up & down stairs
- ☐ Makes vertical stroke
- ☐ Make train of 3-4 cubes
- ☐ Knows 6 body parts
- ☐ 50% of speech understood by stranger

**60-72 Months**

- ☐ Counts to ten
- ☐ Knows ABC's
- ☐ Know opposites
- ☐ Draws person with 6 body parts
- ☐ Plays board games
- ☐ Skips and hops well
- ☐ Ties shoe laces
- ☐ Can define and describe
- ☐ Rides bicycle

**4-5 months**

- ☐ Absent Moro
- ☐ Brings hand to midline
- ☐ Looks at object
- ☐ Un-fisted hand
- ☐ Minimum head lag
- ☐ Pushes with feet
- ☐ Moves head 180°
- ☐ Rolls prone to supine
- ☐ Recognizes mother
- ☐ Turns to sound laterally

**12 – 15 months**

- ☐ Walks alone
- ☐ Walks backwards
- ☐ 4-8 words vocabulary
- ☐ Follows simple commands
- ☐ Points to objects
- ☐ Uncover hidden objects with visible displacement
- ☐ Drinks from cup / 50% spillage
- ☐ Fine pincer grasp
- ☐ Functional play (toss ball)

**36 – 40 Months**

- ☐ 250 Word vocab
- ☐ Ask who/what
- ☐ 75% of speech understood by stranger
- ☐ Names 4 animals
- ☐ Knows name, age and sex
- ☐ Draw circles
- ☐ Walk on toes/broad jump
- ☐ Rides tricycle
- ☐ Has imaginary friends
- ☐ Alternates feet walking upstairs
- ☐ Toilet trained

**Normal bad habits for age**

| Age of onset | Bad Habits | Age of cessation (usually) |
|---|---|---|
| 23 weeks | Finger sucking | 4 years |
| 6 months | Body rocking & breath holding | 2-3 years |
| 8-9 months | Head banging | 4 years |
| 10 years | Onychophagia (nail biting) | 18 years |
| 3 years | Bed wetting | 8 years |
| 3 years | Stool with-holding | 6 years |

# APPENDIX 2-C
## Paediatric AVR Dosing Chart

| Weight | **Abacavir (ABC)** 8 mg/kgTwice Daily | | **Lamivudine (3TC)** 4 mg/kg Twice Daily | | **Zidovudine (AZT,ZDV)** 180/240 mg/m$^2$ Twice Daily | | **Didanosine (ddI)** 120 mg/m$^2$ Twice Daily | **Stavudine (d4T)** 1 mg/kg Twice Daily | **Efavirenz (EFV)** 150 mg/m$^2$ Once Daily (at night) | **Nevirapine (NVP)** 120-200 mg/m$^2$ Twice Daily **[Note: Give as Induction dose Once Daily for first 14 days]** | | **Lopinavir/Ritonavir (LPV/r)** <15 kg: 12-16mg/kg ≥ 15kg: 10 mg/kg Twice Daily [based on LPV] | | **Cotrimoxazole** 4mg/kg Once Daily [prophylaxis] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **KG** | Liquid 20mg/ml | Tablet 300mg | Liquid 10mg/ml | Tablet 150mg | Liquid 10mg/ml | Caps/Tabs 100mg 300mg | Tablet 20mg | Capsules 15,20,30mg | Caps/Tabs 200mg,600mg | Liquid 10mg/ml | Tablet 200mg | Liquid 80/20 mg/ml | Tablet 200/50mg | Liquid 200+40 mg/5ml | Tablet SS/DS |
| 4-4.9 | 2 ml | | 2 ml | | 6 ml | | 1 tab | | 300 mg | 5 ml | | 1 ml | | 2.5 ml | |
| 5-5.9 | 2 ml | | 3 ml | | 6 ml | | 1 tab | 20mg ½ cap | 300 mg | 6 ml | | 1 ml | | 5 ml | ½ SS tab |
| 6-6.9 | 3 ml | | 3 ml | | 7 ml | | 2 tab | 20mg ½ cap | 300 mg | 7 ml | | 1.5 ml | | 5 ml | ½ SS tab |
| 7-7.9 | 4 ml | | 4 ml | | 8 ml | | 2 tab | 20mg ½ cap | 300 mg | 8 ml | | 1.5 ml | | 5 ml | ½ SS tab |
| 8-8.9 | 4 ml | | 4 ml | | 9 ml | 100mg cap | 2 tab | 20mg ½ cap | 300 mg | 9 ml | | 2 ml | | 5 ml | ½ SS tab |
| 9-9.9 | 4 ml | | 4 ml | | 9 ml | 100mg cap | 2 tab | 20mg ½ cap | 300 mg | 9 ml | ½ tab | 2 ml | | 5 ml | ½ SS tab |
| 10-10.9 | 5 ml | | 5 ml | | 10 ml | 100mg cap | 2 tab | 15 mg | 300 mg | 10 ml | ½ tab | 2 ml | | 5 ml | ½ SS tab |
| 11-11.9 | 5 ml | ½ tab | 5 ml | | 10 ml | 100mg cap | 3 tab | 15 mg | 300 mg | 10 ml | ½ tab | 2 ml | | 5 ml | ½ SS tab |
| 12-13.9 | 6 ml | ½ tab | 6 ml | ½ tab | 12 ml | 100mg cap | 3 tab | 15 mg | 300 mg | 10 ml | ½ tab | 2 ml | 1 tab | 5 ml | 1 SS tab |
| 14-16.9 | 6 ml | ½ tab | 6 ml | ½ tab | 15 ml | 300mg ½ tab | 3 tab | 20 mg | 300 mg | 12 ml | 1 tab AM + ½ tab PM | 2 ml | 1 tab | 10 ml | 1 SS tab |
| 17-19.9 | 8 ml | ½ tab | 8 ml | ½ tab | 15 ml | 300mg ½ tab | 4 tab | 20 mg | 300 mg | 15 ml | 1 tab AM + ½ tab PM | 2.5 ml | 1 tab | 10 ml | 1 SS tab |
| 20-24.9 | 10 ml | 1 tab AM + ½ tab PM | 10 ml | 1 tab AM + ½ tab PM | 20 ml | 300mg ½ tab | 5 tab | 20 mg | 300 mg | 15 ml | 1 tab AM + ½ tab PM | 3 ml | 1 tab | 10 ml | 1 SS tab |
| 25-29.9 | 12 ml | 1 tab | 12 ml | 1 tab | 20 ml | 300mg tab | 5 tab | 30 mg | 400 mg | 15 ml | 1 tab | 3.5 ml | 2 tab AM 1 tab PM | 15 ml | 1 DS tab |
| 30-34.9 | 15 ml | 1 tab | 15 ml | 1 tab | | 300mg tab | 5 tab | 30 mg | 400 mg | 20 ml | 1 tab | 4 ml | 2 tab | 20 ml | 1 DS tab |
| 35-39.9 | 15 ml | 1 tab | 15 ml | 1 tab | | 300mg tab | 6 tab | 30 mg | 400 mg | 20 ml | 1 tab | 5 ml | 2 tab | 20 ml | 1 DS tab |
| 40-60.0 | | 1 tab | | 1 tab | | 300mg tab | 6 tab | 30 mg | 600 mg | | 1 tab | 5 ml | 2 tab | 20 ml | 1 DS tab |

# PART III:

# ANTIRETROVIRAL THERAPY

# IN SPECIAL CIRCUMSTANCES

# HIV AND PREGNANT WOMEN

**Preventing Mother-to-Child Transmission (PMTCT)**

A high viral load is the most important risk factor for mother-to-child transmission (MTCT) of HIV. Antiretroviral therapy has been shown to decrease the rate of transmission, though the type of regimen and timing of ART is of paramount importance. The majority of HIV transmission occurs during labor and delivery, though some infants are infected in utero. Additionally, breastfeeding and especially mixed breastfeeding with replacement feeding increases the risk of transmission (Table 3.1).

**Table 3.1: Timing and risk of mother-to-child transmission of HIV**

| Timing | Cumulative Risk of Transmission |
|---|---|
| During Pregnancy (In Utero) | ~ 1-5% |
| During Labor and Delivery (Intrapartum) | ~ 15-20% |
| Overall without Breastfeeding | ~ 25-30% |
| Overall with Breastfeeding to 6 months | ~ 25-35% |
| Overall with Breastfeeding to 18-24 months | ~ 30-45% |

Highly active antiretroviral therapy (HAART) with three ARV drugs is the best regimen for prevention of MTCT because it adequately suppresses viral load while protecting the health of the mother. Additionally, using three ARV drugs in combination reduces the chance that either the mother or baby develops HIV drug resistance.

Single-dose Nevirapine (sdNVP) has been proven to decrease the rates of MTCT, however there is concern that approximately one quarter of mothers given sdNVP and approximately three quarters of children born HIV positive to mothers who received sdNVP may develop NNRTI resistance (Lockman, et al. NEJM. 2007; 356: 135-147). Although dependent on a variety of factors, the relative efficacies of different interventions for PMTCT are listed in table 3.2.

