National Guidelines
For
Implementation of
Antiretroviral Therapy (ART)

DRAFT

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National AIDS Control Organization,

9th Floor Chandralok, 36, Janpath, New Delhi - 110001

CONTENTS

Annexures

I. Training Programme
    a. Training curriculum
    b. Objectives
    c. Course description
    d. Training schedule
II. Individual ARV Identity Card
III. Patient Master Record Card for ARV
IV. ARV Quarter Cohort Analysis Form
V. ARV Cumulative Annual Cohort Analysis Form
VI. Monthly Progress Report
VII. Time line for training
VIII. Drug and Consumables logistic Stock Register
IX. Monthly Treatment Unit Report
X. Antiretroviral Treatment Eligibility Register
XI. Patient Visit Record

GLOSSARY

AIDS:	*Acquired Immune Deficiency Syndrome*
ABC :	*abacavir*
ARVs:	*Antiretroviral drugs*
ART:	*Antiretroviral therapy*
AZT :	*zidovudine (ZDV)*
3TC:	*lamivudine*
BID :	*bi-daily*
ddI (EC):	*didanosine (enteric coated)*
d4T :	*stavudine*
DRAs:	D*rug regulatory agencies*
EFV :	*efavirenz*
FDC:	*fixed dose combination*
GIPA:	*greater involvement of people living with HIV/AIDS*
HIV:	*Human Immunodeficiency Virus*
Hg:	*Haemoglobin*
IDV:	indinavir
LPV/r:	*lopinavir / ritonavir*
NACP:	*National AIDS Control Programme*
NFV:	Nelfinavir
NVP:	*nevirapine*
NNRTI:	*Non-Nucleoside Reverse Transcriptase Inhibitor*
NRTI:	*Nucleoside Reverse Transcriptase inhibitor*
NtRTI :	*Nucleotide Reverse Transcriptase inhibitor*
PLHA:	*People living with HIV/AIDS*
PPTCT:	*Prevention of Parent to Child Transmission of HIV*
RIF:	*rifampicin*
RIT:	*ritonavir (r)*
SQV/r:	*saquinavir / ritonavir*
TB :	*Tuberculosis*
TDF:	*tenofovir*
WHO:	*World Health Organization*

1. INTRODUCTION

Across India today, HIV/AIDS is seen to be moving from high risk groups to the more vulnerable segments among the general population. Political leadership and commitment has shifted significantly in favor of providing access to anti-retroviral treatment (ART) for people living with HIV/AIDS. Treatment is now perceived as a critical component of a comprehensive program to combat HIV/AIDS, along with prevention and the improvement of health care infrastructure for the delivery and monitoring of care and support. This integration has recently become, more feasible.

Earlier, high costs, demanding treatment regimens, and the absence of basic health infrastructure were repeatedly cited as potentially insurmountable barriers.

The "Call to Action" at the UN General Assembly Special Session on HIV/AIDS (June 2001), pushed forward a new global consensus on the need for ART. This led to a cumulative response from diverse quarters. It put pressure on pharmaceutical manufacturers, and ever since, we are witnessing dramatic reductions in drug prices. Brazil's national ART distribution programme added to the public debate. WHO released guidelines for anti-retroviral use in resource constrained settings in April 2002, added 10 ART drugs to its list of "essential medicines" for all countries, and for the first time qualified a number of generic manufacturers. WHO declared the lack of access to ARV treatment for HIV/AIDS a "global health emergency" in September, 2003, and announced that it would release an emergency plan to scale up access to ARV treatment for at least three million people by the end of 2005. This joint WHO/UNAIDS announcement popularly came to be known as the 3 by 5 initiative. The WHO guidelines for anti-retroviral use in resource constrained settings have since been revised in Dec 2003.

Admittedly, antiretroviral therapy is no cure for HIV/AIDS. Effective antiretroviral regimens inhibit the efficient replication of the HIV virus, and reduces viremia to undetectable levels. Lower frequency of opportunistic infections significantly reduces the cost of management of HIV. This helps people lead more

productive lives, with perceptibly reduced stigma and discrimination. Successes achieved in terms of ART delaying the onset of AIDS, has now transformed the common perception about HIV from being an immediately fatal scourge to somewhat more manageable, chronic illness.

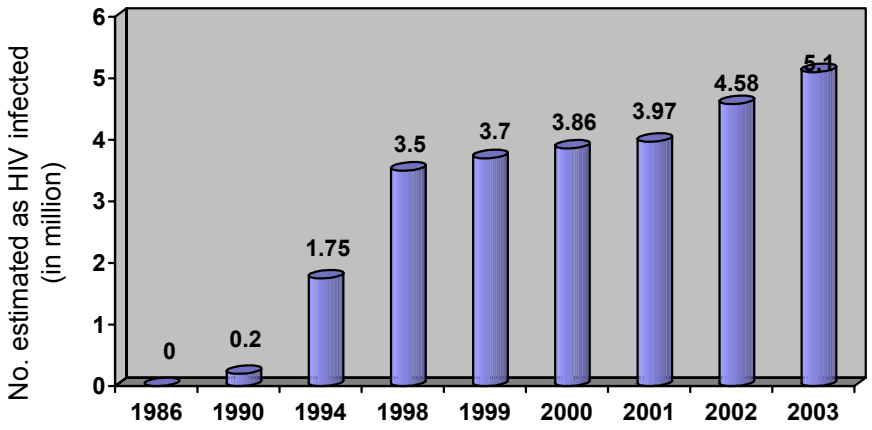
2. EPIDEMIOLOGY OF HIV IN INDIA

(a) Estimation of HIV infections in the country : India initiated sero surveillance for HIV in 1985, in order to assess the magnitude and dimension of HIV infection even before AIDS cases were reported in the country. Since 1998, Government of India has been conducting, each year, a nationwide HIV sentinel surveillance, covering all States and Union Territories, to evaluate the spread and prevalence of the HIV infection. In 2003, we had 455 HIV sentinel sites located among high risk groups and the general population, and these will increase to 670 HIV sentinel sites in 2004. Current trends and estimates indicate that there are 5.1 million persons infected with HIV in the country (an adult prevalence rate of 0.96%). The real problem is that given the large population base, even a small increase of 0.1% will generate half a million infected persons.

The estimated number of HIV infections was 3.5 million in the year 1998, 3.71 million in 1999, 3.86 million in 2000, 3.97 million in 2001, 4.58 million in 2002 and 5.1 million in 2003. These estimates indicate that there has been no dramatic upsurge in the spread of HIV infection across the country. However these figures are a cause of increasing concern to Government. On the one hand, people infected with HIV during the 1980s and 1990s will progress to AIDS, resulting in a steep increase in the number of AIDS patients. This has direct impact on the already over burdened public health delivery systems; on the other, hand large numbers who have HIV are unaware of their sero-status and could transmit the HIV virus to many others.

The spread of HIV infection is not uniform across the States in India. Six states are categorized as high prevalence states, i.e. Andhra Pradesh, Karnataka, Nagaland, Manipur, Maharashtra and Tamil Nadu, *since the HIV prevalence rates among women attending antenatal clinics in these states is 1 percent and above*.

Gujarat, Pondicherry and Goa are categorized as states with moderate prevalence of HIV, since HIV prevalence rates amongst high risk population (STD Clinic attendees) has been found to be 5 percent or more, but among women attending ante-natal clinics, the HIV prevalence rates are below one percent. All remaining States/Union Territories are categorized as low prevalence States since the prevalence rates amongst high-risk population (STD Clinic attendees) is below 5 percent. While it appears that the numbers of people living with HIV/AIDS are increasing, we believe that our comprehensive programme on prevention coupled with care and support has made significant impact. In some pockets, the rate of increase of HIV infection is coming down, and we need to push this trend.

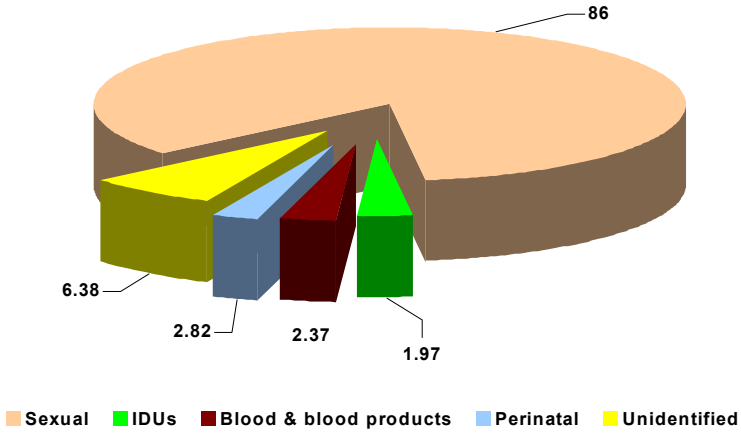


India accounts for 10% of global HIV burden and 65% of that in South and South East Asia.

(b) Routes of transmission in India : A cumulative total of 72,943 AIDS cases have been reported till June, 2004 which includes 19,721 female cases and 53,222 male cases. The main mode of transmission is through heterosexual route, 86% of the infection is attributed to this mode of transmission. The other modes of transmission are perinatal transmission (2.88%), through blood and blood products (2.37%) and through injecting drug use (1.97%) particularly in some of the north-eastern states and metropolitan cities. In 6.38% of cases mode of transmission is not specified.About 90% of the reported HIV/AIDS cases occur in sexually active and economically productive age group of 15-49 years. One in every 4 cases reported is a woman.

Some key factors fuelling the spread of HIV infection across the country is labour migration in search of employment from economically backward pockets to more developed regions, low literacy levels particularly amongst marginalized and vulnerable sections of the society, gender disparity, prevalence of reproductive tract infections and sexually transmitted diseases both among men and women.

Known modes of HIV transmission, 2003



3. NATIONAL AIDS CONTROL PROGRAMME

Following the detection of the first case of HIV positive in 1986 a National AIDS Committee was formed to guide and advise the Govt. in prevention and control of HIV/AIDS. India immediately responded with interventions on surveillance, blood safety and dissemination of information, education and communication. India became committed to putting in place activities for prevention and control of HIV/AIDS. In the year 1992 National AIDS Control Organization was established and National AIDS Control Board was also formed and implement the plan and policies laid down by the Govt. Phase - I of the National AIDS Control Programme (NACP) commenced in 1992, supported by a World Bank credit. Phase - II of the NACP began in 1999, supported by the domestic budget, World Bank and several additional partners. Phase II of the NACP (1999-2004, extendable) is a 100 per cent centrally sponsored scheme (CSS), substantially decentralized, and is being

implemented in 35 States / Union Territories and 3 municipal corporations through the State AIDS Control Societies. The National AIDS Control Organisation has assumed the responsibility for the epidemiological surveillance of HIV and STD, training and capacity building, operational research and monitoring and evaluation. NACO is also responsible for providing guidance for planning, organizing and implementation of the programme, program oversight, allocation of funds to the states, coordination with donor partners. NACO also coordinates the partnership with all donors, and inter-sectoral partners.

In the year 2002, National AIDS Control Committee was formed under chairmanship of Union Health Minister which functions on a policy making body for the guidance and surveillance of the programme. In April 2002, the Government of India adopted the National Policy for the Prevention and Control of HIV/AIDS, and the National Blood Policy. The general objective of the national policy is to prevent the further spread of HIV/AIDS, and to reduce the impact of the spread on the general population, and for those who are infected. Articulation of the Policy has generated ownership of the prevention and control programme among government and non-government organizations at national, state and local levels. It has served to create an enabling environment for prevention and treatment efforts, and strengthened programme management at all levels. It ensured wider availability of safe blood and blood products and provided an impetus for awareness generation and behaviour change activities.

The programme continues to focus on prevention of HIV through enhancing general awareness about HIV transmission, about precautions to be observed to ensure prevention of HIV and these are disseminated among vulnerable populations such as commercial sex workers, street children and migrant labour so that they have access to information and services needed to protect themselves. 993 Targetted Interventions have been implemented between 1999-2004. 738 STD clinics provide treatment of Sexually Transmitted Infections. In order to promote use of condoms in all unsafe sexual encounters, the financial allocations for condom procurement were doubled and 171 million condoms were supplied during the year 2003-04. For ensuring more availability of safe blood, at least one modernized blood

bank is positioned during each district. 1854 licensed blood banks and 81 blood component separation units are functioning.

Prevention of Mother to Child Transmission of HIV is being implemented through 273 Prevention of Parent to Child Transmission Centres (PPCTC) which are established in each medical college and each district of six high prevalence states, and we have commenced extending these services across low prevalence states. School AIDS Education Programme now covers nearly 60,000 schools of higher secondary level out of 1.50 lac schools. Besides this 1.5 lac students have been covered through the University Talk-AIDS Programme. For sensitisation out of school youth, the Village Talk AIDS Programme has been implemented, covering 11,550 villages in 385 districts. Counselling and testing services have been extended to all districts of the country through 709 Voluntary Counselling & Training Centres (VCTCs). For promotion of home/community care, 51 community care centres (CCC) have been established by NGOs being supported through state societies.

Programme implementation is dependent on the capacities of state units. The State AIDS Control Societies have identified 993 NGOs for delivery of targeted interventions among the high-risk groups.

Since the launch of Phase – II of the NACP in 1999, the Government of India (GOI) has demonstrated commitment to provide low cost care to people living with HIV/AIDS, in order to mitigate the impact of HIV related opportunistic infections. GOI has strengthened the capacity of states by training physicians and technicians, installing flow cytometers for CD4/CD8 testing at apex medical institutions across 25 large and medium size states, and allocating financial support for the purchase of drugs to treat common opportunistic infections.

We have now introduced in India, a paradigm shift in the National AIDS Control Programme. In India HIV/AIDS programme enjoys support from the highest political levels. India sponsored the International Policy Makers Conference on 11th May,2002. The first National Convention of the Parliamentary Forum on HIV/AIDS was held on 26th–27th July,2003 with the objective of involving elected representatives in HIV/AIDS programme. The National Convention was inaugurated

by the Hon'ble Prime Minister and addressed by the Leader of Opposition, Speaker of Lok Sabha, Deputy Prime Minister, Dy. Chairman of Rajya Sabha and other dignitaries. All major political parties in the country endorsed a Declaration of Commitment in the fight against HIV/AIDS. The President of India has directed search for an AIDS vaccine for India. Govt. of India launched free antiretroviral on 1st April, 2004 for six high prevalence states: Andhra Pradesh, Karnataka, Maharashtra, Tamilnadu, Manipur, Nagaland and NCT of Delhi through 8 government hospitals in first phase. In Phase I of implementation, the sub-groups among the PLHAs being targeted on priority are : (i) sero-positive mothers who have participated in the PPTCT programme; (ii) seropositive children below the age of 15 years; and (iii) people with AIDS who seek treatment in government hospitals. The number of ART center are planned to be increased to 25 by end of year 2004-05 covering a total to 25000 patients and extend ART facility to 1,00,000 patients by end of 2007.

In the year 2004, a grant amounting to US$ 165 million has been awarded to the Govt. of India by Global Fund for 5 years for expansion of ART.

4. DOCUMENT OBJECTIVES

In view of ART having been introduce in the country the National Treatment Guidelines have been provided to guide the clinicians in the best practices in treatment and achieve uniformity of ART to avoid problems of inadequate and improper treatment which will in the long run predispose to resistance and difficulty in management of HIV.

The document will be reviewed frequently so that it keeps up with newer regimens and protocols for ARV therapy, and also reflects the backward and forward linkages between programmes for treatment and the interventions for prevention of HIV/AIDS, and care & support of people living with HIV/AIDS.

5. TREATMENT AND CARE OPTIONS FOR PLHAs

Government of India has been actively supporting the care and support of People Living with HIV/AIDS (PLHA) by (i) provisioning essential drugs for management of opportunistic infections; (ii) bringing center-stage the HIV-TB co - infection through linkages with the TB control programme for free treatment of TB among people living with HIV/AIDS; (iii) initiating intensive advocacy and sensitization among doctors, nurses and paramedical workers to prevent discrimination, stigmatization and denial of services; (iv) initiating training workshops for clinicians and practitioners, on the clinical management of HIV/AIDS and the rational use of antiretroviral drugs; (v) establishing district level voluntary counseling and testing centres in a phased manner; (vi) providing antiretrovirals in the prevention of parent to child transmission programmes cosponsored by UNICEF; (vii) provisioning of antiretrovirals in the current interventions in cases of post-exposure prophylaxis to health care providers in all Govt. hospitals; (viii) supporting the setting up of community care centres for PLHAs; (ix) supporting PLHA networks to open drop-in-centres; and (x) reducing import and excise duties on antiretroviral drugs in India, and encouraging states to reduce sales tax levies, as well.

Till recently in India, ART delivery had been provided largely through the private sector. Some public sector provision is made through the Central Government Health Scheme (CGHS), Employees State Insurance Corporation(ESIC), the Armed Forces Medical Services, the Railways, as well as through the national AIDS control programme via the interventions on prevention of parent to child transmission, and the post-exposure prophylaxis.

There is no verified data on the numbers of patients on ART, the regimens prescribed, or the clinical outcomes. Clearly, there is need to put in place a national ARV monitoring system and a surveillance for drug resistance.