**Table 3.2: Relative efficacy of Interventions for PMTCT**

| Intervention | Relative Reduction of MTCT | Notes |
|---|---|---|
| Cesearian Section alone[1] | 45% | When combined with HAART, there is <2% transmission. |
| sdNVP during labor[2-3] | 43-53% | Significant concerns with resistance due to long half-life leading to prolonged monotherapy |
| AZT < 4 weeks during pregnancy[2] | 55% | Additional sdNVP during labor may lead to greater reduction in transmission |
| AZT to child alone < 48 hrs after birth[4] | 61% | Most helpful with prenatal or intrapartum interventions as well. |
| AZT > 4 weeks during pregnancy[2] | 74% | Additional sdNVP during labor does not seem to have as much of an effect. Concerns about resistance due to prolonged |

| | | |
|---|---|---|
| | | monotherapy |
| HAART at any point in pregnancy[2] | 81% | Study performed in Botswana; overall result undifferentiated by efficacy (undetectable VL) or timing of HAART. |
| HAART pre-pregnancy[2,5-6] | 94-99% | When viral load suppressed to <400 copies, there is <1% chance of transmission. |


1) The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of HIV-1: a meta-analysis of 15 prospective cohort studies. NEJM. 1999; 340: 977-987.
2) Tlale J et al. IAS Mexico City Aug 2008 (Abs ThAC04)
3) Jackson, Musoke, Fleming, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for the prevention of mother to child transmission of HIV-1 in Kampala, Uganda: 18 month follow-up of the HIVNET 012 randomized trial. Lancet. 2003; 362:859-863.
4) Wade, Birkhead, Warren, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the HIV virus. NEJM 1998; 339: 1409-1414.
5) Cooper, Charurat, Mofenson, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. Journal of Acquired Immunodeficiency Syndrome. 2002; 29: 484-494.
6) Shapiro, Tuomala, Pollack, et al. Mother to Child HIV transmission risk according to antiretroviral therapy, mode of delivery, and viral load in 2895 US women. (PACTG 367) Eleventh Conference on Retroviruses and Opportunistic Infections. February 2004, San Francisco. Abstract S-80.


**Notes on ARV use in pregnancy**

Use of antiretroviral therapy in pregnancy follows the same guiding principles outlined in the adult treatment section of these guidelines. There are however, several points to emphasize:

- Efavirenz is contraindicated in the first trimester of pregnancy due to high levels of teratogenicity in primate studies. Although no demonstrable increased risk of teratogenicity with Efavirenz has been noted in humans yet.
- Although EFV is the only antiretroviral contraindicated in the first trimester, it is preferable to start ART-naïve women after the first trimester since there is low risk of transmission and fetal development could get most affected. For women already taking HAART in the first trimester, treatment *should be continued*.
- The safety of AZT use in pregnancy has been extensively demonstrated across the world. Care, however, must be taken in pregnant women with hemoglobin levels $\leq$9g/dl. More frequent laboratory monitoring (up to every two weeks) should be considered and replacement of AZT with TDF or d4T for women with low baseline hemoglobin or significant decreases is recommended.
- Although no longer used in Guyana, Didanosine and Stavudine have unacceptably high risks of fatal lactic acidosis in pregnant women and should never be used together.
- In areas where there is no AZT or other ARV medications, the minimum PMTCT package is single dose Nevirapine at the onset of labor and single Nevirapine syrup for the baby, though this approach is suboptimal because of significant concerns with resistance.

## Recommendations for ARVS during pregnancy

### HIV Positive Women presenting during pregnancy

For prophylaxis and treatment triple therapy with ARVS is recommended. In cases where ARV naïve HIV positive woman present in labour, the recommended course of action is outlined below. For women who are on ARVs and have become pregnant, ARVs should be continued and necessary modifications to the regimen considering the teratogenicity of Efavirenz in the first trimester.

For ARV naïve women presenting in the first trimester it is important to note that is often the most difficult time of the pregnancy for the woman particularly in regards to hyperemesis garvidarum, which the greatest risk for poor adherence. All efforts therefore should be directed at preparing the woman for ARVS in the second trimester. For details of treatment, please see table 3.3 on antiretroviral dugs during pregnancy.

**Table 3.3: Antiretroviral Drugs during pregnancy**

| CD4 Count | | Recommended Regimen in order of preference. | Alternative Regimen | Comments |
|---|---|---|---|---|
| First trimester | - If the patient is on ARVs- evaluate patients for appropriateness of regimen<br>- If the patient is not antiretroviral therapy, prepare patient for initiation in the second trimester ( clinical evaluation, laboratory investigations, adherence and other counselling)<br>-Begin CTX prophylaxis as needed. | | | |
| Second and third trimesters | CD4<250 | 1.TDF+FTC+EFV<br>2.TDF+FTC+NVP<br>3.AZT+3TC+EFV<br>4.AZT+3TC+NVP | AZT+3TC+LPV/r | In cases where there is a history of sdNVP exposure, PI (LPV/r) would be the preferred regimen |
| | CD4>250 | 1.TDF+FTC+EFV<br>2.AZT+3TC+EFV | AZT+3TC+LPV/r | |

For women with CD4 greater than 350 cells/mm3, ARV prophylaxis for the prevention of mother to child transmission is recommended at the beginning of the second trimester or soon thereafter. In these cases, ARVs can be discontinued after delivery. In cases where patients are adherent and desirous of continuing ARVs, treatment should continue as per treatment guidelines.

### ARV Naïve women presenting in labour.

In a HIV positive woman presenting in labour, the following is recommended:

1- Immediate administration of sdNVP (200mgs orally).

2- Administer Dimune (AZT 300mgs+3TC 150mgs) orally, three hours after the sdNVP is given.

3- In the case of prolong labour repeat sdNVP( 200mgs) after 24 hours

4- Follow up with Dimune ( AZT300mgs+3TC 150mgs)twice daily for six weeks

5- Refer to a care and treatment site for further evaluation within one week.

**ARVS after delivery**

1. For women taking ARVS for their own health (for treatment purposes), ARVs should be continued and will be lifelong

2. Women taking ARVS as prophylaxis (for the prevention of mother to child) will have a starting CD4 >350 cells/mm³.

i) In cases where the woman has been on a LPV/r based regimen ( as with previous ART exposure of sdNVP),and are desirous of remaining on treatment, then change LPV/r to Efavirenz
ii) - In these cases if the woman is not breast feeding then ARVs can be discontinued after delivery. All ARVS should be stopped simultaneously unless the regimen contains an NNRTI (NVP or Efavirenz). In these cases stop the NNRT and continue with the other ARV for 1 week, then stop.
iii) In cases where the woman is breast feeding, ARVs should be discontinued only after the cessation of breast feeding.
iv) In both scenarios above, if the woman has a good history of adherence and is desirous of continuing ARVs, treatment should continue as per treatment guidelines.

**ARVS for the Exposed infants:**

All exposed infants should receive the following:
1. A single dose of Nevirapine of 2mgs/kg at birth
2. Oral AZT of 4 mgs/kg twice daily for 6 weeks.

For an infant whose mother is HIV-infected but did not receive and ARVs nor sdNVP for prophylaxis, the timing of antiretroviral prophylaxis for infants is critical. The infant must receive ARV prophylaxis within 72 hours of birth for prophylaxis to have any effect. In this case sdNVP of 2mgs/kg is given immediately followed with a AZT tail of 4 mgs/kg for 6 weeks.

**Breastfeeding**

HIV is expressed in breast milk and is proven that breastfeeding can be a possible source of HIV transmission to newborn infants. The Ministry of Health recommends the avoidance of all breastfeeding by HIV infected women. In support of this the Ministry provides free replacement feeding for all exposed infant under 18 months of age. Anaemia on the benefits of replacement feeding is provided through out pregnancy and post partum for all HIV infected women, partners and their families as possible.

In cases where mother chooses to breast feed despite counselling the following are recommended:

- Absolute breast feeding- No mixed feeding
- For the mother initiate or continue HAART according to guidelines
- For the exposed infant-administer prophylaxis. In addition to the sdNVP administered at birth, follow up with AZT for 6 weeks as above.
- Abrupt cessation of breast feeding, no later than three months (to avoid mixed feeding)
- Monthly follow up for mother and infant with continuous counselling.

**Table 3.4: Risks and benefits of infant feeding methods**

| Advantages of Exclusive Breastfeeding | Advantages to Exclusive Formula Feeding |
|---|---|
| ▪ Lower overall mortality rates for breastfed children<br>▪ Improved nutritional status<br>▪ Less cost<br>▪ Does not require clean water supply<br>▪ May be more acceptable | ▪ No risk of HIV transmission (apart from in utero and intrapartum transmission)<br>▪ One study suggested a higher maternal mortality rate for breastfeeding mothers, though two other studies showed no difference. |

The risk of HIV transmission in breastfeeding is mediated by several factors – HIV viral load, the presence of mastitis, and other infections, as well as reinfection with the HIV virus and the length of exposure to breast milk. Several studies suggest approximately a 1-2% increase in overall rates of MTCT per each month of breastfeeding. Studies on the use of antiretroviral therapy in breastfeeding mothers significantly decrease the rate of transmission of MTCT, however may increase the incidence of resistance in breastfeeding infants exposed to differing levels of ARVs expressed in breast milk. Therefore, while it is recommended that mothers who are planning to breastfeed infants be offered HAART, it is important that adherence and treatment readiness are addressed.

## PATIENTS WITH CO-INFECTIONS

This section will highlight the management of patients who are infected with other diseases in addition to HIV.

**HIV-TB co-infection**

TB is one of the most common opportunistic infections in Guyana, and a major cause of death in persons who are HIV-infected. Infection with HIV increases the risk of reactivating latent TB by 80-200 fold, and HIV positive patients acquiring TB infection progress faster with much higher mortality rates. Tuberculosis infection increases HIV viremia, temporarily decreases CD4+ cell counts and complicates choice and timing of antiretroviral therapy.

**Screening, Diagnosis, and Isoniazid Preventative Therapy (IPT)**

All patients diagnosed with HIV should receive baseline Mantoux (PPD) testing. Testing should be repeated annually unless there is a positive PPD result. *For patients with a positive Mantoux test, or a history of Isoniazid Preventative Therapy or active TB treatment, DO NOT REPEAT Mantoux screening and follow up patients with annual Chest X ray screening.* Any HIV-positive patient with a Mantoux screening test >5mm should be treated with Isoniazid preventative therapy (IPT) according to Table 3.5, once active tuberculosis is excluded.

Diagnosis of active tuberculosis is made based on symptoms, chest radiography, and presence of acid-fast bacilli (AFB) in sputum as outlined in the National TB Manual. HIV positive patients co-infected with TB have lower sputum AFB detection rates and a higher incidence of extrapulmonary tuberculosis than HIV negative controls. In cases where there is high clinical suspicion of active tuberculosis and negative sputum AFB smears, clinicians are strongly encouraged to obtain a sputum culture for TB. Whenever possible in patients whom extrapulmonary TB is suspected (e.g. TB lymphadenitis), tissue should be obtained for pathologic evaluation and smear.

Isoniazid is compatible with ARV drugs. Care should be taken to closely monitor liver function tests; when possible, Stavudine, Didanosine, and Zidovudine should be avoided as part of the HAART regimen because of the shared toxicity of peripheral neuropathy.

***For persons co-infected with TB and HIV IPT is recommended for 9 months.***

**Table 3.5: Recommended dosages for Isoniazid Preventative Therapy (IPT)**

| | Adult Dose | Pediatric Dose |
|---|---|---|
| Isoniazid | 300mg once daily | 10-15 mg/kg once daily |
| Vitamin B6 | 50mg once daily | NA |

**Management of active Tuberculosis**

TB could occur at high CD4 counts but is associated with rapid disease progression and high mortality rates. It is classified as stage 3 according to the WHO Clinic Staging and therefore an indication for HAART.

While starting ART is the end goal in all patients with active TB infection, care must be taken in the timing of HAART initiation. Treatment for TB should be for at least 2 weeks prior to the initiation of HAART in order to ensure sufficient mycobacterial clearance thus decreasing the possibility IRIS which may occur in up to 25% of all cases. Recent studies suggest in the HAART naive patient integrating HAART sooner rather than later decrease mortality. A risk/immunological stratification approach is recommended as listed in table 3.6.

If the patient is diagnosed with TB disease while on HAART, begin TB treatment immediately.

**Table 3.6: HIV-tuberculosis co-infection: recommendations for management**

| CD4 lymphocyte count | General recommendation |
|---|---|
| All TB /HIV co-infected patients | Offer Cotrimoxazole to all- 960 mgs once daily ( adults and children with weight>25kgs). For children-4mgs/kg once daily. |
| <200 cells/$mm^3$ | Treat TB for 2 weeks and then initiate on HAART* |
| 200-500 cells/$mm^3$ | Treat TB for 2-4weeks and then initiate HAART |
| >500 cells/$mm^3$ | Treat TB for 4-8 weeks and then initiate on HAART* |

*Initiation of HAART at 2 weeks after treating TB can sometimes be difficult due to a number of factors including side effects and poor tolerability of medications. In these situations clinical judgement is required on a case by case basis.

**Choice of HAART**

Rifampicin, a cornerstone of TB treatment, induces cytochrome P450 in the liver, altering levels of many medications, including several antiretrovirals. This results in rapid clearance of antiretrovirals leading to subtherapeutic drug levels and ultimately HIV drug resistance. ***Rifampicin reduces Nevirapine levels by about 37% and these drugs should generally not be used together.*** While small reductions of serum levels

of Efavirenz also occur, Efavirenz should preferably be used with a rifampicin-based TB regimen. Rifampicin also reduces of serum levels of Lopinavir/ritonavir by 75% and should not be used together.

- **For Patients on 1st Line HAART:**

| | Drug regimen |
|---|---|
| Preferred Regimen | Tenofovir( 300mgs)/Emtricitabine ( 200mgs)(TDF/FTC)+ Efavirenz( 600mgs) |
| Alternate Regimen | AZT(300mgs)+3TC ( 150 mgs)+ Efavirenz (600mgs) |

- **For Patients on 2nd Line HAART:**

| | Drug Regimen |
|---|---|
| Preferred Regimen | Tenofovir( 300mgs)/Emtricitabine ( 200mgs)(TDF/FTC)+ AZT ( 300mgs) + Lopinavir/ Ritonavir (400/100mgs) |
| TB regimen | Substitute Rifampicin with Rifabutin 150mgs orally three times weekly. (Rifampicin reduces the levels of LPV/r by 75%) |

*for patients using HAART regimen that includes Nevirapine or Lopinivir/Ritonovir, substitute in the TB regimen Rifampicin with Rifabutin.

In cases where none of the regimen in above table applies, a triple nucleoside regimen of Tenofovir/Emtricitabine (TDF/FTC)(300mgs/200mgs) one tablet daily with AZT (Zidovudine) 300mg twice daily is recommended.

**For Pregnant patients: See table 3.7 below for management for pregnant patients with TB disease.**

**Table 3.7- ARVS in Pregnancy**

<table>
<tr><th colspan="2">CD4 Count</th><th>Recommended Regimen in order of preference.</th><th>Alternative Regimen</th><th>Comments</th></tr>
<tr><td>First trimester</td><td colspan="4">- If the patient is on ARVs- evaluate patients for appropriateness of regimen<br>- If the patient is not antiretroviral therapy, prepare patient for initiation in the second trimester ( clinical evaluation, laboratory investigations, adherence and other counselling)<br>-Begin CTX prophylaxis as needed.</td></tr>
<tr><td rowspan="2">Second and third trimesters</td><td>CD4<250</td><td>1.TDF+FTC+EFV<br>2.TDF+FTC+NVP<br>3.AZT+3TC+EFV<br>4.AZT+3TC+NVP</td><td>AZT+3TC+LPV/r</td><td rowspan="2">In cases where there is a history of sdNVP exposure, PI (LPV/r) would be the preferred regimen</td></tr>
<tr><td>CD4>250</td><td>1.TDF+FTC+EFV<br>2.AZT+3TC+EFV</td><td>AZT+3TC+LPV/r</td></tr>
</table>

**TB/HIV coinfection in Children:**

Given the lack of safety data in children and possible concerns for toxicity, Tenofovir-based regimens should be avoided.

- **Preferred Regimen** in managing children is: ABC (8mgs/kg)+3TC(4mgs/kg)+Efavirenz( 15mgs/kg)*.

Efavirenz should not be used in children less than 10kgs or less than 3 years of age

Efavirenz dosage should never exceed 600mgs.

- **Alternative Regimen:**

-In cases where ABC cannot be used- substitute with AZT or d4T

-In younger children who cannot use Efavirenz, a triple nucleoside is regimen-AZT+3TC+ABC or d4T+3TC+ABC.

**Monitoring considerations:**
Given the hepatotoxicity of antimycobacterials (e.g. Isoniazid, Rifampicin) and antiretrovirals used in TB-HIV co-infection, close monitoring of liver function tests is recommended. Liver function tests should be checked within two weeks of adding any new medications, and should be checked monthly during the course of TB therapy. For more details, refer to the Guyana Tuberculosis Manual.
**Direct observed therapy (DOT) for HAART along with TB medication is recommended** as a treatment method for co-infected patients (The Modified DOT HAART strategy).

**HIV co-infection with Hepatitis B or Hepatitis C**
Considering that HBV or HCV and HIV coinfection and management can result in accelerated liver damage, the following is recommended:
- Baseline hepatitis serology should be performed on all patients and annual for those sexually active.
- Regular monitoring of Liver function as per guidelines.
- Lamivudine, or Emtricitabine plus Tenofovir based regimen are recommended for their antiviral effects in patients with hepatitis B and HIV.

**HIV-malaria coinfection**
Malaria is endemic in certain regions of Guyana; therefore, clinicians will encounter patients with HIV-malaria co-infection. The following should be noted:
- A patient who is HIV-infected and presents with unexplained anaemia and fever should be evaluated for malaria.
- HIV infection appears to increase the severity of malaria infection.
- Pregnant women who are HIV-infected appear to be more susceptible to acquiring malaria, and people who are immunosuppressed seem to have more frequent symptomatic episodes.
- Malaria infection appears to increase viral load, which could result in an increased risk of transmitting HIV as well as an increased risk of HIV disease progression.
- Malaria may cause severe anaemia in women and children. Thus, increased vigilance is warranted in patients who are HIV-infected and at risk for malaria, and in patients who follow a HAART regimen containing drugs that may cause anaemia, particularly Zidovudine.

- Infants born to mothers who are co-infected with HIV and malaria are more likely to die and are approximately twice as likely to be infected perinatally with HIV if a high placental burden of malaria is present in the mother.
- Cotrimoxazole has strong anti-malarial activity and is used commonly for malaria prophylaxis in patients who are HIV-infected. As more and more of these patients take Cotrimoxazole, there is a theoretical danger of patients with malaria developing resistance to Cotrimoxazole and Pyrimethamine/Sulfadoxine (related to Cotrimoxazole).
- Impregnated bed nets are recommended in malaria endemic areas

**HIV-dengue fever co-infection**

The Caribbean is a dengue fever-endemic area with outbreaks of virus types 1, 2 and recently 3 reported. Patients who are co-infected with HIV and dengue fever, and who are taking ARV drugs that may cause anaemia or hemorrhagic reactions should be monitored carefully.

**HIV-sickle cell disease**

Sickle cell disease (SCD) is a genetic disorder characterised by chronic anaemia, vaso-occlusive events, recurrent infections, and functional asplenia. Especially in children, functional asplenia causes recurrent infections that may be exacerbated by the immunocompromised state. The following should be noted when treating patients with HIV-sickle cell co-infection:

- Anaemia and recurrent infections are common to both conditions. Thus, extra vigilance must be mounted to investigate and proactively manage anaemia and infections. In view of the risks of anaemia and jaundice with ARV drugs, caution should be exercised when prescribing ARV drugs.
- Prophylactic antibiotics, pneumococcal vaccine, early identification and treatment of serious bacterial infections, and general prophylaxis are crucial.

**Injecting Drug Users**

The following should be borne in mind when treating injection drug users who are HIV-infected:

- The treatment protocol for injection drug users is the same as for other patients.
- In addition, issues about lifestyle instability, drug dependence, adherence problems, and ARV drug interactions with addictive drugs must be addressed in the treatment programme.
- Direct observed therapy (DOT) should be considered for this group of patients.
- Involvement of Social Worker and Community Outreach Worker is important.

Support systems must be identified to help with drug adherence, and coordination is required with community-based AIDS organizations and drug treatment programmes.

## POST-EXPOSURE PROPHYLAXIS

Post-exposure prophylaxis (PEP) refers to using antiretroviral agents to reduce the risk of HIV transmission following a potentially infectious exposure—occupational exposure in a healthcare setting or sexual assault. Studies have shown that PEP – when initiated as early as possible with AZT alone – reduces the risk of HIV transmission by about 80%. Everyone who is exposed to potentially-infectious bodily fluids should have access to PEP.