A full course of first line fixed dosed combination ARV drugs costs a patient approximately Rs. 1200- 1500 a month, the costs of monitoring therapy with viral load tests, haemotological parameters and CD4 counts increases the costs to about

Rs. 2,000 a month, per patient. The inclusion of protease inhibitors (PIs) for second line ARV therapy may increase the costs of ARV therapy to 2-3 folds of the first line regimens.

India has the capacity to scale up ART with advantages that many other countries do not have such, an established domestic drug manufacturing base and the enviable pool of trained health professionals. However, the unprecedented challenges for programme management and service delivery must be candidly identified, and addressed in a systematic manner.

6. PRIORITY PREVENTION ACTIVITIES NEED STRENGTHENING FOR BETTER INTEGRATION WITH TREATMENT

Providing equitable access to ART for People living with HIV/AIDS is a critical goal for HIV-control programs. However, the ultimate solution in combating the spread and prevalence of HIV/AIDS across the country rests overwhelmingly with effective prevention of new infections.

Some overlap does exist between HIV prevention and treatment programs. Access to treatment provides an important incentive for people to respond positively to prevention campaigns by being tested, and if found HIV positive, by proceeding to obtain complete and accurate information for appropriate care and support. One rationale for extending the availability of ART across the high prevalence states of India is that while the National AIDS Control Programme now has a wide range of interventions for prevention of HIV/AIDS, the same cannot be said for care, support and treatment. Prevention and treatment should proceed in tandem because the availability of effective treatment motivates people to access Voluntary Counseling and Testing (VCT). Higher VCT uptake rates will result in more people receiving prevention counseling. If we can simultaneously improve the referral services from the VCT centres, we may be benefited by improved mobilization of people living with HIV/AIDS to access ART.

Accordingly, this major policy and programme shift in the national AIDS control program, the introduction of ART through the public health care delivery system, is aimed at motivating prevention, especially diagnostic testing. The **709** VCTCs that are currently supported by the National AIDS Control Programme need further expansion. PLHA should be involved as peer counselors at VCTCs and during IEC activities to further reduce stigma and discrimination.

Studies have shown that in North America, Europe, Australia, Uganda, Senegal and parts of Kenya, the combined effect of government interventions and autonomous individual decisions has reduced the frequency of multiple sexual partners, increased condom use, improved treatment for STIs and reduced needle sharing. Resultantly, the incidence of new HIV infections has measurably declined. Similar gains are being documented in Tamilnadu, South India. In all these places, on account of understanding of AIDS and its severe consequences, people have "inhibited" their risky sexual and drug using behaviour.

However, there is sometimes, a discernible trend to the contrary as well which as been documented. Aware that treatment for HIV infection is now more easily available, individuals may relax their preventive behaviour which can lead to "disinhibition". Evidence from Europe and North America shows that the availability of ART may reduce fear and encourage high-risk behaviour, ("dis-inhibition" effect) in the mistaken belief that since people no longer feel sick, they no longer transmit HIV or that HIV is "curable" and prevention is not required. These should not outweigh the beneficial prevention impacts of ART. Intensive counseling for people on treatment and accurate information and education about the precise consequences of ART are required. It is critical to communicate to both HIV positive and negative people that ART drugs do not cure HIV, that HIV can still be transmitted and that ART is not an appropriate substitute for primary prevention.

Greater access to affordable ART drug regimens is an important strategy in prevention and control of HIV infection.

In summary, the positive effects of Antiretroviral Therapy on HIV transmission are SLOW TRANSMISSION. through:

(i) Reduction in infectiousness. ART lower viral loads and may therefore lower the risk of transmission by sexual contact ;

(ii) Encouraging prevention, especially diagnostic testing. ART may increase the uptake rates of prevention activities, particularly voluntary counseling and testing

The negative effects of ART on HIV transmission are SPEED TRANSMISSION through :

(i) Selection for resistance: Partial or incomplete adherence to ART selects resistant strains of the virus, which can then be transmitted.

(ii) Longer duration of infectivity: The longer lifespan of people with HIV/AIDS on ART also means that the risk of HIV transmission to family and communities is extended.

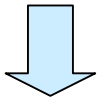
(iii) "Disinhibition" effect for People on ART and HIV positives and negatives in the surrounding community: Due to the availability of treatment for HIV, people may engage in more risky behaviours than they would if ART was not available.

7. LEVELS OF CARE

Level 1 : Community health centers / Community care centres

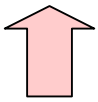
- Staff : trained paramedical personnel, community workers and people living with HIV/AIDS. The latter will act generally as lay counselors, adherence supporters and treatment educators. They will be invaluable in mobilizing people living with HIV to access treatment.
- Services : HIV testing may be considered in future. Opportunistic infection prophylaxis and treatment, management of simple side effects in ARV treatment / referral, as well as, adherence support.
- Low Service Delivery Models : Community level care through NGOs, CBOs, PLHA groups
    - Treatment information sheet for patient providing guidance for better adherence
    - Counseling
    - Treatment education
    - Infant feeding counseling

- Home based care
- Strengthen families of PLHAs
- Transport to hospitals
- Basic information provision
- Legal rights awareness
- Vaccination against tetanus and HBV may be taken



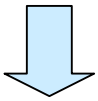
Difficult cases
Referred from Level I
To Level II

Supervision/support
from Level II to Level I



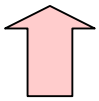
Level 2 : Medical Colleges / District hospitals

- Staff : Doctors, clinical officers, medical assistants, and nurses, trained to administer ARV treatment with one first line fixed dose combination regimen.
- Services : all of the above plus management of severe opportunistic infections such as tuberculosis and cryptoccocal meningitis, management of severe ARV toxicity, and care for pregnant women.
- In addition, alternative first-line regimens, and potentially second-line ARV regimens, lab tests for transaminases (ALT), Haemoglobin (Hg) or Whole Blood Count, and CD4 (using manual or automated methods).
- Service Delivery Models : Secondary level (district hospital) (in phase II)
    - ARVs for HAART
    - Screening prophylaxis and treatment of toxoplasmosis and PCP
    - Nutritional intervention (local low cost nutritious food)
    - Screening, prophylaxis and treatment of TB, toxoplasmosis and PCP
    - Confirmatory diagnosis of HIV related conditions
    - Vaccination against tetanus and HBV may be taken
    - PEP



Difficult cases
Referred from Level II
To Level III

Supervision/support
from Level III to Level II



Level 3 : Referral centers (capital and / or provincial facilities)

- Staff : HIV/AIDS experts, clinical officers and nurses.
- Services : all of the above plus full hospital services and viral load monitoring, community resistance monitoring

Service Delivery Models : Tertiary level (medical college hospital):

- Antiretroviral treatment
- Management of anxiety and depression
- Management of proctocolonic syndrome
- Parenteral nutrition
- PEP among health workers
- Treatment of toxoplasmosis, PCP and other related OIs
- Management of complex manifestations of HIV

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

Clinical Stage I:

Asymptomatic

Persistent generalized lymphadenopathy (PGL)

Performance scale 1: Asymptomatic, normal activity

Clinical Stage II:

Weight loss, < 10% of body weight

Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)

Herpes Zoster, within the last 5 years

Recurrent upper respiratory tract infections (i.e., bacterial sinusitis) and/or Performance scale 2: symptomatic, normal activity

Clinical Stage III:

Weight loss, > 10% of body weight

Unexplained chronic diarrhoea, > 1 month

Unexplained prolonged fever (intermittent or constant), > 1 month

Oral candidiasis (thrush)

Oral hairy leukoplakia.

Pulmonary tuberculosis, within the past year

Severe bacterial infections (i.e., pneumonia, pyomyositis) and/or performance scale 3: bed-ridden, < 50% of the day during the last month

Clinical Stage IV:

HIV wasting syndrome, as defined by CDC

Pneumocystis carinii pneumonia

Toxoplasmosis of the brain

Cryptosporidiosis with diarrhoea, > 1 month

Cryptococcosis, extrapulmonary

Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes

Herpes simplex virus (HSV) infection, mucocutaneous > 1 month, or visceral any duration

Progressive multifocal leukoencephalopathy (PML)

Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)

Candidiasis of the oesophagus, trachea, bronchi or lungs

Atypical mycobacteriosis, disseminated

Non-typhoid Salmonella septicaemia

Extrapulmonary tuberculosis

Lymphoma

Kaposi's sarcoma (KS)

HIV encephalopathy, as defined by CDC

And/or Performance scale 4: bed-ridden, > 50% of the day during the last month

(Note: both definitive and presumptive diagnoses are acceptable.)

WHO staging system for HIV Infection and Disease in Children

Clinical Stage I:

1. Asymptomatic
2. Generalised lymphadenopathy

Clinical Stage II:

3. Chronic diarrhoea > 30 days duration in absence of known etiology
4. Severe persistent or recurrent candidiasis post neonatal period
5. Weight loss or failure to thrive in the absence of known etiology
6. Persistent fever > 30 days duration in the absence of known etiology
7. Recurrent severe bacterial infections other than septicemia or meningitis (e.g., osteomyelitis, bacterial (non-TB) pneumonia, abscesses)

Clinical Stage III:

8. AIDS defining opportunistic infections
9. Severe failure to thrive ("wasting) in the absence of known etiology
10. Progressive encephalopathy
11. Malignancy
12. Recurrent septicemia or meningitis

WHO plans to revise the current staging system for HIV infection in children in 2004. One of the limitations of the current system is that many of the clinical symptoms in the Pediatric Stage II and III are not specific for HIV infection and may significantly overlap those seen in children without HIV infection in resource-limited settings. WHO recommends individual adaptation of the system at the country program level may be appropriate.

Organs dysfunctions which can not be explained by other diseases, such as bone marrow dysfunction (thrombocytopenia), kidney dysfunction (RTA, nephrotic

syndrome, other signs of nephropathy), liver dysfunction (hepatitis), cardiac disorder (cardiomyopathy), lung manifestations such as lymphoid interstitial pneumonitis (LIP). The diagnosis can be made by careful clinical investigation and when blood cell count, blood chemistries and CXR are available.

HIV Paediatric Immune Category Classification System

	< 12 mos		1-5 yrs		6-12 yrs	
Immune category	**No./mm^3**	**(%)**	**No./mm^3**	**(%)**	**No./mm^3**	**(%)**
Category 1: No suppression	≥ 1500	(≥ 25%)	≥ 1000	(≥ 25%)	≥ 500	(≥ 25%)
Category 2: Moderate suppression	750 - 1499	(15%-24%)	500-999	(15% - 24%)	200-499	(15% - 24%)
Category 3: Severe suppression	<750	(< 15%)	< 500	(<15%)	<200	(<15%)

9. TREATMENT OF HIV WITH ART

The advent of antiretroviral drugs in the late 1980s began a revolution in the management of HIV. The primary aim of antiretroviral treatment strategies is to suppress viral replication. Successful outcomes on this parameter restores the balance within the immune system, slows or halts disease progression, prevents drug resistance and improves quality of life.

Patients receiving these regimens are less likely to develop opportunistic infections including TB and require fewer admissions to hospital than patients with untreated disease. Combination antiretroviral therapy (ART) leads to reduction in plasma HIV RNA level (viral load) and rise in CD4 counts with at least partial restoration of immune function. Combination therapy also significantly slows the progression of HIV-1 disease. The primary aim of antiretroviral treatment strategies is to suppress viral replication. Successful outcomes on this parameter restores the

balance within the immune system, slows or halts disease progression, prevents drug resistance and improves quality of life.

Three groups of ARV drugs have been tried, tested and found successful in interrupting viral replication. The use of one or two drug combinations promotes rapid development of resistant strains of HIV and renders the therapy ineffective. Over the past 5-6 years, compelling epidemiological and clinical evidence demonstrates that with strict adherence, the use of combination or three drugs leads to sustained viral suppression for several years.

9.1 Desirable prerequisites for starting ARV Treatment

WHO recommends adoption of a public health approach to the administration and distribution of ART. This implies that ART regimens should be standardized, and that only a single first line, and a limited number of second line regimens should be made available through the public sector for large-scale use. A public health approach to ART treatment aims to provide treatment for as many people as possible, while working towards universal access to ARV treatment. The public health approach for scaling up ARV treatment also calls for early involvement of a range of stake-holders, including those with HIV and other community members.

Selection of first line regimen should be determined on the basis of a number of considerations such as potency, profile of side-effects, ability to keep future treatment options open, ease of adherence, risk during pregnancy, potential of resistant viral strains. WHO does not recommend any dual drug regimens. The current recommendation in all circumstances is for a triple drug regimen.

It is most desirable to have specific services and facilities in place before starting an ART. These are necessary due to the complexity of accessing and continuing the therapy, the need for close clinical and laboratory monitoring and the cost of therapy.

These services include:

- Access to HIV voluntary counselling and testing (VCT) to identify those in need of ART and referral
- Reliable and affordable access to quality antiretroviral drugs, and drugs to prevent and treat opportunistic infections and other related illness.
- Medical services with trained physicians and other health care personnel capable of identifying and treating common HIV-related illnesses and opportunistic infections. Such services should promote effective opportunistic infection prophylaxis.
- Ongoing care and support services to provide treatment adherence counselling and psychosocial support to PLHA and their families. These services should ideally involve trained health care providers, people living with HIV/AIDS and community based care organizations.
- Reliable laboratory services capable of performing routine laboratory investigations such as HIV antibody testing, pregnancy testing, complete blood count and serum chemistries. Access to a laboratory capable of performing CD4+ T lymphocyte count is desirable to monitor therapy.

9.2 Clinical Evaluation prior to initiating ART aims to:

- Assess the clinical stage of HIV infection
- Identify past HIV-related illnesses
- Identify current HIV-related illnesses that require treatment
- Identify co-existing medical conditions and treatments that may influence the choice of first line regimen that will be used

9.3 Recommended medical history

- when and where was the diagnosis of HIV made
- what is this person's possible source of HIV infection
- what are the current symptoms and concerns of the person
- past medical history of symptoms, known diagnoses and treatments given
- history of symptoms of or previous treatment for tuberculosis
- history of possible contact with tuberculosis
- history of possible sexually transmitted infections
- pregnancy history
- current and prior opportunistic infection (OI) prophylaxis
- current and previous ART
- attitude to and readiness to commence ART
- ability to adhere to OI prophylaxis and other drugs (such as anti-tuberculosis therapy) in the past
- ability to keep scheduled appointments in the past
- history of medication and oral contraceptive use in women
- psychosocial, financial and family support status
- social habits (alcohol) and sexual history

9.4 Recommended physical examination

- body weight (BW)
- cutaneous manifestations of possible immunodeficiency such as herpes zoster, papular pruritic eruptions (PPE), diffuse skin dryness.
- lymphadenopathy
- oropharyngeal mucosa: candidiasis, oral hairy leucoplakia (OHL)
- examination of heart and lungs, specifically to exclude active tuberculosis (TB). Active TB should be managed in accordance with RNTCP
- examination of abdomen particularly for liver and spleen enlargement, and abdominal adenopathy
- examination of neurological and musculoskeletal system: mental state, motor and sensory deficit
- examination of optic fundus: retinitis and papilloedema
- examination of the genital tract/gynaecological examination

Recommended laboratory investigations for starting antiretroviral therapy in India

Minimum requirements (community health center)	Desirable (district hospital)	If resources are available (Referral centers)
Rapid HIV Ab test Hemoglobin (if ZDV is being considered) Pregnancy testing sputum smear for TB when cough > 3 weeks	Rapid HIV Ab test Capability to resolve indeterminate rapid HIV Ab test by second serologic method CBC and differential (total lymphocyte count) ALT Pregnancy testing Sputum smear for TB when cough > 3 weeks	Rapid HIV Ab test CBC and differential CD4+ cell count Full serum chemistries (including but not restricted to electrolytes, renal function, liver enzymes, lipids) Pregnancy testing Sputum smear for TB when cough > 3 weeks

9.5 Adult Regimens

The overwhelming short term priority is for first-line regimens which will facilitate the scaling up of treatment. Second-line treatment is not a priority in the short-term. The characteristics of an ideal first-line ARV combination should :

- Be effective and well tolerated, with minimal side effects
- Be potent, even in advanced disease, and favourable resistance profile
- Have no drug interactions or contra indications
- Be safe for use in patients with TB and in pregnant or lactating women
- Be available in a fixed dose combination (once or twice a day)
- Be stable in tropical conditions
- Do not require laboratory monitoring
- Be affordable

9.6 First-Line Combinations

The first recommended choice is d4T/3TC/NVP (Stavudine + Lamivudine + Nevirapine) , taken twice daily (BID) as a fixed dose combination (FDC)

Advantages : it is well tolerated in most cases, has few contra-indications and is appropriate for use in women of child bearing age. It has proven efficacy under actual field conditions, is affordable, and is easy to take.

Limitations : The major side effects with d4T (stavudine) are neuropathy and pancreatitis. Nevirapine causes hepatotoxicity and severe rash. NVP has drug interaction with rifampicin. It should therefore be avoided with rifampicin for both reasons of interaction as well as possibility of haepatoxiciticty. It is ineffective on HIV2.

9.7 Alternate first-line combinations:

(i) AZT/3TC/NVP (Zidovudine + Lamividine + Nevirapine) taken twice daily as a fixed dose combination.

Advantages : Largest experience with Zidovudine use, easy to take , well tolerated. Can be used where d4T (stavudine) use, is contraindicated.