**General Principles**

- Universal precautions guidelines and practices should be actively promoted in all healthcare facilities. Infection control designees can be identified to monitor and oversee universal precautions, PEP drug availability, and utilization.
- Evaluate the HIV status of the source patient- If possible, the source patient should have a rapid test done after anaemia. If source cannot be tested or refuses testing, manage exposed person as if source was HIV-positive.
- The ARV regimen for PEP should be available 24 hours a day including nights and weekends at all healthcare facilities. In Guyana PEP kits are available at all private and public sector hospital emergency departments.
- A confidential log book should be maintained to record all cases of exposure, the specific circumstances of the exposure, and the drugs prescribed.
- After counselling, a rapid HIV test should be offered to anyone exposed to potentially HIV-infectious bodily fluids.
- Documentation of HIV diagnostic testing offered, acceptance or refusal is required.
- PEP to prevent HIV transmission is not required for any person testing HIV-positive.
- Offer complete blood, liver function, and hepatitis B serology tests. Hepatitis B PEP with hepatitis B vaccine should be offered to unimmunized people, as the risk of hepatitis B transmission is as high as 30%—more than 100 times the risk of HIV transmission.
- Initiation of PEP with ART soon as possible, preferably within 2 hours to 72 hours of exposure is recommended.

**Table 3.7: ARV for post exposure prophylaxis**

| | **Recommended Regimen** | **Additional Information** |
|---|---|---|
| Adults | Tenofovir/emtricitabine +Efavirenz | |
| Children <3years of age | Dimune and Lopinavir/Ritonavir | For Lopinavir/Ritonavir- use Kaletra suspension. |
| >3 years of age | Dimune and Efavirenz | |
| Pregnancy | Truvada and Lopinavir/Ritonavir | |

*Nevirapine should* not *be used in PEP regimens because of unacceptably high rates of life-threatening toxicity reported in HIV-negative healthcare workers taking Nevirapine-containing PEP regimens*

- Initiation of PEP 72 hours is not recommended.
- If ARV drug resistance is suspected in the source patient, an expert opinion should be sought from an HIV clinician. At least one or more drugs in a class to which the source patient's HIV is likely to be sensitive should be included.
- Post-traumatic stress counselling is an important component of PEP.
- To ascertain whether seroconversion has occurred, repeat the HIV test at 6 weeks, 3 and 6 months. If there is seroconversion, referral to an HIV treatment centre for follow up is recommended.

**Occupational exposure**

- The average risk of HIV transmission due to percutaneous (needle stick) injury is 0.3%, while the risk due to a mucocutaneous exposure is estimated at 0.09%.

- Potentially infectious body fluids include blood, spinal fluid, pleural fluid, pus, and amniotic fluid. Urine, sweat, and faeces are not considered infectious unless visibly bloody.

**Sexual Assault**

- The risk of HIV transmission in a single sexual assault is comparable to the risk associated with occupational exposure. However, the risk may be higher if the assault caused physical trauma (a rape) or if the source or the exposed individual had genital ulcerative lesions at the time of the incident.
- Reporting of all suspected cases of sexual assault to the police is legally mandated.
- Offer post-coital contraception, STI prophylaxis and psychological counselling.
- Counselling and long term follow up is needed.

**Post Exposure Management**

- Use of barrier methods (condoms) during each sexual encounter or abstain from sexual intercourse for the immediate 6-month following the incident.
- If possible avoid pregnancy during the six month follow up period.
- If possible avoid breast feeding or the use of breast milk during the follow up six month period.
- If possible avoid donation of blood or other tissue during the follow six month period.
- Avoid sharing of needles.

**Recordkeeping and Reporting**

All cases of HIV post exposure prophylaxis require record keeping and reporting. Reports must be filled out using the National Surveillance Form for Occupational and Non- Occupational Exposure. These are available in PEP kits or can be uplifted from the National AIDS Programme Secretariat.

## Appendix 3-A
## Exposure to Blood and Body Fluids

The following guidelines are recommended when managing occupational exposure to blood and body fluids. The PEP guidelines should be widely disseminated to all staff.

**RESPONSIBILITIES:**

THE HEALTH CARE WORKER

Any healthcare workers (HCW) who has been accidentally injured should take the following steps immediately:

- Wash site thoroughly with soap and water. Don't use abrasive cleansers such as bleach, chlorine, alcohol, or methylated spirits.
- Immediately report the incident to supervisor on duty.

THE SUPERVISOR

**The supervisor upon being informed must immediately:**

- Make arrangements for the healthcare worker to be seen by the physician on duty. Inform the source patient of the HCW's injury and refer the patient for HIV diagnostic testing. .
- Offer, obtain consent and refer the HCW HIV diagnostic testing.
- Document incident on the prescribed surveillance form including:
  a. Type of exposure that occurred
  b. Time of incident
  c. Type of injury
  d. Type of instrument causing the injury (solid vs bore)
  e. Exchange of bodily fluids
  f. Type of procedure being undertaken when injury occurred.

THE PHYSICIAN

The physician on duty will:

- Request rapid HIV for the affected HCW.
- Document incident.
- Prescribe PEP treatment according to the national guidelines

THE PHARMACY MANAGER

The Pharmacy Manager must ensure that:

- The director of nursing services/nursing supervisor shall ensure that the stock of the medication is adequate.
- The medication can be dispensed on demand.
- A continuous supply of the medication is maintained in the office of the nursing supervisor to facilitate dispensing of the first dose by the nursing supervisor on duty whenever the dispensary/pharmacy is closed.

THE DIRECTOR OF NURSING SERVICES/NURSING SUPERVISOR

- Ensure all staff are trained in the infection control measures
- Ensure annual training of all staff on the policies and protocols relating to occupation exposure to potentially infectious bodily fluids.

- Ensure ready 24 hour access to PEP antiretroviral medications onsite.

THE OCCUPATIONAL SAFETY AND HEALTH OFFICER

The Occupational Safety and Health Officer shall:

- Be informed of the accident within 48 (forty-eight) hours of its occurrence.
- Document the following information in the accident report:
  a. Date, time and place of the incident
  b. Description of events leading up to the accident
  c. Cause of incident
  d. Nature and location of injury
  e. Actions taken after the incident.

## Appendix 3-B

## Recommendations for co-administering non-nucleoside reverse transcriptase inhibitors (NNRTIs) and

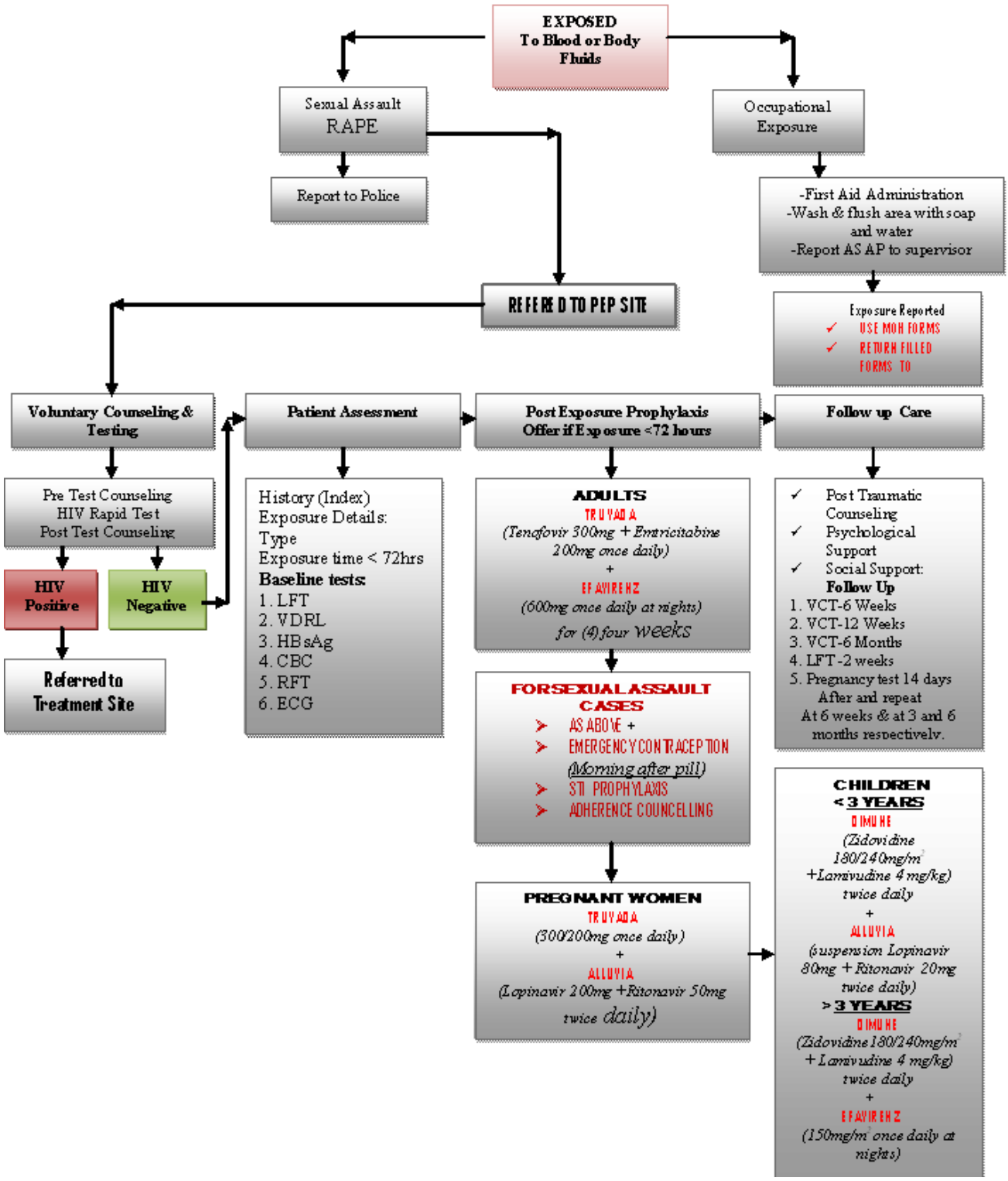
### protease inhibitors (PIs) with rifampin

| NNRTIs | ARV dose change | Rifampin dose change | Comments |
|---|---|---|---|
| Efavirenz (EFV) | None | None (600 mg once daily) | Efavirenz AUC↓by 22%. May reduce efavirenz to 600 mg once daily if 800 mg dose not well tolerated. |
| Nevirapine (NVP) | 200 mg twice daily<br><br>*Nevirapine should only be used if no other option exists and clinical and virologic monitoring is possible.* | None (600 mg once daily) | Nevirapine AUC↓by 37%–58%. |
| **PIs** | **ARV dose change** | **Rifampin dose change** | **Comments** |
| Ritonavir (RTV) | None | None (600 mg once daily) | Ritonavir AUC↓by 35%. No change in rifampin concentration. |
| Lopinavir + ritonavir (LPV+RTV) | *Rifampin and lopinavir/ritonavir should not be used together.* | | Lopinavir AUC↓by 75% and Cr min↓by 99%. |

AUC = area under the curve.