Limitations : Major potential toxicity with AZT are anaemia and neutropenia. In resource poor settings where anaemia is common it may be an issue for concern. Requires Hb monitoring. Zidovudine is more expensive than d4T (stavudine) and therefore this fixed dose combination is also more expensive.

(II) d4T/3TC + EFV (stavudine / Lamivudine + Efavirenz) , taken as EFV (600 mg) once per day plus d4T/3TC as twice daily fixed dose combination.

Advantages : can be used with rifampicin, and easy to take.

Limitations : EFV has potential for CNS toxicity and teratogenecity. It is therefore contra-indicated in pregnant women and women of child bearing age who are not on contraception.

In both d4T + 3TC + NVP and AZT + 3TC + NVP fixed dose combinations Nevirapine should be administered in 200 mg dose as a single drug for 15 days as lead-in dosing and if tolerated only then FDC should be started.

Recommendations on how to begin NVP – containing regimens

For	Start with	Then switch to
d4T- 3TC-NVP	d4T-3TC twice a day plus NVP 200 mg once a day for 2 weeks	d4T-3TC-NVP Fixed dose combination twice a day if patient tolerates 1st 2 weeks of NVP
AZT-3TC-NVP	AZT-3TC twice a day Plus NVP 200 mg once a day for 2 weeks	AZT-3TC-NVP Fixed dose combination twice a day if patient tolerates 1st 2 weeks of NVP

Fixed dose combinations are considered important tools for scaling up in resource-poor, high HIV prevalence settings. They are preferable because they are easy to use, have distribution advantages (procurement and stock management), improve adherence ensures intake of all medicines and reduces the chances of development of resistance. Though once-a-day dosing is an ultimate goal, however it is not essential as field experience clearly has shown that BID regimens with co-formulations are easy for patients to adhere to.

Therefore, WHO must guide both commercial and non-commercial efforts by communicating attributes of the ideal future first-line ARV therapy.

9.8 Recommended first-line ART combination regimens in adults and adolescents with documented HIV infection (WHO 2003)

ARV Regimen	Usage in women in child bearing age or who are pregnant	Major Potential Toxicities
d4T/3TC/NVP	– Can be used	– d4T related neuropathy, pancreatites and lipoatrophy – NVP related heptotoxicity and severe rash
ZDV/3TC/NVP	– Can be used	– ZdV related GI, intolerance, anaemia and neutropenia – NVP related hepatotoxicity and severe rash
d4T/3TC/EFV	– Should be avoided	– d4T related neuropathy, pancreatites and lipoatrophy – EFV related CNS toxicity and potential for teratogenicity
ZDV/3TC/EFV	– Should be avoided	– ZDV related GI intolerance, anaemia and neutropenia – EFV related CNS toxicity and potential for teratogenicity

The physician will prescribe one of the regimens of first line ARV drugs indicated above.

9.9 Government Provision of ART

Govt. has provisioned for first line regimen(s), consisting of fixed does combinations of the following ARV drugs:

Zidovudine/ Lamivudine and Stavudine/ Lamivudine

alongwith Nevirapine and Efavirenz.

(i) Stavudine(30mg) + Lamivudine(150mg) + Nevirapine(200 mg)

(ii) Stavudine(40 mg) + Lamivudine(150mg) + Nevirapine(200 mg)

(iii) Zidovudine(300mg) + Lamivudine(150mg) + Nevirapine(200 mg)

(iv) Stavudine(30 mg) + Lamivudine(150mg)

(v) Stavudine(40 mg) + Lamivudine(150mg)

(vi) Zidovudine (300mg) + Lamivudine(150mg)

(vii) Nevirapine (200mg) for lead in dosage

(viii) Efavirenz (600mg) for single dose

9.10 Dosages and common side effects of ARVs available in National AIDS Control Programme

Nucleoside Reverse Transcriptase Inhibitors (NsRTI)

Generic name	Dose	Adverse effects
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily <50 kg: 2 mg/kg bid	Minimal toxicity Lactic acidosis with hepatic steatosis (rare)
Stavudine (d4T)	>60 kg: 40 mg twice daily <60 kg: 30 mg twice daily	Pancreatitis Peripheral neuropathy Lactic acidosis with hepatic steatosis (rare) Lipoatrophy
Zidovudine (ZDV)	300 mg twice daily ZDV/3TC combination 300 mg/150 mg twice daily	Anaemia, neutropenia, Gastrointestinal intolerance, Headache, insomnia, myopathy Lactic acidosis with hepatic steatosis (rare)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Generic name	Dose	Adverse effects
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily	Skin rash, Stevens-Johnson syndrome Elevated serum aminotransferase levels Hepatitis, life-threatening hepatic toxicity
Efavirenz (EFV)	600 mg once daily (bed time administration is suggested to decrease CNS side effects)	CNS symptoms: dizziness, somnolence, insomnia, confusion, hallucinations, agitation Elevated transaminase levels Skin rash

9.11 Recommended switch over Policy for ART

Regimen	Toxicity	Drug Substitution
D4T/3TC/NVP	• d4T – related neuropathy or pancreatitis	• Switch d4T to ZDV
	• d4T –related lipoatrophy	• Switch d4T to TDF* or ABC*
	• NVP –related severe hepatotoxicity	• Switch NVP to EFV (except in pregnancy)
	• NVP – related severe rash (but not life threatening)	• Switch NVP to EFV
	• NVP –related life threatening rash (Stevens – Johnson syndrome)	• Switch NVP to PI
ZDV/3TC/NVP	• ZDV –related persistent GI intolerance or severe haemtological toxicity	• Switch ZDV to d4T
	• NVP –related severe hepatoxicity	• Switch NVP to EFV (except in pregnancy. In this situation switch to NFV, LPV/r* or ABC*.)
	• NVP –related severe rash (but not life threatening)	• Switch NVP to EFV
	• NVP –related life threatening rash (Stevens - Jhonson syndrome)	• Switch NVP to PI*
D4T/3TC/EFV	• d4T –related neuropathy or pancreatitis	• Switch d4T to ZDV
	• d4T –related lipoatrophy	• Switch d4T to TDF* or ABC*

	• EFV –related persistent CNS toxicity	• Switch EFV to NVP
ZDV/3TC/EFV	• ZDV –related persistent GI intolerance or severe hematological toxicity	• Switch ZDV to d4T

* These or other drugs not supplied under programme will have to be purchased by the patients.

In the event of treatment failure, a number of second line regimens have been found to be effective in prolonging the benefits of ART. Here, the programme needs to guard against cross resistance. Ideally, second line regimens should include at least three new drugs. WHO's recommended second line regimens corresponding to each failed first line regimen are summarized below.

9.12 WHO's recommended second line regimens in adults and adolescents for treatment failure on first line ARV regimen (WHO 2003)

First-line regimen	Second-line regimen
d4T or ZDV + 3TC + NVP or EFV	TDF or ABC + ddI [1] + LVP/r or SQV/r [2]

[1] dose of ddI should be reduced from 400 mg to 250 mg when administered with TDF

[2] LVN/r and SQV/r require secure cold chain. NFV can be considered as an alternative in resource settings without cold chain.

9.13 First-line ARV drug interactions

If patient is taking:	Do not co-administer with these drugs (Call for advice for alternative treatment)	Other cautions
Nevirapine (NVP)	• Rifampin • Ketoconazole	Do not rely on estrogen-based oral contraceptives-switch or use additional protection. If on methadone, will need to increase dose. Monitor for withdrawal signs.
Lamivudine (3TC)	No major drug interactions	
Stavudine (d4T)	Do not give with ZDV (zidovudine, AZT)	Higher risk of d4T neuropathy when also taking INH
Zidovudine (ZDV, AZT)	Do not give with d4T or ganciclovir	Higher risk of anaemia when also taking acyclovir or sulpha drugs
Efavirenz (EFV)	• Diazepam (OK for convulsions in emergency) • Other benzodiazepines other than lorazepam • Phenobarbitol • Phenytoin • Protease inhibitor ARVx	Do not take with high fat meal If on methadone, will need to increase dose. Monitor for withdrawal signs

Possible side effects in patients on ART

- A side effect of the ARV therapy
- A new opportunistic infection, or
- Immune reconstitution syndrome
  (the stronger immune system reacting to an infection that had been invisible; usually within 2-3 months of starting treatment).

Clinical monitoring at the first-level facility requires the ability to consult with the district clinician on your clinical team. This will require support for cell phone or radio telephone communications.

9.14 Recommended responses to common side effects with ART:

Signs or symptoms	Response
Nausea	Take with food (except for ddi or IDV). If on zidovudine, reassure that this is common, usually self-limited. Treat symptomatically.
Headache	Give paracetamol. Assess for meningitis. If on zidovudine or EFV, reassure that this is common and usually self-limited. If persists more than 2 weeks, call for advice or refer.
Diarrhoea	Hydrate. Follow diarrhoea guidelines. Reassure patient that if due to ARV, will improve in a few weeks. Follow up in 2 weeks. If not improved, call for advice or refer.
Fatigue	This commonly lasts 4 to 6 weeks especially when starting ZDV. If severe or longer than this, call for advice or refer.
Anxiety, nightmares, psychosis, depression	This may be due to efavirenz. Give at night; counsel and support (usually lasts < 3 weeks). Call for advice or refer if severe depression or suicidal or psychosis. Initial difficult time can be managed with amitriptyline at bedtime
Blue /black nails	Reassure. It's common with zidovudine
Rash	If on nevirapine or abacavir, assess carefully. Is it a dry or wet lesion? Call for advice. If generalised or peeling, stop drugs and refer to hospital
Fever	Call for advice or refer. (This could be a drug side effect, an opportunistic infection a new infection, or immune reconstitution syndrome.)

9.15 Clinical signs, symptoms, monitoring and management of symptoms of serious adverse effects of antiretroviral drugs that require drug discontinuation

Adverse Effect	Possible offending drug/s	Clinical signs / symptoms	Management
Acute hepatitis	NVP; Less common with EFV, ZDV, ddI, d4T (<1%); and PIs, most frequent with RTV.	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia).	Close clinical monitoring and if possible, monitor serum transaminases, bilirubin. All ARV should be stopped until symptoms resolve. NVP should be permanently discontinued.
Acute pancreatitis	ddI, d4T; Less common with 3TC	Nausea, vomiting, and abdominal pain.	Close clinical monitoring and if possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV, ABC).
Lactic acidosis	All NsRTIs (d4T more common)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia; and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness).	Discontinue all ARV; Symptoms may continue or worsen after discontinuation of ART; Provide supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF.
Hypersensitivity reaction	ABC; NVP	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnea (with or without rash). While these symptoms overlap those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	Discontinue all ARVs until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated or to PI- or NRTI-based regimen if NVP-associated.
Severe rash/ Stevens-	NVP	Rash usually occurs during the first 2-4 weeks of treatment. The rash is	Discontinue all ARVs until symptoms resolve.

Adverse Effect	Possible offending drug/s	Clinical signs / symptoms	Management
Johnson syndrome	Less common with EVZ	usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson Syndrome or toxic epidermal necrolysis (SJS/TEN) has been reported in ~0.3% of infected individuals receiving NVP	Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or SJS/TEN. Once resolved, switch ART regimen to different ARV class (e.g., 3 NsRTIs or 2 NsRTIs and PI). If rash is moderate but not severe and without mucosal or systemic symptoms, change in NNRTI (e.g., NVP to EFV) could be considered after rash resolves.
Severe peripheral neuropathy	ddI, d4T, 3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Stop suspect NsRTI and switch to different NsRTI that is not neurotoxic (e.g., ZDV, ABC). Symptoms usually resolve in 2-3 weeks.

SJS = Stevens-Johnson syndrome, TEN=Toxic epidermiolysis?

9.16 Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

If CD4 Testing Available

- WHO Stage IV disease irrespective of CD4 cell count
- WHO stage III disease with consideration of using CD4 cell counts < 350/mm3 to assist decision making
- WHO stage I or II disease with CD4 cell count $\leq 200/mm^3$

If CD4 Testing Unavailable:

- WHO Stage IV disease irrespective of total lymphocyte count
- WHO Stage III disease irrespective of total lymphocyte count
- WHO Stage II disease with a total lympocyte count = $1200/mm^3$

9.17 Criteria for starting ARV therapy in infants and children*:*

(i) For HIV sero-positive infants aged below 18 months, WHO recommends initiation of ARV therapy, if;

- The infant has virologically proven infection (using HIV DNA PCR, HIV RNA assay or immune complex dissociated p24 antigen and has:

  (a) WHO Paediatric stage III HIV disease (e.g. clinical AIDS) irrespective of CD4%

  or

  (b) WHO Paediatric Stage II disease with consideration of using CD4<20% to assist in decision making

  or

  (d) WHO Paediatric stage I (e.g. asymptomatic) and CD4< 20%(to be treated only if CD4 assay available)

- If virologic tests to confirm HIV infection status are not available but CD4 cell assays are available, WHO recommends that ARV therapy can be initiated in HIV-seropositive infants who have WHO stage II or III disease and CD4

percentage <20%. In such cases, HIV antibody testing must be repeated at age 18 months to definitively confirm that the child is HIV infected; only infants with confirmed infection should have ARV therapy continued.

(ii) For HIV seropositive children ≥ 18 months, WHO recommends initiation of ARV therapy if:

(a) WHO Paediatric stage III HIV disease(e.g. clinical AIDS) irrespective of CD4%

or

(b) WHO Paediatric Stage II disease with consideration of using CD4< 15% to assist in decision making

or

(c) WHO Paediatric stage I (e.g. asymptomatic) and CD4< 15%.

The following is generally recommended :

- First-line protocols for paediatric patients should mirror those of adults at all levels of care (Level I,II,III). This is currently difficult because of the lack of appropriate paediatric formulations, particularly for children under 10-15 kilos.
- To facilitate the use of currently available products, the producers and manufacturers need to develop dose ranges that are based on weight. WHO needs to also guide the paediatric attributes of ideal ARV therapy.
- The priority need is for the development of low dosage or breakable tablets. The dispersible preference should be to develop alternatives to existing individual liquid formations, which are considered too difficult to use (complexity of three different drugs, lack of adequate dose measurement, volume, storage, bad taste etc.), while powders are considered impractical (textures, lack of pure water)
- Preferred for infants are capsules with content that can be mixed with food, or FDC liquid formulations in small volumes and with weight based dispensers.
- The penetration of ARVs into human milk in lactating women has not been quantified for most of ARV. Although some ARVs, such as Nevirapine, are known to be present in breast milk, the concentration and the quantity of drug that would be ingested by the infant would be less than needed to achieve therapeutic levels. Thus if breast feeding infant is ill enough to require ARV treatment, ARVs

at standard paediatric doses should be initiated regardless of whether mother is receiving ARV therapy or not.

9.18 Criteria For ARV Treatment Of Infants And Children

The effectiveness of highly active antiretroviral therapy to reduce HIV-related morbidity and mortality in infants and children is similar to that observed in adults. However, treatment of HIV-infected children is more complex than in adults. Reasons include:

- Limited number of pediatric formulations of antiretrovirals
- Differences among individuals in their response to drugs, especially of protease inhibitors
- Adherence to combination therapy for many years is difficult
- Problems taking medication during sleep time or at school
- Unwillingness of young children and adolescents to take medication
- Poor palatability of medication
- Side effects of medication

Baseline viral loads in children are higher, which may be a barrier to reaching undetectable viral loads. In most paediatric studies virological response rates to HAART are inferior to those in adults. In studies of antiretroviral therapy in children, the best virological responses were seen in protease inhibitor containing regimes, which are normally unavailable in resource limited settings such as India.

The general principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons, there are unique considerations needed for HIV-infected infants and children. These include:

- Many perinatally infected children have exposure to zidovudine, nevirapine and other antiretroviral medications, which may result in the development of resistance

- Difficulties in the diagnosis of HIV infection in children <18months of age in resource limited settings

- Differences in immunologic markers in young children. CD% and not CD4 count is used to measure immune function

- Changes in drug pharmacokinetics with age caused by the continuing development and maturation of organ systems and changes in body weight

The Programme intends to offer ARV therapy to children who qualify based on diagnostic criteria listed below. Essentially, children that are HIV positive and have a CD4 count below a certain level (see details below) will be eligible for treatment. At the moment, there are limitations to the ARV drugs that are available for use in infants and children.

9.19 HIV testing in Infants and Children

Viral diagnostic assays

HIV infection can be definitively diagnosed in most infected infants by age 1 month and in virtually all infected infants by age 6 months by using viral diagnostic assays. (detection of HIV by culture or DNA or RNA polymerase chain reaction [PCR]). These assays may not be available in resource limited settings. HIV DNA PCR is the preferred virologic method for diagnosing HIV infection during infancy. Detection of plasma HIV RNA (viral load) is an alternative. WHO also recommends immune-complex dissociated p24 antigen as a second alternative. This test has a high false positive rate in infants under 4 weeks of age. If available, virologic testing should be performed before the infant is age 48 hours, at age 1–2 months, and at age 3–6 months.

HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virologic tests, two of which are performed at age >1 month, and one of those being performed at age > 4 months.