*Source:* National Center for HIV, STD, and TB Prevention. Division of Tuberculosis Elimination. TB/HIV Drug Interactions. *Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors*. Retrieved 3 November 2004, from http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/Table1.htm.

## Appendix 3–C
## Guyana's Post-exposure Prophylaxis Algorithm



# PART IV:

# PROPHYLAXIS AND MANAGEMENT

# OF COMMON OPPORTUNISTIC INFECTIONS

# OPPORTUNISTIC INFECTIONS

An opportunistic infection is an infection caused by pathogens (bacterial, viral, fungal or protozoan) that usually do not cause disease in a healthy host, i.e. one with a healthy immune system. A compromised immune system, however, presents an "opportunity" for the pathogen to infect

Opportunistic infections are serious in that they create increased morbidity and mortality in HIV infected patients. Before the advent of HAART these infections caused the death of most infected patients. The early detection of the HIV virus and the advent of HAART have resulted in fewer cases of opportunistic infections. There are however patients who still seek care relatively late and may present with opportunistic infections depending on the CD4 count. Because of the high morbidity and mortality associated with opportunistic infections, it is important for all healthcare providers to understand how to prevent, recognize signs and symptoms, diagnose and treat these infections.

In it also critical that opportunistic infections be ruled out and if present be treated, in all patients prior to the initiation of HAART. Failure to do so can result in life threatening situations with immune reconstitution syndrome (see section in guideline). This section will discuss primary and secondary prevention as well as treatment of the most common opportunistic infections found in Guyana.

## Toxoplasmosis

**Infectious Agent*:*** *Toxoplasma gondii* (intracellular protozoan parasite).

Primary asymptomatic infection occurs in immunocompetent hosts, after which the organism becomes dormant causing latent disease. Immunocompromised patients, (e.g AIDS) with CD4 lymphocyte count below 100 cells/microL can present with reactivation diseases due to T. gondii. Patients with AIDS and <100 CD4 cells/microL, who are toxoplasma seropositive, have an approximately 30 percent probability of developing reactivated toxoplasmosis if they do not receive effective prophylaxis. (Up-to-date)

**T. gondii infections:**

**Toxoplasmic encephalitis** — the incidence of toxoplasmic encephalitis varies in relation to the seropositivity rates of the population. The introduction of anti-toxoplasma prophylaxis and highly active antiretroviral therapy (HAART) has altered the occurrence of toxoplasmic encephalitis like other OIs. In the Multicenter AIDS Cohort Study (MACS), the incidence of CNS toxoplasmosis decreased from 5.4 per 1000 person-years in 1990 to 1992 to 3.8 per 1000 person-years in 1993 to 1995 and, 2.2 per 1000 person-years in 1996 to 1998 after the introduction of HAART (UpToDate). Clinical presentation includes headaches, altered mental status, seizures, fever (not always present), focal neurological deficits, and signs of increase intracranial pressure (nausea and vomiting).

**Extracerebral toxoplasmosis**

- Pneumonitis: presents with cough, fever, dyspnea with reticulonodular infiltrates on chest X-ray. PCP infection must be ruled out in such cases.
- Chorioretinitis: presents with eye pain and decrease visual acuity.

- Other organ involvement can occur including the gastrointestinal tract, heart, musculoskeletal system and bone marrow.

**Diagnosis:** Presumptive diagnosis and treatment for T. gondii infection is imperative to the reduction of morbidity and mortality of AIDS patients with high clinical suspicion of T. gondii disease and CD4 counts below 100copies/mm3.

- ***Clinical*** – signs and symptoms most reliable diagnostic tools in all settings.
- ***Laboratory***: T. gondii antibodies will be present in patients with prior exposure to the organism. Anti-toxo IGM are usually absent and quantitative IGG are not helpful in acute diagnosis.
- ***Radiologic:*** Multiple ring enhancing lesions with edema on C-T scan is typical of T. gondii encephalitis.
- Biopsy remains the only definitive means of diagnosis.

***See tables below on the primary and secondary prophylaxis and treatment.***

## Pneumocystis

**Infectious Agent:** Pneumocystis jirovecii (fungus)

Current school of thought regarding PCP infection includes - primary asymptomatic infection in immune-competent and disease in immune-suppressed persons with varying serotypes of the P. jirovecii via airborne transmission. Reactivation of latent organism may also result in disease for immune-suppressed patients. Colonization of the respiratory tract may also occur in the absence of pneumonia.

The incidence of PCP in HIV-infected patients in developed countries has greatly decreased since approximately 1988. This reduction appears to have resulted both from recommendations for primary prophylaxis against the infection in patients with CD4 cell counts <200cells/microL and widespread adoption of highly active antiretroviral therapy (HAART). In a study of more than 1100 individuals with HIV infection, the Pulmonary Complications of HIV Infection Study Group confirmed the relationship between CD4 cell count and PCP. Ninety-five percent of patients who developed PCP had a CD4 count below 200 cells/microL. HIV transmission category, age, smoking history, and use of antiretroviral therapy did not predict development of PCP; black subjects had one-third the risk of PCP compared to white patients. (UpToDate)

**Infection:**
**Pneumonias:** patient presents with non-productive cough, fever, progressive dyspnea on exertion, and tachypnea.

**Diagnosis:** Presumptive diagnosis and treatment of PCP results in decrease morbidity and mortality of AIDS patients with high clinical suspicion of PCP and CD4 counts below 200copies/microL**.**
**Clinical:** signs and symptoms indicative of PCP are the corner stone for diagnosis.
**Laboratory:** P. jivorecii cannot be cultured hence microscopy with staining of induced sputum specimen is required for identification of the organism.

**Radiologic:** Diffuse bilateral interstitial or alveolar infiltrates, however 25% of AIDS patients present with normal chest X-rays despite acute pneumocystis infection.

***See tables below on the primary and secondary prophylaxis and treatment***

## Candidasis

**Infectious Agent:** Candidia genus (fungus) – variety of species – C. Albicans (most common), C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis. C. parapsilosis and C. dubliniensis (found in HIV patients).
Candidiasis infections can be acute or chronic, localized or systemic and is the most common OI in AIDS patients occurring usually at CD4 counts below 200 cells/mm³. Disseminated candidiasis is life-threatening. The great majority of candidiasis is caused by Candida albicans which is detectable in normal flora of approximately 50% of people. C. albicans is a commonly found in the oropharyngeal cavity, gastrointestinal tract, and vagina of humans but is capable of causing opportunistic infection following disruption of the normal flora, a breach of the mucocutaneous barrier, or a defect in host cellular immunity. (UpToDate).

**Infections:**
**Local Mucus Membrane Infection**

- **Oropharyngeal infections:** oral thrush presenting with white plaques on the buccal mucosa, plate, tongue, orophargynx, and/or angular chelitis**.**
- **Esophagitis**: clinical presentations include odynophagia, pain on swallowing, or retrosternal pain. Oral thrush may or may not be present. Occurring at CD4 counts below 100cells/microL.
- **Vulvovaginitis**: clinical signs and symptoms include vaginal discharge, dysuria, vulvovaginal itching, dysparnia and vaginal discomfort.

**Other infections**:
Dermatitis, endophthamitis, meningitis, endocarditis.

**Diagnosis:** is often base on clinical presentation and findings.
**Laboratory**: Culture and gram staining when available are useful diagnostic tools.

***See tables below on the primary and secondary prophylaxis and treatment***

## Cryptococcus:

Infectious Agent: Cryptococcus neoformans (encapsulated yeast - two varieties - neoformans (subtype D), grubii (subtype A) and subtypes B and C are of a separate species C. gattii).

C. neoformans and grubii have been found in soil samples worldwide in areas frequented by birds, especially pigeons and chickens. Direct transmission from pigeons to humans has not been reported neither has documented spread form human to human. C. neoformans causes infection following inhalation through the respiratory tract. The organism disseminates hematogenously and has a propensity to localize to the central nervous system (adapted from UpToDate).

Cryptococcal infection is the fourth most common opportunistic infection in patients with AIDS. The number of cryptococcosis cases has declined since the availability of HAART, but this infection is still a relatively common AIDS presenting illness. The rate of cryptococcal meningitis in patients with AIDS in sub-Saharan Africa is 15 to 30 percent, in Guyana the rates are unknown however clinical cases treated empirically for CNS cryptococcosis have responded well to therapy. Cryptococcosis is uncommon in children, even those with AIDS. The reason for the reduced incidence in children is not known (adapted from UpToDate).

**Infection:**
Pulmonary crytococcosis: presents with fever, cough, dyspnea and may result in acute respiratory distress syndrome (ARDS).
Cryptococcal meningoencephalitis may occur insidiously over period of months with varying CNS signs and symptoms.