HIV Antibody Testing

In the absence of viral diagnostic assays, HIV antibody testing is used. However, the diagnosis of HIV infection in infants and children by HIV antibody testing is complicated by the persistence of maternal antibodies in children up to 18 months of age. Two or more negative HIV antibody tests performed at age 6 months with an interval of at least 1 month between the tests also can be used to reasonably exclude HIV infection among children with no clinical evidence of HIV infection. HIV infection can be definitively excluded if HIV antibody is negative at age 18 months. Breastfeeding infants are at risk of HIV infection during the period of breastfeeding and a negative virologic or antibody test during the breastfeeding period does not exclude the child becoming infected at a later time point.

A negative HIV test result at 6 months after discontinuation of breastfeeding rules out HIV infection. A persistent HIV positive test result after 18 months post delivery confirms HIV infection regardless of breast feeding.

9.20 Recommended First-line ARV Regimens in Infants and Children :

- In order to improve adherence, regimens chosen for children should be taken into account of those eventually used by the parents to avoid different timings, and if possible, permit the use of same drugs
- Drug doses must be adjusted as the child grows, or there is a risk of under dosage and development of resistance; therefore, dosing in children is based on either body surface area or weight
- Formulations appropriate for use by young children who cannot swallow whole tablets or capsule are not currently widely available in resource-limited settings
- WHO recognises that until formulations can be made widely available, the splitting of adult dose sold formulations ARVs, while suboptimal, may be the only

way a severely ill child can currently receive therapy, and should be considered when no other alternatives are available

- The preferred first line treatment option for children includes d4T or ZDV + 3TC plus an NNRTI (NVP or EFV) for the same rationale as discussed for adult initial ARV regimens. A caveat is that EFV cannot be used for children under 3 years due to lack of appropriate formulation and dosing information. Thus for children aged <3 years or weighing < 10 kg, NVP should be the NNRTI of choice.
- The use of ZDV + 3TC + ABC as the first line of therapy is now considered a secondary alternative
- For children < 3 years who require ARV therapy while receiving anti-TB therapy, use of ZDV+3TC+ABC should be considered, as SQV/r is not available in a formulation appropriate for children of this age
- Laboratory assessments in children on ARV therapy are the same as recommended in adults. In addition to the clinical assessments recommended in adults, clinical monitoring of ARV treatment in children should include:
    - Nutrition and Nutritional status
    - Weight and height growth
    - Developmental milestones
    - Neurological symptoms
- Because of age-related decline in CD4 absolute count through age 6 years, when nearly adult levels are reached, it is difficult to use CD4 cell count to assess failure of therapy in younger children. For children 6 years or more, similar CD4 count criteria as used in adult are appropriate.

9.21 Second-line ARV therapy for Infants and Children:

Second line therapy for children in the event of first line regimen failure would include change in nucleoside backbone based on the same principles as for adults(e.g., from ZDV+3TC to ABC + ddI) plus a protease inhibitor (LPV/r orNFV). TDF can not be recommended for paediatric treatment at the current time due to limited data on appropriate dosing in children, particularly children under age 8 years. However SQV/r can be considered in children who can swallow capsule and are > 25 kg weight and can therefore receive adult dose.

First Line Regimen	Second-Line Regimen
d4T or ZDV Plus 3TC plus NNRTI: NVP or EFV If age < 3 yrs or wt < 10 kg ---NVP If age > 3 yrs or wt > 10kg NVP or EFV	ABC Plus ddI Plus Protease Inhibtor LPV/r or NFV or SQV if weight > 25 kg

9.22 Dose of ARV drugs and dose frequency in Children

ARV Drugs	Age (Weight)	Dose	Frequency
1. Stavudine	< 30 kg 30 kg to 60 kg Maximum dose:>60kg	1 mg / kg / dose 30 mg /dose 40 mg/dose	Twice daily Twice daily Twice daily
2. Zidovudine	< 4 weeks 4 week - 13 yrs ≥ 13 yrs	4mg / kg / dose 180 mg/m2/dose maximum dose ≥13 yrs 300mg/dose	Twice daily Twice daily Twice daily
3. Lamivudine	< 30 days ≥ 30 days or < 60 kg	2 mg/kg/dose 4 mg/kg/dose Maximum dose: >60 kg: 150 mg/dose	Twice daily Twice daily Twice daily
4. Nevirapine	15-30 days	5mg/kg/dose 120 mg/m2/dose	Once daily for 2 weeks, then Twice daily for 2

		200mg/m2/dose	weeks, then Twice daily
5. Abacavir	Only prescribed to more than 3 months of age < 16 yrs or <37.5 kg weight: >16 years or> 37.5 kg:	 8mg/kg/dose Maximum dose 300 mg/dose	 Twice daily Twice daily
6. Efavirenz	Only for children over >3 years 10 to 15 kg: 15 to <20 kg: 20 to < 25 kg: 25 to < 33 kg: 33 to < 40 kg: ≥ 40 kg	 200 mg/dose 250 mg/dose 300 mg/dose 350 mg/dose 400 mg/dose Maximum dose: 600 mg/dose	 Once daily Once daily Once daily Once daily Once daily Once daily
7. Nelfinavir (NFV)	< 1 year: >1 yr. to 13 yrs. ≥ 13 yrs.	50 mg/kg/dose OR 75 mg/kg/dose 55 to 65 mg/kg/dose Maximum dose: 1250 mg/dose	Three times daily Twice daily Twice daily Twice daily
8.Lopinavir/retonavir (LPV/r)	6 months of age or older > 6 months to 13 yr: OR Weight based dosing:	 225 mg/m2 LPV/ 57.5 mg/m2 ritonavir/ dose	 Twice daily

	7-15 kg:	12 mg/kg LPV/3mg/kg ritonavir/dose	Twice daily
	15-40 kg	10mg/kg LPV/5mg/kg ritonavir/dose	Twice daily
	> 40 kg:	Maximum dose 400 mg LPV/100 mg ritonavir	Twice daily

No Paediatric formulations for fixed dose ARV drugs combination

9.23 Reasons for Changing ARV Therapy in Infants and Children

The management of drug toxicity and the principles on which to base changes in ARV for children are similar to those in adults.

Clinical failure

Clinical signs of drug failure in children include:

- lack of growth among children who show an initial response to treatment
- decline in growth among children who show an initial growth response to therapy
- a loss of neurodevelopmental milestones or the development of encephalopathy
- Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be distinguished from immune reconstitution syndrome, which can occur in the first 3 months following the initiation of ARV and does not signify treatment failure

- recurrence of infections, such as oral candidiasis that is refractory to treatment

Before an ARV regimen is thought be failing based on clinical criteria, the child should have had a reasonable trial on the therapy (e.g. have received the regimen for at least 24 weeks).

Immunological failure

Immunological failure is defined as a return in CD4 cell percentage (or for children >6 years of age, absolute CD4 cell count) to pre-therapy baseline or below, in absence of other concurrent infection to explain transient CD4 decrease or a >50% fall from peak level on therapy of CD4 cell percentage (or for children >6 years of age, absolute CD4 cell count), in absence of other concurrent infection to explain transient CD4 decrease.

9.24 Summary of pediatric drug formulations and doses

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
Nucleoside analogue reverse transcriptase inhibitors				
Zidovudine (ZDV)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	< 4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 yrs: 180 mg/m^2/dose twice daily Maximum dose: ≥13 yrs: 300 mg/dose twice daily	Large volume of syrup not well tolerated in older children, Syrup needs storage in glass jars and is light sensitive Can give with food Doses of 600 mg/m^2/dose per day required for HIV encephalopathy

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				Capsule can be opened and contents dispersed or tablet crushed and contents mixed with small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T (antagonistic antiretroviral effect)
Lamivudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages	< 30 days: 2 mg/kg/dose twice daily ≥30 days or < 60 kg: 4 mg/kg/dose twice daily Maximum dose: > 60 kg: 150 mg/dose twice daily	Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be crushed and contents mixed with small amount water or food and immediately taken
Fixed-dose combination of ZDV plus 3TC	No liquid available Tablet: 300	Adolescents and adults	Maximum dose: > 13 yrs or > 60 kg: 1 tablet/dose	Ideally, tablet should not be split Tablet can be

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
	mg ZDV plus 150 mg 3TC		twice daily (should not be given if <30 kg weight)	crushed and contents mixed with small amount of water or food and immediately taken At weight <30 kg, ZDV and 3TC cannot be dosed accurately in tablet form
Stavudine (d4T)	Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg/dose twice daily 30 to 60 kg: 30 mg/dose twice daily Maximum dose: > 60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles. Capsules can be opened up and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)
Fixed dose	No liquid	Adolescents and	Maximum dose:	Ideally, tablet should

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
combination of d4T plus 3TC	available Tablet: d4T 30 mg plus 3TC 150 mg; d4T 40 mg plus 3TC 150 mg	adults	30-60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	not be split See comments under individual drug components
Didanosine (ddI, dideoxyinosine)	Oral suspension pediatric powder/ water: 10 mg/ml. In many countries needs to be made up with additional antacid Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg Enteric-coated beadlets in capsules: 125 mg; 200 mg;	All ages	< 3 mos: 50mg/m2/dose twice daily 3 mos to < 13 yrs: 90-120 mg/m^2/dose twice daily or 240 mg/m^2/dose once daily Maximum dose: ≥13 yrs or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	Keeps suspension refrigerated; stable for 30 days; must shake well Administer on empty stomach, at least 30 minutes before or 2 hours after eating If tablets dispersed in water, at least 2 of appropriate strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
	250 mg; 400 mg			
Abacavir (ABC)	Oral solution: 20 mg/ml Tablet: 300 mg	Over age 3 months	< 16 years or < 37.5 kg: 8 mg/kg/dose twice daily Maximum dose: > 16 years or ≥37.5 kg: 300 mg/dose twice daily	Can give with food Tablet can be crushed and contents mixed with small amount water or food and immediately ingested MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
Fixed-dose combination of ZDV plus 3TC plus ABC	No liquid available Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg	Adolescents and adults	Maximum dose: > 40 kg: 1 tablet/dose twice daily	Ideally, tablet should not be split At weight <30 kg, ZDV/3TC/ABC cannot be dosed accurately in tablet form MUST WARN PARENTS ABOUT HYPERSENSITIVITY

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				REACTION ZDV/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs
Non-Nucleoside reverse transcriptase inhibitors				
Nevirapine (NVP)	Oral suspension: 10 mg/ml Tablet: 200 mg	All ages	15 to 30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m^2/dose twice daily x 2 weeks, then 200 mg/m^2/dose twice daily > 30 days to 13 yrs: 120 mg/m^2/dose once daily for 2 weeks, then 120-200 mg/m^2/dose twice daily Maximum dose: > 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200	If rifampicin co-administration, avoid use (see Tuberculosis section) Store suspension at room temperature; must shake well Can give with food Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with small amount of water or food and immediately administered MUST WARN PARENTS ABOUT RAS

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
			mg/dose twice daily	Do not dose escalate if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug) Drug interactions
Efavirenz (EFV)	Syrup: 30 mg/ml (note: syrup requires higher doses than capsules, see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 yrs	Capsule (liquid) dose for > 3 yrs: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily 15 to < 20 kg: 250 mg (300 mg = 10 ml) once daily 20 to < 25 kg: 300 mg (360 mg = 12 ml) once daily 25 to < 33 kg: 350 mg (450 mg = 15 ml) once daily	Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste Can give with food (but avoid after high fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
			33 to < 40 kg: 400 mg (510 mg = 17 ml) once daily Maximum dose: ≥40 kg: 600 mg once daily	effects Drug interactions
Fixed-dose combination of d4T plus 3TC plus NVP	No liquid available Tablet: 30 mg d4T/150 mg 3TC/200 mg NVP; 40 mg d4T/150 mg 3TC/200 mg NVP	Adults and adolescents	Maximum dose: 30-60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, tablet should not be split At weight <30 kg, d4T/3TC/NVP cannot be dosed accurately in tablet form; if tablets are split, NVP dose requirements will be inadequate for very young children and additional NVP is needed to give total of 200 mg/m^2/dose twice daily Since contains NVP, requires dose escalation (see NVP dosing recommendations) See comments under

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				individual drug components
Protease inhibitors				
Nelfinavir (NFV)	Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 ml scoop): 5 ml Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)	All ages However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants < 1 yr	< 1 yr: 50mg/kg/dose three times daily or 75mg/kg/dose twice daily > 1 yr to < 13 yrs: 55 to 65 mg/kg/ dose twice daily Maximum dose: ≥13 yrs: 1250 mg/dose twice daily	Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. – do not use acidic food or juice (increases bitter taste); solution stable for 6 hours Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given Powder and tablets can be stored at room temperature Take with food Drug interactions

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				(less than ritonavir-containing protease inhibitors)
Lopinavir/ritonavir, (LPV/r)	Oral solution: 80mg/ml lopinavir plus 20 mg/ml ritonavir Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir	6 mos of age or older	> 6 mos to 13 yrs: 225 mg/m2LPV/57.5 mg/m^2 ritonavir twice daily or weight-based dosing: 7-15 kg: 12mg/kg LPV/3 mg/kg ritonavir/dose twice daily 15-40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily Maximum dose: > 40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml) twice daily	Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25^0C (77^0F) for 2 months; at temperature >25^0C (77^0 F), drug degrades more rapidly Liquid formulation has low volume but bitter taste Capsules large Capsules should *not* be crushed or opened, but must be swallowed whole Should be taken with food Drug interactions

* Meter^2 body surface area calculation: square root of (height in centimeters times weight in kilograms divided by 3600)

10. Monitoring Antiretroviral Therapy

Once ART is started, a reasonable schedule for the clinical monitoring includes a first follow-up visit one month after initiation (which may be useful also to evaluate and possibly reinforce adherence to ART), and a minimum of every three/four months thereafter. Monthly visits, which can be combined with drug dispensing, are encouraged, as they are useful opportunities to reinforce adherence. At each visit, inquiries should be made regarding any new symptoms that may be related to drug side effects, to HIV disease progression or to intercurrent processes.

To promptly diagnose a new or a recurrent HIV-related opportunistic illness as well as drug-related side effects, it is advisable to regularly perform the history taking process regarding the period from the last clinical evaluation.

Questions to be asked during history taking

History taking	2 weeks	1 month	3 months	6 months	9 months	Every 3-6 months thereafter
HIV related diseases incl. TB			√	√	√	√
Cough > 2 weeks			√	√	√	√
Fever			√	√	√	√
Weight loss			√	√	√	√
Diarrhoea			√	√	√	√
Other symptoms as GI, CNS, neurology, skin			√	√	√	√

History taking	2 weeks	1 month	3 months	6 months	9 months	Every 3-6 months thereafter
rash						
Other medications taken			√	√	√	√

GI = gastrointestinal tract, CNS = central nervous system

10.2 Schedule for physical examination

Physical examination	1 month	3 months	6 months	9 months	Every 3-6 months thereafter
BW		√	√	√	√
ENT		√	√	√	√
Skin		√	√	√	√
Lymph nodes		√	√	√	√
Respiratory system		√	√	√	√
CVS		√	√	√	√
Abdomen		√	√	√	√
GU		√	√	√	√
Neurology		√	√	√	√

BW = body weight, , ENT = ear nose throat, CVS= cardiovascular system, GU = Genitourinary tract,

10.3 Laboratory investigations

Routine laboratory testing is sometimes necessary to monitor drug adverse effects, and appearance of new disease or progression of disease. Tests may include complete blood cell count (CBC), serum alanine transaminase (ALT) or aspartate transaminase (AST), serum creatinine, blood glucose, and serum lipids depending on the drug regimen and possible drug adverse effects. Those patients on the Primary first line regimen of d4T-3TC-NVP are unlikely to need many tests in the first year of treatment besides ALT or AST in case of suspected hepatitis due to NVP. At the time of follow up, history and physical examination may indicate other relevant tests.

In India monitoring of disease progression and response to treatment will be by clinical indicators and CD4 cell count where available. It may not be possible to perform viral load due to the cost of the test and lack of laboratory facilities and

trained personnel WHO recommendations for laboratory monitoring of ART in the resource limited settings of community and district hospital levels are detailed in the following table.

10.4 Basic laboratory monitoring for WHO recommended first-line ARV regimens at community health (Level 1) and district hospital (Level 2) centers

Regimen	Laboratory Assessment at Baseline (Pre-Therapy)	Laboratory Assessment on Therapy
d4T/3TC/NVP	Not required CD4 count desirable:	Symptom directed ALT for liver toxicity CD4 every 6-12 months if available for efficacy
ZDV/3TC/NVP	Haemoglobin recommended CBC and CD4 desirable	Symptom directed Hb, WBC, ALT for toxicity CD4 every 6-12 months if available for efficacy
d4T/3TC/EFV	Not required CD4 and pregnancy testing are desirable	Symptom directed testing but none routinely required for toxicity CD4 every 6-12 months if available for efficacy
ZDV/3TC/EFV	Haemoglobin recommended CBC, CD4, pregnancy testing desirable	Symptom directed Hb, WBC for toxicity CD4 q6-12 months if available for efficacy

11. DEFINITION OF TREATMENT FAILURE

Treatment failure can be defined as clinical failure, immunologic failure and/or virologic failure. Clinical failure is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration. This needs to be differentiated from an immune reconstitution syndrome which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline. Immune reconstitution syndrome is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent antiretroviral therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously sub-clinical opportunistic infection. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections. Recurrence of tuberculosis may not represent HIV disease progression as reinfection may occur. In immune reconstitution syndromes, changing the antiretroviral regimen is not indicated.