**Diagnosis:**
**Clinical:** meningoencephalitis often present with CNS clinical findings including intermittent headache for months, fever is observed in approximately 50 percent of cases, lethargy, coma, personality changes, and memory loss typically develop over 2 to 4 weeks. Elevated open CSF pressure during lumbar puncture is indicative of cryptoccocal meningitis. While pulmonary disease present with signs and symptoms discussed previously in this section.
**Laboratory**: Evaluation of the cerebrospinal fluid (CSF) with India ink and/or cryptococcal antigen testing should suggest the diagnosis in most cases. Culture is gold standard for diagnosis.
**Radiologic:** MRI (more sensitive) or CT-scan can be used to identify CNS cryptococcal lesions. In cases of pulmonary crypotococcosis there may be solitary or few well defined non calcified nodules, hilar/mediastinal adenopathy, and/or pleural effusion.

***See tables below on the primary and secondary prophylaxis and treatment***

## Mycobacterium Avium Complex

Infectious Agents: M. avium or M. intracellulare (nontuberculosis mycobacterium species). Organisms found the environment worldwide (water, soil, etc) with modes of transmission via inhalation or ingestion. One international study found significantly higher rates of disseminated MAC in developed compared to developing countries (10 to 22 percent versus 2 to 3 percent). UpToDate. The risk of MAC infections increases with declining CD4 counts below 50cells/microL. Latency infection doesn't occur with this organism hence infections are likely due to new acquisition instead of reactivation of the organism.

**Infections:**
**Disseminated infection** — commonly presenting with nonspecific signs and symptoms including fever, night sweats, abdominal pain, diarrhea, and weight loss (which often precedes the onset of fever).

**Localized disease** — in patients with HIV infection, localized disease was uncommon prior to the HAART era. Several series have described patients with HIV infection who have developed

a focal inflammatory lymphadenitis shortly after the initiation of HAART. In all of these cases the patients had a prior history of a low CD4 cell number that may have predisposed them to colonization with MAC. (UpToDate). The presenting signs and symptoms include fever and focal inflammation of lymph node (cervical, intraabdominal, mediastinal).

**Diagnosis:**
**Clinical: as specified above.**
**Laboratory** abnormalities frequently include anaemia, leukocytosis, elevated alkaline phosphatase and lactate dehydrogenase. The diagnosis is confirmed by the isolation of MAC from the blood or on biopsy.
**Radiologic**: Abdominal CT scan can be useful in disseminated disease in the presence of intraabdominal lymphadenopathy however 25% of cases may have no intraabdominal pathology.

***See tables below on the primary and secondary prophylaxis and treatment***

## Prophylaxis of opportunistic infections among adults and adolescents

**Table 4.1: Prophylaxis of selected opportunistic infections among adults and adolescents**

| Condition | Eligibility | Regimens | Discontinuation |
|---|---|---|---|
| Primary *Pneumocystis jiroveci (*formally *Pneumocystis carinii)* pneumonia (PCP) prophylaxis in **adults**<br><br>*PCP prophylaxis may be given to eligible pregnant women after 1st trimester.* | ▪ CD4 <200 cells/mm$^3$<br>▪ Symptomatic HIV infection<br>▪ **WHO Stage 3 or 4 (including oropharyngeal candidiasis, and TB irrespective of CD4)** | ▪ Trimethoprim-sulfamethoxazole (TMP-SMX) 960mg once daily*<br>▪ Alternative dapsone 2 mg/kg body weight by mouth once daily (In case of allergy or intolerance to cotrimoxazole | CD4 lymphocyte >200 cells/mm$^3$ for 2 consecutive measurements over 6-12 months in response to HAART |
| Primary toxoplasmosis prophylaxis in **adults** | ▪ Toxoplasma IgG positive<br>▪ CD4 <100 cells/mm$^3$ | ▪ TMP-SMX 960 mg PO once daily *OR*<br>▪ Dapsone 50 mg + pyrimethamine 50 mg once daily | ▪ Discontinue when CD4 >200 cells/mm$^3$ for 2 consecutive measurements over 6-12 months while receiving HAART.<br>▪ Re-start if CD4 falls to <200 cells/mm$^3$ |
| M..tuberculosis | ▪ HIV infection with positive PPD test (>5 mm) without active TB | ▪ Adults: Isoniazid 10–15 mg/kg (max 300 mg once daily x 9 months) + | Stop after completing duration of prophylaxis (9 months) |

| | | | |
|---|---|---|---|
| | **OR**<br>▪ Had contact with a case of active sputum-positive TB infection **PLUS**<br>Active TB excluded in HIV-infected person | Vitamin B6 (pyridoxine) 50 mg once daily | |
| Mycobacterium Avium Complex (MAC) | CD4 <50 cells/mm$^3$ and active MAC and TB ruled out | ▪ Azithromycin* 1200 mg PO once weekly *OR*<br>▪ Clarithromycin 500 mg PO twice daily | ▪ Discontinue when CD4 >100 cells/mm$^3$ for >3 months on HAART.<br>▪ Re-start if CD4 falls to <50–100 cells/mm$^3$. |
| Malaria | All HIV infected patients living in endemic areas | Recommend bed nets especially children and pregnant mothers CTX has been shown to decrease incidence of malaria | Continue |
| HPV | Annual VIA on all HIV women age 15 and above | | Annually |

## Treatment of and Secondary Prevention for Opportunistic Infections among adults and adolescents

**Table 4.2: Treatment of and Secondary Prevention for Common Opportunistic Infections in Adults and Adolescents**

| Opportunistic Infection | Recommended Therapy (Treatment) | Alternative therapy | Secondary Prevention |
|---|---|---|---|
| Oral candidiasis | Fluconazole 200 mg. day one then 100 mg daily 7-14 days | Nystatin Suspension 4-6 ml. 4 times a day | NA |
| Esophageal candidiasis | Fluconazole 200 mg/daily orally or IV for 14 days | Itraconazole 200mg/orally daily for 14-21 days | NA |
| PCP Pneumonia CD4 <200 | TMP-SMX 1920 mg TD for 21 days<br>If needed:<br>Prednisone<br>Prednisone doses (beginning as early as | Primaquine 15–30 mg (base) PO daily plus clindamycin 600–900 mg IV q6h to q8h or clindamycin 300–450 mg PO q6h to q8h | TMP-SMX 960 mg daily. May decrease to 480 mg/day if tolerated better or Dapsone 50 mg BD Until CD4 count >200 |

| | | | |
|---|---|---|---|
| | possible and within 72 hours of PCP therapy) (AI):<br>Days 1–5 - 40 mg PO bid<br>Days 6–10 -40 mg PO daily<br>Days 11–21- 20 mg PO daily | | for 2 consecutive measurements over 6-12 months |
| Toxoplasmosis<br><br>CD4 <100 | TMP-SMX 1440 mg BD for 21 days<br><br>If mass effect consider dexamethasone Rx. | ▪ Clindamycin 600 mg 3 times daily PLUS pyrimethamine 100 mg once daily loading dose followed by 50 mg once daily + folinic acid 10 mg once daily.<br>▪ Dilantin (200-200 mg/day) to control seizures | On HAART<br>CD4 count >200 for 2 consecutive measurements over 6-12 months |
| Pulmonary TB, EPTB-New Cases | INH, RIF, EMB, PZA,<br>Treatment duration<br>• New PTB-6 months<br>• EPTB Bone, CNS, joint 9-12 months<br>• EPTB other sites 6-9 months | Consult NTP or GCC for defaults, relapses | Monitor -annual Chest X-rays<br>**DOTs a must!!!** |
| TB Meningitis | Treat with INH, RIF, PZA and substitute ETB with Streptomycin<br>9-12 months<br>Consider steroids | Consult with TB consultant at the NTP or GCC | Monitor -annual Chest X-rays<br>DOTs a must. |
| Cryptococcal Meningitis | ▪ amphotericin B (IV)<br>0.7 mg/kg once daily + flucytosine | ▪ Fluconazole PO 400 mg twice daily x 8 weeks, | On HAART<br>Fluconazole 200 mg once daily for 12 months. |

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| | 100 mg/kg x 2 weeks followed by Fluconazole 400 mg once daily for 8 weeks,. | | Continue until CD4 >200 for over 2 consecutive measurements over 6-12 months |
| Mycobacterium Avium Complex R/O active TB | Azithromycin 500-600 mg/day plus EMB 15 mg/kg/day (max. 1600 mg/day for adults) Duration until sustained immune recovery on HAART | | Same as treatment drugs Discontinue with sustained immune recovery on ART (CD4 count >100 for 2 consecutive measurements over 6-12 months |
| Bacterial Pneumonias-always rule out Pulmonary TB and PJP | Augmentin or Azithromycin for 2 weeks | Erthromycin or doxycycline | NA |

**Primary Prophylaxis of opportunistic infections in HIV exposed and infected children**

**Table 4.2: Prophylaxis of selected opportunistic infections in children**

| Condition | Eligibility | Regimens | Discontinuation |
|---|---|---|---|
| **Primary Pneumocystic Jiroveci (PCP)** | -All Exposed Infants -All infants of undeterminant status HIV positive children ≤5 years All HIV+ children ≥6 years with a CD4 <200 | TMP-SMX (CTX) 4mg/kg once daily (max 960mg/day) Or allergic to CTX Alternative: dapsone 2 mg/kg body weight by mouth once daily. (max. dose 100 mg/day | Children >6 yrs. on HAART for >6 months and Have a CD4>200 for two consecutive measurements over 6-months period |
| **Mycobacterium TB** BCG is not given to exposed infants until they have tested negative for HIV on DBS (DNA-PCR) | TST ≥5mm or close contact to a person (index case) with active TB in the home | INH 10-15 mg/kg once daily (max. dose 300 mg/day) plus vitamin B6 25 mg/day If index case is INH resistant consult the NTP or GCC | Discontinue after 9 months |
| **Toxoplasmosis Encephalitis** | Children <6 years with a CD4 <15% Children >6 years CD4 <200 | TMP-SMX (CTX) 4mg/kg once daily (max 960mg/day) Or allergic to CTX Alternative: dapsone 2 mg/kg body weight | HAART for > 6 consecutive months and age >6 years continue CTX until CD4 >200 on 2 consecutive |