Immunologic failure can be defined as a return of CD4 cell to pre-therapy baseline or below without other concomitant infection to explain transient CD4 cell decrease or a greater than 50% fall from on therapy CD4 peak level without other concomitant infection to explain transient CD4 cell decrease.

Virologic failure has no uniformly accepted definition but repeated, continued detectable viremia is indicative of incomplete viral suppression. As measuring viral load is not an option in the majority of resource-constrained settings, it is not recommended for the routine monitoring of treatment in the present guidelines. The reader is referred to other existing guidelines for further reading on the use of viral load to monitor ARV treatment.

Treatment failure may occur due to a number of reasons. These include unsatisfactory patient adherence, viral resistance to one or more drugs, impaired drug absorption, and altered drug pharmacokinetics.

12. ART TREATMENT IN SPECIAL SITUATION:

12.1 Treatment of Opportunistic Illnesses

As ART in India has been introduced through the public health system, we find that the appropriate diagnosis and management of life threatening opportunistic infections (OIs) remains the most important aspect of the care of patients with HIV. OIs occur progressively as uncontrolled HIV replication destroys the immune system. The clinical manifestation of the OI is related to the severity of the immune depletion. Wherever there is poor adherence to ART, HIV becomes resistant, and this is leading to the return of opportunistic infections. Preventing the onset of OIs is the most cost effective approach in settings where ART is not widely available. It is however true that treating OIs in the absence of ART does very little to alter the course of the HIV disease, nor does it have any lasting impact on the underlying immune deficiency, which enables the OI to manifest.

Across India, Thailand, and much of Asia, TB accounts for nearly 50 per cent of OIs, and it is possible that TB contributes significantly to HIV mortality in India. Given that 60 per cent of all people in late stage of AIDS in India have TB, it must be assumed that at least 50 per cent of people living with HIV have latent TB. HIV infection per se increases the risk of latent TB becoming clinically active from a 10 per cent lifetime risk to a 10 per cent per year risk. Judicious use of chemo-prophylaxis treatment to prevent the development of clinical TB should be considered in HIV positive patients in many settings in India.

12.2 Managing HIV/TB Co-Infection

HIV/TB co-infection is one of the most challenging issues in the scale-up efforts since more than 25% of people living with HIV develop TB. Likewise, in some high-prevalence countries like South Africa, 55-60% of people with TB are HIV positive. Patients with TB merit special consideration because co-management of HIV and TB is complicated by rifampicin drug interactions with NNRTIs and PIs, pill burden, adherence and drug toxicity. Data to support specific treatment recommendations are incomplete and research is urgently needed in this area.

The management of patients with HIV and TB poses many challenges including patient acceptance of both diagnosis. Pending ongoing studies, WHO recommends that ART in patients with CD4 cell counts < 200 / mm^3 be started 2 weeks to 2 months after the start of TB therapy, when the patient has stabilized on TB therapy. This provisional recommendation is meant to encourage rapid initiation of therapy in patients who may have a high mortality rate. However, deferral of ARV initiation may be reasonable in a variety of clinical scenarios. For example, patients with higher CD4 cells may wait to start ART until after the induction of first phase of TB is completed in order to simplify management of their treatment.

ART Recommendations for Individuals with Tuberculosis disease and HIV coinfection

CD4 Cell Count	Recommended Regimen	Comments
CD4< 200 mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months) (1) EFV containing regimens (2,,3)	Recommended ART. EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception
CD4 between 200-350 mm^3	Start TB treatment. Start one of the below regimens after initiation phase (if severely compromised start earlier): EFV containing regimens (2)	Consider ART
CD4> 350 mm^3	Start TB treatment	Defer ART
CD4 not available	Start TB treatment	Consider ART (1,5)

[1] Timing of ART initiation should be up to clinical judgement based on other signs of immunodeficiency as per WHO guidelines. For extra pulmonary TB, ART should be started as soon as TB treatment is tolerated irrespective of CD4 cell count.

[2] Alternatives to the EFV portion of the regimen include SQV/r (400/400 mg bid or 1600/200 qd in sge), LPV/RTV (400/400 mg bid) and ABC (300 mg bid).

[3] EFV containing regimens include d4T/3TC/EFV or ZDV/3TC/EFV

[4] Unless non-TB stage IV conditions are present as per WHO guidelines. Otherwise start ART upon completion of TB treatment.

[5] If no other signs of immunodeficiency are present and patient is improving on TB treatment. ART should be started upon completion of TB treatment

Since TB may be masked in people with advanced HIV disease, new innovative tools that are more sensitive and specific are needed to support diagnosis, so that TB can be definitively diagnosed before ARVs are considered.

A number of service delivery strategies can be used for improving adherence to ARV treatment and safe behaviour. Experience from TB and Leprosy prevention and control programmes has shown that early community involvement is essential for good treatment outcomes. Much experience has been gained from the Revised National Tuberculosis Control Programme (RNTCP) in which the DOTS strategy is used for delivery of anti TB drugs. However, in RNTCP twice weekly regimen is provided and during first eight weeks patients are administered drugs in the presence of a DOTS providers. But in case of antiretroviral treatment the drugs have to be taken on daily basis and at least twice a day. It may, therefore not be possible to translate the DOTS strategy used in RNTCP for application in HIV treatment. New strategies and tools have to be developed to support treatment adherence and safe behaviour to prevent transmission of HIV.

Treatment education is an important component of this strategy. It is important that the patient on ART knows how drugs work in the body and why it is important to adhere to treatment regimes. It should be done in a setting where the person is morally supported to integrate this into his or her life.

12.3 ARV treatment for patients with coexistent Hepatitis

Co-infection with Hepatitis B and C is common in HIV + IDU. Alcoholic liver disease is also frequent. The resultant hepatic disease may increase the risk of liver toxicity and impair the metabolism of some anti-retroviral agents. The management of patients with chronic hepatitis B or C and HIV is evolving rapidly. Use of agents active against both HIV and Hepatitis B such as lamivudine (3TC) and tenofovir may be useful for patients with this coinfection. Despite the common association between hepatotoxicity and antiretroviral agents, about 90% of HIV+ patients, regardless of whether they are co-infected by hepatitis viruses, will tolerate ART treatment without severe liver toxicity.

Among the nucleoside analogues, hepatotoxicity has been more commonly reported with AZT, ddI or d4T in the form of liver enlargement, liver enzyme abnormalities and/or lactic acidosis. Abacavir or 3TC have also been involved but at a lesser degree. Among the non-nucleoside reverse transcriptase inhibitors (NNRTI) hepatic toxicity is frequent and severe with nevirapine. The protease inhibitors are often associated with mild hepatotoxicity. Ritonavir, especially if administered at full doses as a single PI is significantly more hepatotoxic than the others. Unlike the hepatotoxicity associated with NNRTIs which turns up during the first weeks of therapy in most cases, that associated with PIs can appear at any time during the treatment.

In managing these patients it is helpful to classify them according to the degree of liver damage. In chronic hepatitis without signs of hepatocellular insufficiency the usual ART doses are used but there may be a greater risk of hepatic toxicity. Nucleoside analogues and efavirenz appear better tolerated than nevirapine or PIs.

In patients with cirrhosis or severe hepatic insufficiency impaired hepatic metabolism may increase the risk of lactic acidosis with nucleosides but dose reduction is only advised for zidovudine. Efavirenz can be administered at full doses in patients with liver insufficiency but nevirapine should be avoided if possible. PI dosing is difficult in patients with decompensated liver disease. If drug level monitoring is available this is helpful for adjusting doses but usually a trial and error approach is the only option.

12.4 ARV therapy for Women, with specific reference to pregnancy

ART recommendations for HIV-infected pregnant women are based upon the principle that therapies of known benefit to women should not be withheld during pregnancy unless the risk of adverse effects on the mother, foetus or infant outweighs the expected benefit to the woman. Pregnancy, or the desire to become

pregnant, should not preclude the use of optimal antiretroviral therapy. However, considerations related to pregnancy may affect decisions regarding the choice of antiretroviral regimen. Additionally, the potential impact of such therapy on the foetus and infant must also be considered when treating women of childbearing age, unless they use effective contraceptives. For pregnant women who do not yet need ART for their own HIV disease, the use of antiretroviral drugs to reduce the risk of mother-to-child HIV transmission is recommended.

12.5 Choice of antiretroviral drugs in non-pregnant women of childbearing age

In non-pregnant women, the recommendations for starting antiretroviral therapy are similar for men and women.

The choice of ART in women with the potential to become pregnant must include consideration of the possibility that the ARV drugs may be received during the early first trimester, prior to recognition of pregnancy and during the primary period of foetal organ development. Effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy should be available for women receiving ART. NNRTIs (NVP and EFV) and the PIs (NFV and all low dose RTV-boosted PIs) lower blood concentrations of oral contraceptives and additional or alternative contraception methods need to be used to avoid pregnancy in women receiving these drugs. EFV may be associated with severe birth defects and should be avoided in women who desire to become pregnant.

12.6 Choice of antiretroviral drugs in pregnancy

ARV regimens given for treatment to pregnant women should preferably include drugs shown to be effective in reducing mother-to-child transmission. Drugs shown to be effective in reducing transmission include ZDV, ZDV/3TC, and NVP. The most successful experience in terms of efficacy and maternal and foetal safety is with ZDV; thus, first-line treatment regimens in pregnant women should include ZDV whenever possible. Combination of ZDC/3TC should be the first choice for use in pregnancy. Maternal antiretroviral drugs should be continued during the period of

labor.

Pharmacokinetic studies of ZDV, 3TC, d4T, and ddI in pregnant women indicate that the dose used for these drugs in pregnancy should be the same as in non-pregnant individuals. ABC has not been formally evaluated in pregnant women. The dual NsRTI combination of d4T/ddI should not be used pregnancy when due to the increased risk of acute lactic acidosis and death with this combination in pregnant women.

NVP is the NNRTI of choice for use in pregnancy. EFV should be avoided in pregnancy due to its teratogenic effects.

PIs are associated with the development of glucose intolerance and diabetes mellitus. Pregnancy is also a risk factor for hyperglycemia; it is not known if the use of protease inhibitors exacerbates the risk for pregnancy-associated hyperglycemia. Hyperglycemia in pregnancy can lead to an increased risk of macrosomia, foetal distress, pre-eclampsia and stillbirth. Symptoms of hyperglycemia (e.g., increased urination and thirst, weight loss) should be discussed with pregnant women receiving protease inhibitors and they should be instructed that should such symptoms occur, they should see their health care provider.

NFV, followed by SQV, are the most common protease inhibitors used to treat pregnant HIV-infected women in resource-rich countries. NFV has been well-tolerated by pregnant women; when administered as 1250 mg twice daily it produces adequate drug levels, and is the first choice PI for use during pregnancy. IDV carries the theoretical risk of exacerbating neonatal hyperbilirubinemia if used near to or during labor, and therefore is a less desirable PI choice in pregnancy. LPV/r has not been studied in pregnant women.

12.7 Women first diagnosed with HIV infection during pregnancy

Women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10-12 weeks gestation due to potential teratogenic effects of ART. However, the goal of ART in pregnancy is the maintenance of maternal health and this is the basis for the decision to initiated ART any time during

pregnancy. The guidelines for initiating ART in pregnant women are the same as for non-pregnant women and for men. The choice of drugs is described above.

HIV-infected women receiving antiretroviral drugs who become pregnant

For women who become pregnant while receiving ART, the options are to temporarily discontinue therapy during early pregnancy (first trimester), to continue the same therapy, or change to a different drug regimen.

A switch in ART during pregnancy should be considered if the drug being received has teratogenic potential (i.e., EFV); if there are concerns regarding risk of severe toxicity to the pregnant woman (e.g., d4T/ddI); or there is significant intolerance of the drug that could be compounded by pregnancy (e.g., gastrointestinal intolerance compounded by morning sickness) and lead to poor drug adherence.

12.8 Breastfeeding

Current WHO/UNAIDS/UNICEF guidelines recommend that women with HIV infection be fully informed of both the risks and benefits of breastfeeding and be supported in their decision about feeding practices.

HIV-infected women should preferably avoid breastfeeding to reduce the risk of mother-to-child transmission where safe alternatives are available, affordable and acceptable.

However, safe alternatives to breastfeeding may not be available in some resource-limited settings, and in such situations, exclusive breastfeeding for the first 6 months of life is recommended.

Women who require ART and who are breastfeeding should continue their ongoing antiretroviral therapeutic regimen. However, the efficacy of potent ART of the mother to prevent postnatal transmission of HIV through breast milk is unknown.

HIV-infected women who have received short-course antiretroviral prophylaxis to reduce mother-to-child transmission and require treatment postpartum

Short-course ARV drug regimens that do not fully suppress viral replication that are used to prevent MTCT of HIV may be associated with the development of antiretroviral drug resistance. This is most likely to occur with prophylaxis regimens using antiretroviral drugs for which a single point mutation can confer drug resistance, such as NVP or 3TC. This concern will need validation by further studies.

Issues related to adherence to therapy in pregnancy and postpartum

Adherence to treatment may be more difficult in pregnant and immediately postpartum women than in non-pregnant individuals. Potential obstacles to adherence that are unique to pregnancy include morning sickness and gastrointestinal upset, which can be further compounded by ART associated nausea, and fears that antiretroviral drugs might harm the foetus. To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and re-started simultaneously.

The physical changes of the postpartum period coupled with the stresses and demands of caring for a newborn infant may make adherence to treatment especially difficult after birth. Particular attention to provision of additional support for maintaining adherence to therapy during the ante- and post-partum periods is important.

12.9 Injection Drug Users

Special considerations for this population include dealing prospectively with life style instability which challenges drug adherence and accounting for the potential drug interactions of ARV's with agents such as methadone. Development of programmes which integrate care of drug dependence and HIV is encouraged. In such settings, approaches such as directly observed therapy can be implemented. Once daily ARV

regimens are being intensively explored in this arena and lend themselves to such approaches however many are very expensive or not available in India.

The number of ARVs which are approved internationally or being investigated for once daily use is progressively expanding and includes 3TC, FTC, ddI, d4T, TDF, ABC, EFV, SQV/r, LPV/r and ATV. In addition, once a day fixed dose combinations of FTC-TDF-EFV are currently undergoing FDA review. If approved for use, such FDCs could make once a day DOT even more feasible in this setting.

In India, the combination of once a day ddI EC 250 mg* + 3TC 300 mg*+ EFV 600 mg (for people weighing less than 60 kg, and ddI EC 400 mg* + 3TC 300 mg* + EFV 600 mg for people with weight above 60 kg) is available locally. This combination may be useful in situations where directly observed therapy is needed in order to ensure adherence to treatment.

A number of different models are currently employed to provide primary medical care for HIV patients who are in addiction treatment. One model is to provide medical care by referral of patients to a nearby HIV clinic. This approach may be most effective for patients who are stable, but it may be less appropriate for more complex patients, such as those actively using drugs, who may have minimal or strained relationships with health care providers. Also, IDUs often require ongoing adjunctive care for coexisting psychiatric problems. Untreated behavioral problems can interfere with medical care. Drug users may have difficulty keeping appointments, and may be fearful of or ambivalent about medical care. Medical staff in HIV or primary care clinics may not be fully trained to manage the psychiatric and substance use problems that can interfere with adherence to medical care. If the medical clinic is conveniently and closely situated, however, the referral model can work effectively.

A second model of primary medical care for HIV-infected drug users consists of establishing a substance abuse treatment component at an AIDS clinic. This model would allow HIV-infected IDUs to obtain substitution therapy (methadone or buprenorphine) and other treatment for substance use disorders on-site in a primary care HIV medical clinic. One limitation of this model in many countries, however, is the difficulty of responding to the regulatory requirements for methadone treatment.

A third model is to provide on-site primary medical care for IDUs in an addiction treatment facility, such as a methadone maintenance treatment program. The methadone treatment setting is efficient for providing medical services in a "one-stop shopping" approach. Referral of patients to off-site primary care clinics can sometimes result in patients failing to reach medical care. Continued primary medical care for IDUs with HIV infection is critical. National plans in countries with substantial numbers of IDUs should incorporate all 3 approaches if appropriate and attempt to evaluate and compare them.

A major challenge in delivering care to HIV-infected IDUs is their need for multiple services simultaneously. Successful programs delivering medical care (including HIV/AIDS-care) to active ID-users have identified certain important principles:

- Care must be accessible. The services should be located in places that are accessible by the client and situated in facilities that are part of the general healthcare infrastructure.

- Care should be comprehensive. The maximum possible number of the most-needed services should be available at one location. Necessary services such as gynecology and family planning are most efficiently delivered if they can be accessed at the same site as HIV care. Social services, counseling and education should be integrated in the medical care setting. Substance abuse or psychiatric services may be vital ingredients in a successful management plan for many IDUs and should be accessible from the primary HIV care setting.

- Care should be offered to patients at any level they are able to utilize. Injection drug users newly diagnosed with HIV are sometimes difficult to engage in comprehensive care. Feelings of denial, anger and guilt may overwhelm them. It is important to offer care at whatever level of intensity the patient can handle so as not to drive him or her away entirely. This may mean starting with very simple interventions like opportunistic infection prophylaxis and advancing to more complex care including anti-retroviral therapy later. Education and counseling, especially utilizing peer group members can be very helpful in drawing such patients into comprehensive care.

- Outreach strategies are vital. Successful treatment programs for stigmatized diseases like HIV/AIDS especially in marginalized groups like IDU have developed effective outreach strategies to bring potential patients into the treatment system and to retain patients in care. The most effective programs have formed strong links with community-based organizations representing or serving the affected groups and have utilized peer educators and counselors drawn from these groups.

- Methadone Maintenance as part of HIV/AIDS -service structure. Where substitution therapy is available or contemplated consideration should be given to offering HIV care and dispensing HIV medication at the same site where substitution therapy is delivered. This approach can achieve maximal levels of treatment supervision which should enhance efficacy and reduce the risk of HIV drug resistance. In addition co-location of these services facilitates management of the important drug-drug interactions between methadone and HIV medications . A multidisciplinary team should be established to provide care and treatment to the HIV+ IDU. Members should include the clinician (physician or other practitioner), social worker and counseling staff at a minimum. The team should meet on a regular basis to review the status of patients in the treatment program.

12.10 Choosing an ART treatment regimen for Injecting Drug Users.

There are widely held opinions that injection drug users are poor candidates for anti-retroviral therapy (ART). This is usually based on the perception that drug using behavior will prevent adherence to the treatment regimen or that the medical complications of drug use such as Hepatitis C infection will make drug users intolerant to ART. Although these limitations are indeed a problem for many patients, extensive experience and numerous publications have documented that individualized HIV care for injection drug users is often highly successful. The key to effective treatment is careful assessment and education of the patient leading to development of an individualized treatment plan to maximize adherence. Some authorities have taken the position that injection drug users must demonstrate prolonged abstinence before they should begin ART. This approach is unnecessary and has adverse effects on the credibility of the treatment program. While abstinence is desirable for several reasons it is often impossible to achieve especially in the setting of a recently-diagnosed life-threatening illness. Although abstinence should be encouraged, health care workers as well as drug users must understand that a harm-reduction approach to both substance abuse and to ART can be very successful. If drug users are able to keep medical care appointments and adhere to a schedule for taking medications they are likely to have a successful response to ART even though not fully abstinent. In a non-judgmental care environment any relapse or ongoing substance abuse can be addressed as a problem needing additional attention rather than as a moral failing which jeopardizes care entirely.

Other considerations in choosing regimens for drug users include the following:

Active hepatitis may be exacerbated more by nevirapine than other agents; efavirenz may precipitate psychiatric decompensation in individuals with prior psychotic disorders. In alcohol abusers the potential for pancreatitis with ddI or peripheral neuropathy with d4t may be increased.

National programs will need to base procurement largely on cost so that access is maximized. The regimen widely recommended for developing country programs (D4t, 3TC and nevirapine) is an acceptable one. However, flexibility may be needed in order to ensure effective care of IDU. For example, a once daily regimen utilizing efavirenz may offset its greater cost with the benefit of once daily

DOT dosing. Similarly some patients intolerant of nevirapine due to liver disease may require EFV or protease inhibitor therapy.

12.11 Medication Dispensing

Special attention should be paid to the process of dispensing antiretroviral therapy. Ongoing supervision of medication dispensing is an excellent way to detect adherence problems. If possible, medication should be dispensed at the site of overall patient care allowing care providers maximum information about treatment problems. If not feasible, careful communication strategies need to be in place so that information about patients who are late or fail to pick up medications or report problems to the pharmacist can be quickly accessed by the care team.

As a rule, small amounts of medicine should be dispensed at frequent intervals when a patient begins treatment. This approach has two benefits: Frequent visits to pick up medication provide an opportunity to detect and address adherence problems before they lead to drug resistance; and if there are disruptions in treatment the amount of medication available to be misused by the patient is limited which therefore also reduces the potential for resistance to develop. As patients become stabilized on care, medication dispensing intervals can be lengthened. Conversely, stable patients whose behavior becomes erratic can be returned to a more frequent pick up schedule so that maximum supervision and support is provided.

While true DOT is desirable for some patients it is usually impractical. It may become more feasible with once daily regimens. Substance abuse treatment facilities are strategically appealing sites for trials of this approach. Existing harm reduction programs should be evaluated for the possibility of integrating DOT strategies at needle-exchange points and other outreach sites.

12.12 Medication dose adjustments for patients on methadone

Methadone is extensively metabolized by cytochrome enzymes, and the methadone level may decrease when methadone is used together with cytochrome inducers

such as carbamazepine and rifampin -- necessitating higher doses. Coadministration of methadone with EFV or NVP in HIV infected individuals with a history of IDU also resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. Conversely, methadone levels could be raised by cytochrome inhibitors. In turn, methadone inhibits the metabolism of zidovudine (AZT) and can elevate AZT levels.

It is essential to note that additional analgesics are needed to treat acute or chronic pain in the HIV-infected drug user who is on methadone maintenance treatment, because patients do not obtain adequate pain relief from their usual daily dose of methadone, to which they have become tolerant.

Pharmacologic interactions may produce either changes in methadone concentrations, or changes in concentrations of the antiretroviral agents being used. Studies suggest that nevirapine, efavirenz, and ritonavir decrease methadone concentrations through induction of the cytochrome P450 system (principally CYP 3A4), and produce clinically significant opiate withdrawal in some patients. Signs and symptoms of methadone withdrawal typically occur 4-8 days after starting a new drug and include chills, sweating, piloerection, nausea, diarrhea, abdominal cramping, rhinorrhea and lacrimation, myalgias, tremulousness, and anxiety. Precipitating opiate withdrawal may trigger relapse of heroin use, distrust of medical providers, and unwillingness to take antiretroviral therapy. Frequent, open communication between HIV provider, patient, and methadone maintenance staff is prudent when new antiretroviral therapy is initiated. But usually an immediate and a substantial increase in methadone dose is not appropriate because the increase in methadone dose required is not as great as might be expected from the pharmacokinetic data. Medical assessments should be done frequently for such patients to monitor withdrawal symptoms, increasing methadone dose in increments of 10mgs from day 8-10 onwards.

Alterations in antiretroviral concentrations, especially NRTIs, may result when administered with methadone. At present 2 potentially relevant interactions have been described. First, zidovudine concentrations are increased approximately 40% when administered with methadone. No empiric dose reduction is currently

recommended, but signs of zidovudine toxicity should be closely monitored. Second, didanosine concentrations have been found to be reduced approximately 60% when administered with methadone. This may lead to didanosine underexposure, incomplete viral suppression, and the development of resistance. Of note, these pharmacologic data are based on the buffered-tablet formulation of didanosine, given twice daily. There are no data on the powder or enteric-coated capsule formulations. Until more information is available, use of the buffered tablet didanosine formulations in methadone recipients should be avoided if other options exist.

12. 13 Interactions Between Antiretrovirals and Methadone

ANTIRETROVIRAL AGENT	EFFECT ON METHADONE	EFFECT ON ANTIRETROVIRAL AGENT	COMMENT
NRTIs			
Zidovudine (AZT)	None	↑AUC* by 40%	Watch for nausea, vomiting, asthenia, headache, and bone marrow suppression in recipients. If methadone trough levels are normal, suspect that problem is zidovudine toxicity rather than methadone withdrawal.
Didanosine (ddI)	None	↓AUC by 60%	This has only been studied with twice-daily administration of the buffered tablets and was hypothesized to be due to reduced bioavailability of didanosine in the setting of slower transit through the acidic environment of the stomach in patients taking methadone. Additionally, there was great interindividual variability in didanosine pharmacokinetic data. The effects of methadone on didanosine powder or enteric-coated tablet formulations are unknown.
Zalcitabine (ddC)	Unknown	Unknown	
Stavudine (d4T)	None	↓AUC by 18%	Decreased stavudine concentrations probably not clinically significant.
Lamivudine (3TC)	None	None	No known interactions.
Abacavir (ABC)	↑clearance by 23%	↓peak by 34% ↑time to peak	Data sparse, risk of opiate withdrawal low.
NNRTIs			
Nevirapine (NVP)	↓AUC 46%, withdrawal reported	Unknown	In a case series of chronic methadone recipients initiating nevirapine, 50%-100% increases in the daily methadone doses were required to treat opiate withdrawal. Withdrawal symptoms generally occurred between 4 and 8 days after starting nevirapine.
Efavirenz (EFV)	↓levels	Unknown	See nevirapine.
Protease Inhibitors			
Indinavir	None	None	Studies limited, but no reported interactions.

(IDV)			
Ritonavir (r)	↓levels 35%-50%	None	Studies limited. Observe closely for signs of methadone withdrawal.
Saquinavir (SQV)	None	None	Studies limited, but no reported interactions.
Nelfinavir (NFV)	↓levels 29%-47%	None reported	Clinical withdrawal was not reported in studies in which decreased methadone concentrations were reported.
Amprenavir (APV)	Unknown	Unknown	
Lopinavir/ritonavir (LPV/r)	Unknown	Unknown	Methadone withdrawal possible from low-dose ritonavir.

13 ADHERENCE TO ART

Structured HIV management conducted by trained and committed health care workers, together with informed patients results in improved adherence to ART. This can lead to:

- *delayed onset of viral resistance*
- *delayed virological failure*
- *delayed treatment failure*
- *improved quality & length of life*

A large number of ART related adverse effects have a direct or indirect impact on treatment outcomes. Differences in diet, environment and physiology are important factors. The population level occurrence of ART related adverse effects should be monitored in new populations taking ART. At any rate, the occurrence of adverse effects in individuals needs to be anticipated and planned for. Patients taking ART should be counseled in advance about these effects so that their occurrence is not totally unexpected.

13.1 Guidelines For Treatment Adherence

Studies of drug adherence in the developed World have suggested that higher levels of drug adherence are associated with improved virological and clinical outcomes and that rates 95% are desirable to maximise the benefits of ART. It is a challenge to achieve rates this high over a long period of time. Interventions that improve treatment adherence and safe behaviour are:

(i) The decision to enroll a patient into the ART programme should be based on the patient's medical and psycho-social parameters. The decision should be taken in a team approach involving among others, doctors and counselors / psychologists

(ii) Education and counseling: Once the person is enrolled in the ART programme, the physician and health workers (counselor) should educate the persons about the possible side effects of drugs, follow-up dates and importance of adherence to ARV treatment and consequences of non-adherence. During every follow-up visit to

ART clinic, the patient should also be asked to bring drugs along with him so that the pills can be counted in order to assess the level of adherence. Linkages should be developed with the existing VCCTC for back-up support.

(iii) ART clinic counselors should maintain a register of all visits. During every visit the patient should be counseled on adherence of ARV treatment and in case of any side effects of drugs the patients should be referred to treating physician. Counselors should be part of the training programme on ARV treatment and they should be trained properly in monitoring of adherence to ARV treatment. Counselor should also emphasize that ART is merely a treatment and not a cure and the need to practice safe sexual behaviour, with consistent condom use. It might be useful to ensure condom availability during every visit of the HIV/AIDS patients on ARV treatment.

(iv) Participation of Family Members / guardian: Patient should be motivated to bring a family member or guardian along at the time of commencing ARV treatment. The guardian should be educated about the illness and the need for lifelong treatment and adherence to drugs. They should be encouraged to accompany patients on the follow-up visit, if possible. All efforts should be made to encourage guardian supported ARV treatment so that the adherence of therapy could be ensured.

(v) Reminders in case of drop out: In case the patient does not visit the ARV treatment unit on the scheduled fixed date, NGOs/Networks of PLHAs should be involved to contact the patient or guardian in a confidential manner to mobilize the patient to continue treatment. The role of communities and NGOs in mobilizing communities to support adherence is extremely important. Maintaining confidentiality and privacy are of utmost importance.

(vi) Involvement of Primary Health Care Systems: A patient residing in a rural area would find it difficult to re-visit the district hospital for follow-up. Efficient linkages between the district hospital providing antiretroviral treatment and the relevant PHCs/CHCs of the district, should be developed. The MOs and Pharmacists of PHCs and CHCs should be trained in delivery of ARV treatment to HIV/AIDS patients.

(vii) Depending upon the patients attached to a PHC/CHC, ARV drugs should be made available by the district hospital. However, patient should be referred from PHC/CHC to district hospital once in six months for laboratory investigations and opinion of the treating physician.

(viii) Treatment adherence may be more difficult in pregnant women and in immediate post partum period. Pregnancy associated morning sickness and gastro-intestinal upset may complicate ART and this may be further complicated by side effects associated with ARV drugs. In the post partum period, physical changes and the demands from the newborn may compromise maternal drug adherence. Family support would be essential for ensuring adherence to ARV treatment. Maternal child health staff, traditional birth attendants, Auxiliary Nurse Midwife or Anganwari Workers (ICDS) may be of great help in achieving treatment adherence. The patient should have the choice of linkage to Community based workers. They should be adequately trained in various aspects of HIV/AIDS particularly issues of confidentiality, dosage, schedule of ARV drugs, side effects and referrals etc.

(ix) Treatment adherence in children is a special challenge, particularly if family unit is disrupted by health or economic conditions. Family based HIV care programmes are one of the best approaches to ensure that the health of the children is looked after. As currently, pediatric formulations are not widely available for all ARV drugs, WHO recognizes that until appropriate formulations can be made more widely available, the splitting of adult dose formulation of ARV drugs, should be considered. Health care providers need to be aware that current fixed dose combination formulations may not contain the appropriate doses of each of the component drugs for children on a weight basis. The Paediatrician should educate the family member(s) accompanying the child about the correct dosage of drugs and frequency at which it should be given. Health care providers should be adequately trained about the importance of adherence to ARV treatment.

Key to successful adherence strategies is the proper education of the patient before the initiation of therapy, support ARV initiation as patient first starts medications' and continuously monitor and support adherence. Reinforcement of adherence principles to

the patient by treatment supporters (guardian), relatives, friends and community support personnel is of great help. A checklist is provided below for the use of health care providers on ARV therapy, adherence, support and monitoring.

13.2 Prepare for ARV therapy

(i) Assess

i. Patient's goals for today's visit
ii. Understanding of ARV therapy
iii. Interest in receiving therapy

(ii) Advise on

i. HIV illness, expected progression
ii. ARV therapy
    a. Benefits -lifesaving drugs
    b. Very strong medicines
    c. The treatment does not cure HIV
    d. The treatment does not prevent HIV transmission to others
iii. Need for complete adherence to daily treatment
iv. Must be taken twice daily, without interruption
v. Must be taken at right time, every 12 hours
vi. If stopped, then will become ill
vii. Possibility of side effects and drug interactions
viii. Importance of disclosure of HIV status
ix. Importance of testing partner and children
x. Drugs must not be shared with family or friends - patient must take full dose

(iii) Agree

i. Establish that the patient is willing and motivated and agrees to treatment, before initiating ARV therapy
    a. Has the patient demonstrated ability to keep appointments, to adhere to other medications?
    b. Has the patient disclosed his or her HIV status? If not, encourage him or her to do so.

c. Does the patient want treatment and understand what treatment is?
d. Is the patient willing to come for the required clinic follow-up?
e. Patient can identify a treatment guardian

(iv) Assist

i. Help the patient develop the resources/support/arrangements needed for adherence:
   a. Ability to come for required schedule of follow up. Discuss how patient will do this
   b. A reasonable food supply
   c. Home and work situation that permits taking medications every 12 hours without stigma
   d. Regular supply of free or affordable medications
   e. Supportive family or friends / Guardian
   f. ARV adherence support group
   g. Treatment supporter

(v) Arrange

i. When patient is ready for ARV therapy, discuss at clinical team meeting then make plan

13.3 Support ARV initiation

(i) Assess

i. Patient's goals for today's visit
ii. Check understanding of the information given before - make sure the patient understands the illness, treatment and possible side effects

(ii) Advise on

i. Reinforce the information given below
ii. Advise on details of first line regimen:
   a. Explain the purpose of and how to take each pill. Provide and explain card summarizing treatment

iii. Make sure patient understands the importance of adherence
iv. Advise on diet
v. Explain limits on alcohol and drug use
vi. Explain the side effects
    a. Prepare patient and treatment supporter to handle common side effects.
    b. Explain which side effects are likely to be transitory
    c. Explain which are more serious and require return to clinic
vii. Explain that patient can still transmit HIV infection when on ARV therapy. It is very important to still practice safer sex and other practices to prevent transmission

(iii) Agree

i. Make sure the patient agrees to the regimen and is a true partner in the treatment plan
ii. Make sure patient understands that his/her life depends on taking the medicine every day
iii. Agree on plan for support by treatment buddy and support groups

(iv) Assist

i. Develop a concrete plan for the specific ARV regimen
    a. When to take/times for every 12 hour dosing / how to make it a habit
    b. How to remember - provide and explain written schedule, pillbox, pill chart , other aids
ii. Prepare patient and treatment supporter for adherence, possible common side effects, what to do if they occur, and when to seek care
iii. Provide psychosocial support
iv. Encourage patient to join ARV adherence support group
v. Arrange home visits, if feasible

(v) Arrange

i. Next follow-up visit in clinic, home visit if feasible, and next visit with district clinician
ii. Agree on best way to access help between visits
iii. Make sure patient understands where/when/ s/he will see health worker

13.4 Monitor and support adherence

(i) Assess

Do clinical review and respond to any problems or changes in status.