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| | | by mouth once daily. (max. dose 100 mg/day | measurements over 6-months |
| **Mycobacterium Avium Complex** | Infants <12 months with CD4<750<br>Age 1-2 years CD4 <500,<br>Age 2-5 CD4 <75<br>Age 6 CD4 <50 | Azithromycin 20 mg/kg (max 1200 mg **weekly)** | Do not discontinue in children<2 yrs. of age. If age >2 yrs, after >6 consecutive mos. of HAART and<br>• Age 2–5 yrs: CD4 count >200 cells/$\mu$L for 2 consecutive measurements over a 6 months period<br>• Age >6 yrs: CD4 count >100 cells/$\mu$L for 2 consecutive measurements over a 6 month period |
| **Malaria** | All HIV positive and exposed children | Bed nets<br>CTX prophylaxis has been proven to decrease malaria in adults and can be used in endemic regions | Continue bed nets lifelong |

## Treatment of and Secondary Prevention for Opportunistic Infections in HIV Exposed and Infected Children

**Table 4.3: Treatment of and Secondary Prevention for common Opportunistic Infections in HIV Exposed and Infected Children**

| Opportunistic Infection | Recommended therapy | Alternative therapy | Secondary Prevention |
|---|---|---|---|
| **Mycobacterium Tuberculosis**<br><br>**H=Isoniazide-INH**<br>**R=Rifampicin-RIF**<br>**Z=Pyrazinamide-PZA**<br>**E=Ethambutol-ETB** | <u>New patients-PTB</u><br>**Intensive Phase** (2 months)<br>**HRZE**- see dosing table<br>**Continuing phase** (7 months)<br>**HR** see table on dosing<br>EPTB Rx for 12 months total<br><u>Retreatment patients</u><br>Default or Relapse | **Consult with NTP or GCC** | Chest X-Rays annually |

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| | patients consult with NTP and GCC | | |
| **Mycobacterium Avium complex (MAC)** | Azithromycin 10-12 mg/kg/day (max dose is 500mg)<br>Plus<br>ETB-15-20 mg/kg (max. dose 2.5 grams/day<br><br>For 12 months duration<br><br>*See secondary prophylaxis* | Consult with the NTP or GCC | Azithromycin 5mg/kg/day (max.dose250 mg) plus ETB 15-25 mg/kg/day (max 2.5 grams) with or without rifabutin<br>**Criteria to discontinue secondary prophylaxis**<br>If all of the following criteria fulfilled<br>• Completed >6 mos of HAART<br>• Completed at least 12 mos MAC therapy<br>• Asymptomatic for signs and symptoms of MAC<br>• Age 2–5 yrs: CD4 count >200 cells/mm3 maintained on 2 separate measurements over 6 months<br>• Age >6 yrs: CD4 count >100 cells/mm3 maintained on 2 separate measurements over a 6 mos period |
| **Pneumocystis Pneumonia** | TMP-SMX 20 mg/kg/day IV or orally divided into 3-4 doses for 21 days<br>If very ill consider prednisone 1 mg/kg orally BD for 5 days<br>0.5mg/kg BD for 11-21 days and wean slowly<br><br>*See secondary prophylaxis* | Dapsone 2mg/kg/one time per day (max dose 100mg /day. | TMP-SMX (CTX) 4mg/kg once daily (max 960mg/day)<br>Or allergic to CTX<br>Alternative: dapsone 2 mg/kg body weight by mouth once daily. (max. dose 100 mg/day<br>**Discontinue secondary prophylaxis**<br>If all of the following |

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| | | | criteria fulfilled<br>• Completed >6 mos of HAART<br>• Age 1–5 yrs: CD4 percentage >15% or count or >500 cells/mm3 for 2 consecutive measurements over 6 month period<br>• Age >6 yrs: CD4 percentage >15% or count >200 cells/mm3 for 2 consecutive measurements over 6 mos |
| **Toxoplasmosis** | Pyrimethamine: loading dose, 2 mg/kg body weight (max 50 mg) orally once daily for 3 days, then 1 mg/kg body weight (max 25 mg) orally once daily; PLUS sulfadiazine, 25–50 mg/kg body weight (max 1.0–1.5 g/dose) orally per dose 4 times daily; Treat for at least 6 weeks<br><br>*See secondary prophylaxis* | TMP-SMX (5 mg/kg body weight TMP PLUS 25 mg/kg body weight SMX per dose IV or orally twice daily) has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children | TMP-SMX 4 mg/kg/day (max dose 960 mg/day) If all of the following criteria fulfilled **May discontinue RX for secondary prophylaxis if following criteria met**<br>• Completed >6 mos of HAART<br>• Completed initial therapy for toxo<br>• Asymptomatic for toxo<br>• Age 1–5 yrs: CD4 percentage >15% or count >500 cells/mm3 for 2 consecutive measurements over a 6 month period )<br>• Age >6 yrs: CD4 percentage >15% or count >200 cells/mm3 2 consecutive measurements over 6 |

| | | | |
|---|---|---|---|
| | | | mos |
| **Oral Candidiasis** | Fluconazole, 3–6 mg/kg body weight 7-14 days<br><br>(max 400 mg/dose) orally once daily | Nystatin suspension: 4–6 ml orally 4 times daily; OR 1–2 200,000 U flavored pastilles orally 4–5 times daily | **NA** |
| **Esophageal Candidiasis** | Fluconazole, 6 mg/kg body weight orally once on day 1, then 3–6 mg/kg body weight (max 400 mg/dose) orally once daily (**AI**) *Treatment duration: minimum of 4–21 days* | • Itraconazole cyclodextrin oral solution, 2.5 mg/kg body weight orally twice daily or 5.0 mg/kg body weight orally once daily (**AI**) | **NA** |
| **Cryptococcus CNS Disease** | Amphotericin B, 0.7–1.0 mg/kg body weight (or liposomal amphotericin B, 6 mg/kg body weight) IV daily; PLUS flucytosine, 100 mg/kg body weight orally daily divided 4 times a day<br>or<br>Amphotericin B (dose above)<br>Plus<br>Fluconazole 6-12 mg/kg body weight (max 800mg) Iv or orally<br>**All of the above Rxs are followed by Fluconazole, 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max 800 mg) IV or orally daily;**<br>**And then begin:** *secondary* | Fluconazole, 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max 800 mg) IV or orally daily; PLUS flucytosine, 100 mg/kg body weight orally daily divided 4 times a day (**BII**) (offered only if amphotericin B-based therapy not tolerated | Fluconazole, 6 mg/kg body weight (max 200 mg) orally daily<br>Criteria to discontinue secondary prophylaxis<br>If all of the following criteria fulfilled**:**<br>• Age >6 yrs<br>• Asymptomatic and received >6 mos of secondary prophylaxis for cryptococcus<br>• Completed >6 mos of HAART<br>• CD4 count >200 cells/mm3 for 2 consecutive measurements over 6 mos |

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| | *prophylaxis* | | |

## SYNDROMIC CARE OF HIV RELATED ILLNESSES

### Diarrhoea

**Definition**: Three or more loose or watery stools per day; chronic diarrhea is defined as diarrhea lasting for four or more weeks.
Etiologies: infectious (including HIV-induced enteropathy), medication induced, infiltrative disease (Kaposi, lymphoma), endocrine, or allergic.

**Clinical presentation base classification**
**Small bowel involvement**: characterized by watery voluminous stools, gas, bloating, cramping and may have associated weight loss.
**Large bowel involvement**: characterized by frequent, small volume, often painful stools. The pain associated with these illnesses is not related to the region of the gut but to the type of pathogens that cause disease in the colon. Malabsorption of nutrients does not occur in a diarrhea that is limited to the large bowel. Nutritional compromise does not occur in patients who have infection confined to the large bowel, unless the pathogen is also capable of causing a disseminated infection, a "typhoidal" presentation. In HIV-infected patients, the typhoidal syndrome may be caused by Salmonella or by disseminated infection due to a range of organisms including cytomegalovirus (CMV), MAC, M. tuberculosis or fungi, such as Histoplasma or Cryptococcus. UpToDate
**Anorectal involvement**: characterized by severe tenemus, dyschezia and urgency.

| Pathogen | Small bowel | Colon |
|---|---|---|
| Bacteria | Salmonella<br>Escherichia coli<br>Campylobacter<br>Clostridium perfringens<br>Staphylococcus aureus<br>Aeromonas hydrophila<br>Bacillus cereus<br>Vibrio cholera | Salmonella<br>Enteroinvasive E. coli<br>Campylobacter<br>Shigella<br>Clostridium difficile<br>Yersinia<br>Vibrio parahaemolyticus<br>Plesiomonas shigelloides<br>Klebsiella oxytoca(rare) |
| Virus | Rotavirus<br>Norovirus<br>Cytomegalovirus | Cytomegalovirus<br>Adenovirus<br>Herpes simplex virus |
| Protozoa | Cryptosporidium<br>Microsporidium<br>Isospora | Cryptosporidium<br>Microsporidium<br>Entamoeba histolytica |

| | | |
|---|---|---|
| | Cyclospora<br>Giardia lamblia | |

Adapted from UpToDate

**Diagnosis**

**Laboratory**

Stool examinations should be ordered for culture of bacteria, C. difficile toxin assay, and examination for ova and parasites. An acid-fast smear should also be requested to look for Cryptosporidium, Isospora, and Cyclospora. In patients with CD4 counts <100 cells/microL, the possibility of Microsporidium should also be investigated via trichrome staining of a stool specimen if available.

Blood cultures — consider for MAC infections.

**Endoscopy** — in patients with advanced immunocompromise states and either persistent diarrhea or diarrhea with fever, more extensive workup is reasonable, with small bowel biopsies looking for MAC, lymphoma, or microsporidiosis. In patients with colitis and negative stool examinations, colonoscopy and biopsy looking for CMV or other inflammatory enteridites should be considered. UpToDate.

**Radiographic**: Not useful in evaluation, CT scan may show signs of billary tract disease, colitis (CMV, HSV, etc), or organomegaly.