To assess adherence:

- Review the medications with the patient and their treatment supporter
- Ask questions in a respectful and non-judgemental way.
- Ask about the common and locally important factors that may interfere with adherence
- Ask about stigma related to taking the pills
- Count pills
- How many pills forgotten yesterday, last 3 days, last month?

If poor adherence (less than 95%) : Determine what the problem is:

- Simply forgot?
- Which dose missed: morning or evening
- Misunderstood?
- Not comfortable taking medication around others
- Stigma
- Different timing: holiday, travel, weekend
- Seldom at home and disorganised
- Problems with diet
- Another medical problem
- Screen for excess alcohol use and depression and treat, if present
- Ran out of pills
- Cost

- Reminds you of HIV
- Changed work situation

(ii) Advise

i. Reinforce the information given before
ii. Give additional information that may help with adherence problem
iii. Advise on any suggested changes in the regimen

(iii) Agree

i. Agree on any changes in Treatment Plan and solutions to adherence problems
ii. Discuss the agreements you have reached and check for their commitment

(iv) Assist

i. Provide adherence support
ii. Reinforce interventions which match the patient's needs and adherence problems
iii. Make sure the patient has any device or skills
iv. Make sure patient has the support he or she needs
v. If adherence a problem:
    a. Gentle help! Call for advice or refer back sooner but do not "just refer"
    b. Seek help from district clinic adherence staff if regimen is too complicated or not tolerated or low adherence

(v) Arrange

i. Record adherence estimate on patient's card
ii. Arrange for refills
iii. Arrange for next follow-up visits:
    a. In clinics
    b. Home visits
iv. Make sure that the patient and guardian understand the follow-up plan and how to contact the clinic team if there is a problem

14. CRITICAL CHALLENGES

It is important to articulate precisely what are the roles, tasks and expectations and at which level for delivering care, prevention and treatment.

1) HIV prevention, HIV care and HIV treatment need to be considered as a single comprehensive strategy with complementary and mutually reinforcing activities.
2) the continuum of care must ensure sustainability and referrals.
3) Existing capacity within the primary health care system must be strengthened to carry on the work. New capacity must be developed to reinforce existing infrastructure for providing structured ART. Capacity strengthening will focus on diagnostic facilities, equipment and infrastructure as well as on developing trained health care providers.
4) Sustained national leadership must ensure that the ART programme for ART will continue. Availability of ART should ensure significant reduction of stigma and discrimination. This will improve access to diagnosis and treatment and accelerate prevention.
5) Involvement of PLHAs for care support and treatment: PLHAs will be excellent allies in the effective monitoring of treatment adherence to ART to prevent the development of treatment failure and drug resistance.
6) Intensive counseling of patients must focus on adherence as a tool for avoiding treatment failure and containing drug resistance. Prevention support must increase with ART. We need to anticipate correctly the needs of increasing numbers of people living with HIV. Community based care for sick individuals and community support for impacted families must be developed.

The challenges in the provision and scaling up access to antiretroviral (ARV) treatment that needs to be addressed are:

14.1 Strategic framework for scaling up ART

Goal: Prolong survival and restore quality of life for individuals with HIV/AIDS by providing universal access to antiretroviral therapy (ART) as a human right, within the context of a comprehensive response to HIV/AIDS

Objective: To scale up ART within the context of a comprehensive response to HIV/AIDS in India. The initiative aims to decrease the morbidity and mortality, by making ART available and accessible and strengthen the existing local health care delivery system (trained manpower and infrastructure). It is hoped that this Initiative is the first step towards greater access to HIV care in resource-limited settings.

Target: To place 100,000 people living with HIV/AIDS on structured ART by the end of 2007 and be able to provide treatment to additional of 15-20% of people living with HIV/AIDS each year, thereafter, for a period of five years.

Entry Points for ART Delivery

- PPTCT
- VCCTC
- TB DOTS centers
- STD clinics
- Blood banks
- Government Hospitals especially the district hospitals
- Networks of people living with HIV

14.2 Core strategy elements:

a) Mobilizing political and bureaucratic leadership commitment
b) Resource mobilization
c) Strengthen capacity of health system for ARV delivery
d) Ensuring uninterrupted supply of antiretroviral drugs and diagnostics
e) Ensuring treatment adherence and community participation
f) Monitoring, evaluation, surveillance and research
g) Developing communication strategies for enhancing community participation and support

15. INVOLVING AND MOBILISING STAKEHOLDERS

Involving and mobilising stakeholders should happen at all levels i.e. central, state and implementation levels. By developing formal and informal linkages and partnerships,

the success of an ARV treatment programme can be maximised. Different types of stake holder who may be involved are:

(i) Networks of People living with HIV/AIDS
(ii) Health care workers
(ii) Non governmental Organisations (NGOs)
(iii) Community based Organisations (CBOs)
(iv) Faith based Organisations (FBOs)
(v) Medical Associations
(vi) Panchayat Raj Institutions (PRIs)
(vii) Private sector through CII and FICCI
(viii) Private Practitioners
(ix) Academic Institutions

The benefits of involving a range of stakeholders include:
i. Access to an increased resource base
ii. Ownership of resources
iii. Improved impact and out-reach
iv. Enhanced acceptability and care

Stakeholders will be able to contribute to the process of planning, implementing, maintaining and support on ARV treatment programme. If there is opportunity for shared decision-making and clear understanding of expected outcomes. However, stakeholder's agendas or objectives must not be allowed to overshadow the programme or to interfere with the overall process of stakeholder's participation.

It will be helpful to map the range of stakeholders and their actual or potential relationship with the programme. Regular review of partnerships and involvement with stakeholders is recommended as part of monitoring and evaluation.

State AIDS Control Societies should carry out stakeholder analysis with each key stakeholder in order to match its capacity and willingness to be involved with the needs of the ART programme. This should ensure greater efficiency and clearer focus on the process of working with the key stakeholders.

16. ENSURING THE GREATER INVOLVEMENT OF PEOPLE WITH HIV/AIDS (GIPA)

People living with HIV/AIDS are the most important stakeholders in an ARV treatment programme. Ensuring the greater involvement of people with HIV/AIDS (GIPA) in all aspects of ARV treatment is a true reflection of political commitment. GIPA in all aspects of ARV treatment is also consistent with rights based approach, which acknowledges that people have a part to play in decisions that affects their lives.
State AIDS Control Societies and ARV treatment unit in hospitals should involve PLHA network effectively in ARV treatment programme.

People living with HIV/AIDS can be involved in the following areas:

(i) Advocacy: People with HIV who have benefited from ARV treatment programme are powerful advocates and educators for other accepting treatment; their ability to live a healthy and productive life with HIV is believable testimony that HIV infection can be a chronic but treatable condition rather than a rapidly fatal one.

(ii) (Peer) Counseling: People with HIV who are newly diagnosed or starting treatment value counseling from other people with HIV who have similar experience.

(iii) Mobilizing AIDS patients and facilitating referral linkages with ARV treatment Units: Through their networks, People with HIV are aware of other people who live with HIV and need treatment services.

(iv) Reducing stigma: Greater visibility of people with HIV on treatment is a powerful tool for combating stigma and thus encourage more people to access HIV testing, counseling and treatment, if required.

(v) Educator: as "expert patients" selected people with HIV can be trained to assist in education of clinical and support staff to ensure that training and services are grounded in real life experiences and offer realistic treatment and support.

(vi) Enhancing adherence: active participation of patients in their own treatment encourages closer cooperation with health care workers and better feed back on the effects of treatment.

17. PUBLIC PRIVATE COLLABORATION

Engaging the private sector providers to scale up access to ARV treatment can be helpful means of achieving goals of ART programme in expanding the coverage of ARV treatment programme; ensuring the quality and safety of ARV treatment; and achieving service integration with other prevention, care and support interventions, as well as public health programmes such as STI and TB programme.

18. IEC STRATEGY FOR DELIVERY OF ART DELIVERY

NACO is in the process of developing a communication strategy for the anti-retroviral therapy programme. In the initial stage of the programme, the focus should be on Inter-personal communication that should address the following:

Information on ART, demand generation, treatment adherence, patient follow-up, community care and support
Sensitization of health care staff
Involvement of PLHAs
Partnership with other sectors for a multisectoral response

18.1 Health Care providers should provide the following key messages to people living with HIV/AIDS

Prevent transmission to Self and Others
Warn about the risks of infecting self with OIs, STIs or different HIV strain
Warn about the risks of infecting others with HIV, OIs, STIs

- Explain risk of infection to and from sexual partners
- If on ARV therapy: you can still transmit HIV infection
- If HIV+ you should prevent transmission of HIV to others, and acquiring other infections by self.

Counsel on safer sex and provide condoms

Safer sex is any sexual practice that reduces the risk of transmitting HIV and other sexually transmitted infections (STI) from one person to another.

- Counsel on options for sexual expression:
  - Delay sexual activity
  - Reduce the number of sexual partners. Ideally stay faithful to one partner
  - Condom
  - How to negotiate condom use
  - Provide condoms
- Counsel on less risky sex - choose sexual activities that do not allow semen, fluid from the vatgina, or blood to enter the mouth, anus or vagina of the partner
- For men:
  - Counter any myths of cleansing of HIV infection such as sex with virgins or young girls.

If woman of childbearing age or any man, counsel on reproductive choices

- Advise on the risk of maternal to child transmission and discuss PMTCT interventions
- Offer family planning:
  - Advise on possibility of tubal ligation, vasectomy
  - All contraceptive methods may be used, however:
    - Do not encourage IUD in women at risk of STI
    - Avoid oral contraception - these can interact with some ARV drugs
    - Encourage condom use in all'
    - Inform about female condom

If considering pregnancy:

- Discuss interventions available to prevent maternal to child transmission (PMTCT)
- Once pregnant, resume using condoms again to protect oneself

If pregnant:

- Use antenatal guidelines if woman wants to complete the pregnancy
- Discuss whether the couple is considering pregnancy termination - warn on dangers of unsafe abortion and, where this is safe and legally available and desired by the woman, discuss option of pregnancy termination

- Provide family planning counseling and services, to enable couple to prevent or delay future pregnancies.

18.2 Respond to concerns about sexual function:

18.3 Advise on prevention of non-sexual spread:

- Do not share needles or razor blades or tattoo instruments
- Cover any open cuts or sores on patient'
- Protect the care giver

18.4 IEC STRATEGIES FOR DELIVERY OF IEC:

IEC is an essential component for successful implementation and up-scaling ARV treatment programme. It requires multi-pronged communication strategies such as interpersonal communication, printed materials and mass media to target patients seeking ARV treatment and their family members, health care providers, facilitator groups such as civil society and PLHA networks, and community in general. The main messages that need to be communicated and the methods of communication for specific target groups are outlined below:

Community:

- AIDS is an illness like any other disease and can be treated
- Free treatment is available for AIDS at select health care facilities
- The facilities where treatment can be availed
- Drugs available free from the government
- Eligibility criteria for treatment
- Know your HIV status, in the event of threat perception
- The places, where counseling and testing can be availed
- HIV/AIDS afflicted people are like any other patients and need your support

Appropriate channels for community oriented messages are mass media

PLHAs receiving treatment:

- ARV treatment adds years and quality to life, though it is not a cure
- ARV treatment suppresses the virus multiplication but does not remove it completely
- Risks of transmission continue to exist, therefore, one needs to practice safe sexual behaviour (such as one faithful partner and consistent condom use and/or safe injection practices (use of sterile needles) etc
- The benefits of treatment can be obtained only if it is taken regularly
- There can be side effects of the drugs which are transient. Do not give up drug intake. If the side effects persist, consult the treating doctor
- The common side effects and the instances when the patient should consult the doctor immediately
- Visit the doctor on the scheduled date without fail, it is important that you are checked regularly and given medicines regularly
- Inform the treating doctor if you are being treated for tuberculosis or are taking oral contraceptives to avoid pregnancy, so that (s)he can choose the right medicine or give right advice

Appropriate channel for patients under ARV treatment is Interpersonal Communication (IPC) through health care workers, PLHA networks and NGOs. In addition, printed leaflets in vernacular will also help educate patients who can read or whose support person can read

Families of PLHAs under treatment:

- ARV treatment adds years and quality to life; the patient can lead normal productive life
- The benefits of treatment can be obtained only if it is taken regularly. Ensure that the medicines are taken as prescribed, preferably under your observation
- There can be side effects of the drugs which are transient. Do not let the patient give up drug intake. If the side effects persist, consult the treating doctor
- The common side effects and the instances when the patient should consult the doctor immediately
- Patient needs your support, particularly during the events of side effects. Stand by him and motivate and encourage the patient to continue with the treatment

  Appropriate channel for family members/ support persons of patients under ARV treatment is Interpersonal Communication (IPC) through health care workers, PLHA networks and NGOs. In addition, printed leaflets in vernacular will also help them

PLHA Networks/ NGO/ Employer /Health Care Providers

These groups should be identified in the catchment area of a health facility providing ART, assessed for their motivation and willingness to support the patients on ART.

Messages:

- Ensure treatment adherence of the patient you are supporting
- Conditions when a patient can default and appropriate action to be taken
- Conditions under which patient should be referred
- Provide psychological support to and encourage the patient by citing success stories
- Encourage and motivate people to seek VCT & PPTCT services
- Maintain confidentiality
- Techniques of IPC for people willing to work as outreach workers

Group discussion/ short training programmes are suitable approaches to communicate to the members of these groups.

(The same is given in tabular form below, if you think that it looks more appropriate)

IEC STRATEGIES FOR DELIVERY OF IEC:

IEC is an essential component for successful implementation and up-scaling ARV treatment programme. It requires multi-pronged communication strategies such as interpersonal communication, printed materials and mass media to target patients seeking ARV treatment and their family members, health care providers, facilitator groups such as civil society and PLHA networks, and community in general. The main messages that need to be communicated and the methods of communication for specific target groups are outlined below:

Target Group	Messages	Media/Channels
Community	• AIDS is an illness like any other disease and can be treated • Free treatment is available for AIDS at select health care facilities • The facilities where treatment can be availed • Drugs available free from the government • Eligibility criteria for treatment • Know your HIV status, in the event of threat perception	Mass Media

	• The places, where counseling and testing can be availed • HIV/AIDS afflicted people are like any other patients and need your support • (Main objective is creating awareness about ART programme and demand generation)	
PLHAs seeking treatment	• ARV treatment adds years and quality to life, though it is not a cure • ARV treatment suppresses the virus multiplication but does not remove it completely • Risks of transmission continue to exist, therefore, one needs to practice safe sexual behaviour (such as one faithful partner and consistent condom use and/or safe injection practices (use of sterile needles) etc • The benefits of treatment can be obtained only if it is taken regularly • There can be side effects of the drugs which are transient. Do not give up drug intake. If the side effects persist, consult the treating doctor • The common side effects and the instances when the patient should consult the doctor immediately • Visit the doctor on the scheduled date without fail, it is important that you are checked regularly and given medicines regularly • Inform the treating doctor if you are being treated for tuberculosis or are taking oral contraceptives to avoid pregnancy, so that (s)he can choose the right medicine or give right advice	• Interpersonal Communication through health care workers, PLHA networks and NGOs • Printed leaflets
Family member/ support person of PLHAs under treatment	• ARV treatment adds years and quality to life; the patient can lead normal productive life • The benefits of treatment can be obtained only if it is taken regularly. Ensure that the medicines are taken as prescribed, preferably under your observation • There can be side effects of the drugs which are transient. Do not let the patient give up drug intake. If the side effects persist, consult the treating doctor • The common side effects and the instances when the patient should consult the doctor immediately • Patient needs your support, particularly during the events of side effects. Stand by him and motivate and encourage the patient to continue with the treatment	• Interpersonal Communication through health care workers, PLHA networks and NGOs • Printed leaflets
PLHA Networks/ NGO/ Employer	• Ensure treatment adherence of the patient you are supporting • Conditions when a patient can default and appropriate action to be taken • Conditions under which patient should be referred • Provide psychological support to and encourage the patient by citing success stories • Encourage and motivate people to seek VCT & PPTCT services • Maintain confidentiality • Techniques of IPC for people willing to work as outreach workers	• Group discussion/ short training programmes

	(These groups should be identified in the catchment area of a health facility providing ART, assessed for their motivation and willingness to support the patients on ART)	

19. PLAN FOR PHASED SCALE UP

The delivery of the treatment programme will be implemented in 3 phases:

(i) First Phase:- ART teams from the following eight tertiary level Govt. institutions are trained and strengthened to deliver ART to ensure delivery of ARV therapy with effect from 1st April,2004:

a) Osmania Medical College, Hyderabad, Andhra Pradesh
b) Lady Curzon & Bowring Hospital, Bangalore Medical College, Bangalore, Karnataka
c) Sir. J .J. Hospital, Mumbai, Maharashtra
d) Regional Instt. of Medical Sciences, Imphal, Manipur
e) Naga District Hospital, Kohima, Nagaland
f) Govt. Hospital for Thoracic Medicine, Tambaram
g) RML Hospital, Delhi
h) LNJP Hospital, Delhi

(ii) Second Phase: In this phase, ART will be extended to additional 8 Govt. hospitals from August, 2004 and by end of year 2004 total 25 centers are targetted to be covered on ART. Most of these centers will be from six high prevalence States. Training of staff at first 8 to 8 center have already been completed and training of remaining centers staff will be completed before December, 2004.