**Nutritional Support**

- Oral rehydration fluids recommended, daily maintenance fluid requirement plus replacement of all loses (each stool).
- Small frequent meals – every 3-4 hours
- Avoid food and beverages with sugar, fructose, high-fructose corn syrup, lactose, or high grain content.
- Avoid caffeinated beverages.
- Avoid spicy foods.

**Table 4.4: Etiological management of diarrhoea**

| Symptoms | Suspected Organism | Treatment |
|---|---|---|
| Upper or mid-abdominal cramps, bloating, and nausea suggest gastric or small bowel involvement, or both. | Cryptosporidium | ▪ Nitazoxanide 500-1500mg/day for 14 days<br>▪ Paromomycin 25-35mg/kg/day for 14 days |
| | Giardia | ▪ Metronidazole 500 mg twice per day for 3 days<br>▪ Paromomcin 10 mg/kg orally three times per day for 5 to 10 days<br>▪ Nitazoxanide 500 mg orally two times per day for three days<br>▪ Mebendazole 200 mg orally three times per day for 5 days |
| | Isospora belli infections | ▪ Trimethoprim-sulfamethoxazole 960 mg four |

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| | | time per day for 10 days then twice daily for 3 weeks<br>▪ Pyrimethamine 75mg/kg for 3 – 4 weeks |
| Severe watery diarrhea resulting in dehydration, electrolyte disturbances, and weight loss. | Intestinal cryptosporidiosis | ▪ See above |
| Hematochezia, tenesmus, and lower abdominal cramps usually imply colonic infection caused by opportunistic | CMV | ▪ HAART<br>▪ Ganciclovir 5mg/kg twice per day for 3-6 six weeks (if available) |
| | Salmonella | ▪ Amoxicillin 500mg three times per day for 10 days<br>▪ Trimethoprim-sulfamethoxazole 960 mg twice day for 10 days<br>▪ Rocephin (IV) 1gm daily for 5 days |
| | Yersinia | ▪ Ciprofloxcin 500mg twice per day for 5 day or longer<br>▪ Trimethoprim-sulfamethoxazole 960 mg twice per day for 5 days or longer |
| | Shigella | ▪ Ciprofloxcin 500mg twice per day for 5 day or longer<br>▪ Trimethoprim-sulfamethoxazole 960 mg twice per day for 5 days or longer<br>▪ Avoid the use of antimotility agents |
| | Campylobacter | ▪ Erythromycin 500mg twice per day for 5 days<br>▪ Azithromycin 30mg/kg for 1 dose |
| Weight loss accompanying chronic diarrhea | Opportunistic infection | ▪ Treat accordingly |
| | Infiltrative disease | ▪ HAART |
| | Malabsorption | ▪ HAART, nutritional support |
| | Small bowel overgrowth syndrome | ▪ Metronidazole 500mg three times per day for 10 days |
| Lower gastrointestinal bleeding | Kaposi's sarcoma | ▪ HAART |
| | Bartonella infection – Bacillary Angiomatosis | ▪ HAART plus antimicrobial therapy – see below<br>▪ Erythromycin 500mg four times per day for 3 months<br>▪ Doxycycline 100mg twice per day for 3 months<br>▪ Azithromycin 500mg daily for 3 months |

# PART V:

# FUTURE CONCERNS

# Part V: Future Concerns

## DRUG RESISTANCE SURVEILLANCE

- With the implementation and scale-up of antiretroviral therapy in Guyana—and the complexity and life-long duration of ARV treatment—resistance to ARV drugs will surely emerge with the possibility of compromising treatment regimens.
- Resistance to available drugs will lead to treatment failure, and will increase direct and indirect healthcare costs, transmission of resistant HIV strains to treatment naïve subjects, and the need for continuously new antiretroviral drugs.
- Currently resistance testing is not available in Guyana. However, to assess the level of baseline resistance to ARVs, the most common types of resistance patterns and the drug resistance trend over time, Guyana will be involved in the World Health Organization Surveillance of HIV Drug Resistance Network.

## CONTINUING MEDICAL EDUCATION

There is a crucial need for medical education in HIV management, in order to train health workers in the use of ARVs. A strategic National HIV Management Training Plan has been rolled out to provide systematic training of different health cadres in the care and treatment of chronic HIV disease management, using the National Treatment Guidelines as a template. This training was approved by the MoH and the Guyana Medical Council and implemented through the National AIDS Program Secretariat. It includes state-of-the art lectures, case discussions, group work, preceptorships, evaluation assessment and recognition of certification from the Guyana Medical Council. Physicians thus certified will be approved to prescribe ARVs and receive free government ARV supplies with accountability.

There will be pre-service training targeting medical, nursing, and laboratory technology; and student and in-service training targeting physicians, nurses, pharmacists, medex and laboratory technicians both in government and private sector.

## LOCAL OPERATIONAL RESEARCH

Given the current access to care and treatment programmes across the country, it is important to answer certain crucial operational research questions relevant to program refinement and sustainability. These include but are not limited to:

- Baseline CD4 count profile in sero-negative Guyanese.
- Prevalence of TB, HBV, and HCV in the HIV-infected population receiving treatment.
- The need for third line medications.
- Local adherence strategies that work best.
- Prevalence and presentation of opportunistic infections, etc.

**PART VI:**

**REFERENCES**

British HIV Association (BHIVA) 2003. *Guidelines for the treatment of HIV-infected adults with antiretroviral therapy*. Retrieved 3 November 2004, from http://www.bhiva.org/guidelines/2003/hiv/index.html

# Part VI: References


Caribbean Epidemiology Centre (CAREC). *Caribbean guides related to HIV post exposure prophylaxis*. Retrieved 22 November 2004, from http://carec.org/documents/hiv_prophylaxis.pdf

Lynen L. and Biot M (eds.). 2000. *Clinical AIDS care guidelines for resource-poor settings*. Brussels, Belgium. Médecins Sans Frontières.

Pan American Health Organization (PAHO). October 2002. *Building blocks: guidelines for antiretroviral treatment in adults for Latin American and Caribbean countries—based on recommendations of a PAHO advisory group (August 2001) and on the WHO document "expansion of antiretroviral treatment in low-resource settings" (2002).* Washington, DC. Retrieved 3 November 2004, from http://www.paho.org/English/HCP/HCA/arv_adultos.htm

Panel on Clinical Practices for Treatment of HIV Infection Convened by the Department of Health and Human Services (DHHS). 2004. *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents*. Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/adult/AA_032304.pdf

Public Health Service Task Force. 2004. *Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States*. Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/perinatal/PER_062304.pdf

Public Health Service Task Force. 2004. *Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States*. *Supplements: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy*. Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/perinatal/ST_062304.pdf

Rabkin M, W El-Sadr, and E Abrams. 2003 *The MTCT-Plus Clinical Manual.* Mailman School of Public Health, Columbia University. Retrieved 3 November 2004, from http://www.mtctplus.org/pdf/ClinicalManual.pdf

Rachlis AR and DP Zarowny, for the Canadian HIV Trials Network Antiretroviral Working Group. Guidelines for antiretroviral therapy for HIV infection. *CMAJ* 1998;158:496–505. Retrieved 3 November 2004, from http://www.cmaj.ca/cgi/reprint/158/4/496.pdf

Rapid Advice-Antiretroviral therapy for HIV infection in adults and adolescents: WHO, November 2009

Guidelines for the use of Antiretroviral agents in HIV infected adults and adolescents, DHHS, December 2009, Office of AIDS Research Advisory Council

Republic of Namibia. Ministry of Health. Guidelines for Antiretroviral Therapy. First edition.2003.Windhoek, Namibia, p 13. Retrieved 24 November 2004, from http://hivinsite.ucsf.edu/pdf/countries/namibia_guideline.pdf

WHO, 2006. Antiretroviral drugs for the therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach. Retrieved August 8, 2006, from http://www.who.int/hiv/pub/guidelines/WHO%20CTX.pdf.

# Part VI: References


WHO 2006. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach. Retrieved August 8, 2006 from http://www.womenchildrenhiv.org/wchiv?page=wx-resource&rid=56-7883&topic=cw2&type=prgd

WHO 2006. Case definitions of HIV for surveillance and revised clinical and immunological classification of HIV-related disease in adults and children August 2006. Accessed on: August 25, 2006. Available at: http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html.

WHO. 2004. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Guidelines on guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings*. Retrieved 3 November 2004, from http://www.who.int/hiv/pub/mtct/en/arvdrugsguidelines.pdf

WHO. 2004. *Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach*: 2003 Revision. Retrieved 3 November 2004, from http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

WHO. [Not dated]. *World Health Organization – ARV toolkit.* Retrieved 3 November 2004, from http://www.who.int/hiv/toolkit/arv/en/index.jsp

WHO Rapid Advice: use of ARV drugs in pregnant women and preventing HIV infection in infants. November 2009

WHO HIV-AIDS Rapid Advice ARV therapy for HIV Infection for adults and adolescents, December 2009

WHO executive summary of recommendations ART for HIV infection for infants and children: towards universal access 2010

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. 2004. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/pediatric/PED_012004.pdf

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. 2004. *Guidelines for the use of antiretroviral agents in pediatric HIV infection. Appendix: characteristics of available antiretroviral drugs.* Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/pediatric/APP_PED_012004.pdf

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. 2004. *Guidelines for the use of antiretroviral agents in pediatric HIV infection. Supplement: pediatric antiretroviral drug information.* Retrieved 3 November 2004, from http://www.aidsinfo.nih.gov/guidelines/pediatric/SUP_PED_012004.pdf

# Part VI: References

**Additional resources**

http://www.aids-etc.org/
http://www.carec.org/
http://www.cdc.gov/nchstp/od/gap/
http://www.fxbcenter.org
http://www.mtctplus.org/
http://www.womenchildrenhiv.org/

## FOOTNOTE

***Guidelines, as the name implies, are written to serve as a "guide." They are not intended to prevent clinicians from using sound clinical judgement or attending to patients during unscheduled visits. In certain instances, the clinician may find it necessary to refer a patient to a physician with experience in caring for children with HIV infection.***