(iii) Third Phase: In this phase of the training most of the ART teams from the 25 tertiary level health care institutions would be allocated 4-6 districts for training ART teams from district hospitals. However it should be ensured that where district ART teams are being deputed for training, the district hospitals have adequate clinical material and their own

diagnostic facilities are linked to some other hospitals/laboratory for this purpose. The methodology of the training should lay stress on hands on training and not didactic teaching only. This phase of the training would be completed by July, 2005.

(iv) In subsequent phase, training of MOs and key paramedical staff of block level PHCs/CHCs in six high prevalence States will be undertaken by the district ART teams with effect from 1st January,2006.

(v) Training of ART teams of Medical colleges in low prevalence States: Although in this phase of ART treatment programme, Govt. is not contemplating to provide free ART in concentrated and low prevalence States, however, training of ART team will be carried out in order to promote structured delivery of antiretroviral therapy. Composition of ART team will be the same as mentioned above.

(vi) The training of ART teams of Govt. medical colleges in the States will be conducted at Sir. J. J. hospital, Mumbai, Christian Medical College, Vellore, Govt. Hospital for Thoracic Medicine, Tambaram and Regional Institute of Medical Sciences, Imphal.

(vii) Each phase of the Training should involve people living with HIV/AIDS as part of the resource team to talk about their "positive" experiences and of doctor patient relationship. This will help in encouraging PLHA to adhere to drug regimes and undertake treatment as part of positive living. This will also help health care providers to understand the difficulties faced by PLHAs and will overcome their initial hesitation to treat people living with HIV.

19.1 Details of the ART scale-up:

Phase I

Phase I has been implemented initially in 8 institutions , six in high prevalence states (arranged alphabetically) and two in Delhi from April, 2004

I. Osmania Medical College, Hyderabad, Andhra Pradesh
II. Bangalore Medical College, Bangalore, Karnataka
III. Sir. J .J. Hospital, Mumbai, Maharashtra
IV. Regional Instt. of Medical Sciences, Imphal, Manipur
V. District Naga Hospital, Kohima, Nagaland
VI. Govt. Hospital for Thoracic Medicine, Tambaram, Tamil Nadu
VII. Dr. RML Hospital, Delhi
VIII. LNJP Hospital, Delhi

List of additional 8 Medical Institutions where the ART is being upscaled w.e.f. 25th August,2004.

I. Madras Medical College, Chennai, Tamil Nadu
II. Govt. Medical College, Madurai, Tamil Nadu
III. Karnataka Medical College, Hubli, Karnataka
IV. Mysore Medical College, Mysore, Karnataka
V. Government Medical College, Guntur, A.P.
VI. Government Medical College, Vizag, A.P.
VII. Government Medical College, Sangli, Maharashtra
VIII. Jawaharlal Nehru Hospital, Imphal, Manipur

List of additional 9 Medical Institutions where the ART is being upscaled w.e.f. 15th September,2004.

I. B. J. Medical College, Pune, Maharashtra
II. Govt. Medical College, Nagpur, Maharashtra
III. District Hospital, Namakkal, Tamil Nadu
IV. B. J. Medical College, Ahmedabad, Gujarat
V. Calcutta Medical College, Kolkatta, West Bengal
VI. BHU Banaras Institute of Medical Sciences, Varanasi, U.P.
VII. PGIMER, Chandigarh
VIII. SMS Hospital, Jaipur, Rajasthan
IX. Medical college, Panaji, Goa

Following Institutions have already been trained in ART:-

Karnataka:-

1. VIMS, Bellary, Bangalore,
2. Vani Vilas Hosp., Bangalore, Karnataka
3. Indira Gandhi Instt. of Child Health, Bangalore
4. Bowring & Lady Curzon Hosp., Bangalore
5. Mysore Medical College, Karnataka
6. Karnataka medical College, Hubli, Karnataka

Andhra Pradesh:-

7. Osmania Medical college, Hyderabad
8. Guntur Medical college, Guntur, Andhra Pr.
9. Andhra pr. Med. College, Vishakhapatnam

Tamil Nadu:-

10. GHTM, Tambaram, Tamil Nadu
11. Stanley Medical College, Chennai
12. Madras Medical College, Chennai
13. Govt. Medical College, Namakkal
14. Kilpauk M. C., Chennai
15. CMC, Vellore

Maharashtra

16. JJ Hospital, Mumbai
17. Sion Hosp., Mumbai
18. KEM Hospital, Mumbai
19. Nair Hosp., Mumbai
20. Govt. Medical College, Sangli
21. B.J. Medical college, Pune

Manipur

22. RIMS, Manipur

Nagaland

23. Naga Hospital, Kohima

Delhi

24. AIIMS, Delhi
25. LNJP Hosp., Delhi
26. GTB Hosp., Delhi
27. RML Hosp., Delhi

Pattern of Assistance for ART centers **:** The ARV treatment programme is led by the Head of the Department of Medicine of each Institution with the provision that he/she has received 5 days training in ART from the designated institution by NACO/SACS. Care and treatment will be provided to AIDS patients as an integral component of the out patient or

in patient services. It will be the responsibility of the institutional based trained team to ensure that each and every faculty member in the Department of Medicine, Paediatrics and related departments has been adequately trained as per training guidelines / curriculum recommended by NACO.

In the first stage, the hospital has to establish an ARV treatment unit, which will look after both adult and children in the department of Medicine in order to ensure that there is proper documentation of the care and follow up of the individual patient. The unit, though logistically situated in the Department of Medicine, should draw faculty from the Paediatric Department also in order to provide comprehensive care to both adults and children. Linkages with VCCTC, Department of Microbiology and other related departments should be established. For this purpose, the following support will be provided to the Department of Medicine of the Institution:

(a) Senior Medical officer dedicated to ARV Unit	-	1
(b) Medical Officer dedicated to ARV Unit	-	1
(c) Counselor	-	1
(d) Lab Technician	-	1
(e) Record keeper cum Computer operator	-	1

In case the PD SACS or the institutional Head desires a change in any post they should submit a separate proposal for the same to NACO

A dedicated Computer along with printer and internet facility will be provided to ARV treatment Unit.

The main function of the Medical officers is to coordinate and supervise the operations of the ARV treatment unit and report to HoD of Medicine.

The Medical officer should be a clinician (post graduate in medicine / pediatrics / OBG) with experience in analysis and interpretation of data with adequate knowledge of computers. He/she will provide monthly / quarterly analysis on ART adherence to the HoD and assist the faculty in delivery of ART. The senior Medical Officer and Medical Officer

will be paid consolidated monthly remuneration comparable to their counterparts in the States.

The main function of the counselor is to provide counseling services to all the patients and emphasise the following messages:

- Drugs do not cure HIV disease, but convert it into a manageable chronic ailment
- Drug treatment has to be taken life long
- Drug treatment improves the longevity and quality of life
- Patients remain infective and must assume safe behaviour even while on ARV treatment
- Drug treatment should be taken only from the treating physician
- Drugs should be taken according to prescription only and not be stopped without the physicians advice
- Drugs should not be shared with relatives/ friends
- If there are adverse effects with drugs then the treating physician must be consulted

The counselor should be trained in HIV /AIDS counseling especially preparedness and adherence counseling before placement and they should fulfill the qualification criteria as per NACO guidelines. Counselors will be paid a consolidated salary up to Rs. 6500/- per month.

The counselors will be trained in counseling issues across the HIV disease continuum, specifically on the following areas:

- Disclosure
- Discrimination and Stigma
- Dealing with the impact of emotional reactions including shock, denial, depression, anger, fear, guilt, anxiety, suicidal thoughts
- Disease progression
- Changes in physical appearance
- Deterioration in health
- Death and dying
- Loss and grief
- Dealing with relationship- partners, family, friends

- Financial difficulties and employment
- Treatment issues particularly to adherence, side effects
- Interventions for psychological issues to develop support, network and self help skills
- Developing support groups and linking with community networks and other referral agencies
- Emotional and spiritual support
- Palliative and home based care
- Community outreach

The Record keeper will be responsible for maintaining individual patient's master card, which should be completed on each visit of the patient to the Clinic. He will also prepare monthly progress report, analyse quarterly cohort analysis and cumulative cohort analysis report, as well as maintain all correspondence related to ARV treatment clinic in the hospital.

Record keeper cum computer operator should be a graduate with adequate knowledge in MS Word, Excel. Experience of working on Internet would be preferable. They will be paid a consolidated salary up to Rs. 6500/- per month depending upon the experience and working knowledge of the candidate.

The following records / reports will be maintained by the ARV Treatment Unit in every hospital. All records and reports must be kept confidential and should be accessible only to health care staff directly involved in treatment based on the concept of shared confidentiality. A system to keep patient information confidential should be devised:

(i) Individuals ARV Identity Card (The card will be given to each individual patient) (Annexure II)
(ii) Individual Patient Master Record Card for ARV (Annexure III)
(iii) ARV Quarterly Cohort Analysis Form (Annexure IV)ARV Cumulative Annual Cohort Analysis Form (Annexure V)Monthly Progress Report form (Annexure VI)
(vi) Drug and Consumables stock Register (Annexure VII)
(vii) Monthly Treatment unit Report (Annexure VIII)

(viii) Antiretroviral Treatment eligibility register (Annexure IX)

Laboratory Technicians should be engaged on contractual basis with monthly consolidated remuneration of Rs. 6500/-. The qualification and experience should be as per NACO guidelines. He/She should assist in conducting various investigations to microbiologists, incharge of the laboratory.

Each center will be provided an annual contingency grant of Rs. 100,000 (Rupees one Lakh) during the Ist year of the operations, and Rs. 50,000 (Rupees fifty thousand) in subsequent years as a contingency grant.

Family counseling center / Drop In Center (DIC)

A family counseling center / drop in center (DIC) manned by people living with HIV will also be established in each of these centers. This space will be available for people living with HIV and their families to meet as support groups. This will also be a point of entry for treatment education, and to discuss the issues of adherence and resistance. This space will also be utilized for supporting family members / guardians participating in care, drawing up treatment plans for individual people living with HIV. This should be developed subsequently as a comprehensive resource center for all information on life after infection.

The pattern of assistance for Family Counselling/ Drop in Center(DIC):

19.2 <u>Phase II</u>

Phase II, delivery of ART programme will be implemented in all Govt. Medical college hospitals in six high prevalence States, which will be started from 2005 in a phased manner. In States of Manipur and Nagaland, there are no medical colleges except RIMS, Imphal in State of Manipur. Therefore in these two states, this phase of the delivery of ART programme will include district hospitals. The district teams for the ART delivery programme will be trained at RIMS in Manipur and District Naga Hospital, Kohima in Nagaland.

The ARV treatment unit in each of the medical college / district hospitals will be led by the Head of the Department of Medicine within the provision that he has received five

days hands on training in ART programme from the designated institutions by NACO / SACS.

Staffing pattern of ART center taken in 2nd Phase and budgetary provision will remain same as for Phase-I.

The qualifications and functions of the Counselor and record keeper cum computer operation will be the same as described in Phase I implementation of ART except for district hospitals in States of Manipur & Nagaland, where counselor will not be provided under the programme. For the purpose of counseling, services of VCCTC of the hospitals should also be utilised.

19.3 Phase III

In Phase III, Implementation of ART programme will include all district hospitals in six high prevalence States. It is envisaged to initiate Antiretroviral treatment programme w.e.f. January, 2006. The ARV treatment unit will be headed by the senior most physician in the department of medicine with the provison that he has received 5 days training programme from the identified training institution by NACO / SACS. For this purpose, the following support will be provided to ARV treatment unit of the district hospitals.

(i) Record keeper cum Computer operator - 1

A dedicated Computer with operator will be provided as per World bank procedure.

The qualifications and functioning of the record keeper cum computer operator will be the same as described in Phase II implementation of ART programme. Services of the counselors in VCTC should be utilised for providing counseling to patients as indicated in Phase I implementation.

A contingency grant of Rs. 100,000/- (Rupees one Lakh) will be provided during the first year of the programme. From the second year onwards, a contingency grant of Rs. 50,000 /- will be provided to each ART unit

In other (low and moderate prevalence) States, training of ART treatment teams will be conducted in order to ensure that the prescription for ART are as per National

guidelines. At present, Govt. of India will provide support to these hospitals for management of opportunistic infections.

A family counseling center / Drop in Center manned by people living with HIV will also be established in each of these centers and in each of the phase it will be integrated into the hospitals and centers providing ARV treatment.

20. STRUCTURES AND RESPONSIBILITIES FOR IMPLEMENTATION

20.1 At National Level (NACO):

Training :

The National AIDS Control Organization will support State AIDS Control Societies in organizing trainings and capacity building for scaling up of ART.

Establishing the certification process: NACO is working with WHO to develop national certification standards and mechanism for HIV/AIDS training and assessing training providers and certifying their competence. NACO will identify experts of national and international repute for this purpose.

NACO has identified a core team of National trainers who have hands on experience in ARV treatment programme. The core teams of trainers will be drawn from both public and private health sectors and will be multidisciplinary. The national team of trainers will be deputed to States for training of State level training teams as well as providing back-up support in implementation of the ARV treatment programme.

NACO will provide a set of guidelines and training material to States for carrying out training to trainers up to district level. Networks of people living with HIV will also be part of the resource team for training programs. Guidelines for training including curriculum are annexed at Annexure I

Procurement

Procurement of ARV drugs will be made by NACO centrally based on estimates from SACS and distributed to the State AIDS Control Societies. A procurement plan will be developed and clear and transparent procurement procedures will be followed.

Diagnostics

NACO is working out with Confederation of Indian Industries (CII) to develop a network of public private laboratories for availing diagnostic services from the existing laboratories for institutions/hospitals where CD4 cell counts facility is not available. NACO envisions at least one CD4/CD8 counters for two-three districts and is currently in the process of purchasing CD4/CD8 counters in phases to update facilities using different funds including from WHO and monies received from the Global Fund.

The quality control of CD4 testing will be done by linking it to NACO's quality assurance programme.

Drug resistance Surveillance

NACO in collaboration with ICMR will identify the state-of-the-art laboratories that are already working on HIV molecular biology such as NARI Pune, TRC Chennai and NICED Kolkata to carry out HIV drug resistance surveillance in the country as per protocol of the WHO HIV drug resistance surveillance teams (HDRST).

Adherence

National institute of Epidemiology would be involved in carrying out studies on ART adherence and related subjects in partnership with PLHA networks.

Accreditation of Treatment Centers

NACO will accreditate treatment units provided they fulfill the following requirements:

- Basic physical infrastructure
- Trained personnel
- Laboratory facilities
- Availability of care and support including ART
- Facilities for adequate follow-up
- Achieved targets for basic health care

20.2 At State Level (SACS):

Coordination

State AIDS Control Societies are advised to form a State advisory body on ARV treatment programme under the chairpersonship of Health Secretary and should include representatives from department of Finance, Planning, Indian Medical Association, health professionals knowledgeable in HIV/AIDS, in clinical management of HIV infection including the ARV treatment faculty of medical academic and research institutions, representatives of NGOs and CBOs involved in care and support of people living with HIV/AIDS, business community and networks of people living with HIV/AIDS. Director General Health Services and Director Medical Education may be the co-chairs of the group and Project Director, SACS be the convener.

Nodal Officer for ART programme in State AIDS Control Society: Project Director, SACS should identify a senior technical officer, preferably, Addl. Project Director as a nodal officer for this programme for the effective supervision and monitoring of the implementation of ARV treatment programme in the State.

Planning

A state level consultation workshop may be convened before starting the ARV treatment programme. Chief Minister, Health Minister and other State authorities should be invited to convey a strong political commitment in rolling out the ARV treatment along with prevention programmes. State Govt. should be motivated for resource mobilization to strengthen health infrastructure required for delivery of ARV treatment programme through public health care delivery system.

Identification of Training Centers

State AIDS Control societies are expected to carry out a situation analysis for planning of the rapid training of existing health manpower. State AIDS Control Societies should identify: institutions/hospitals for imparting hands on training to State core teams of trainers. Hospitals identified for this purpose should be those where HIV/AIDS patients are being admitted without any discrimination so that the trainers get adequate clinical experience during bedside clinics conducted during training sessions. The hospitals/institutions should have investigation facilities for diagnosis of opportunistic

illnesses and monitoring of ARV treatment. The following laboratory facilities should be in place:

a. Serodiagnosis for HIV
b. CD4 counts
   (In ART centers, where CD4 machines are yet not available shall be guided by Total Lymphocyte count for initiation of ART)
c. Diagnosis for opportunistic infection and STDs
d. Liver function tests
e. Serum amylase test
f. Serum lactic acid

Trainings

State AIDS Control Societies in consultation with Directorate of Health Services/Medical Education should identify a dedicated multidisciplinary team of trainers from the institution(s) identified for human resource development in scaling up ARV treatment programme. The team should consist of Physician / Infectious disease specialist (from the Dept. of internal medicine or Infectious diseases (1); Pediatrician (1); OBG Specialist (1); Microbiologist (1); Community Medicine (1); Senior Staff Nurse (1); Psychologist / Psychiatrist (1); TB specialist (1); STD Specialists (1) and private physicians from IMA (2). The State level training teams will be responsible for training of ARV treatment teams in other hospitals in the State up to the district level.

State AIDS control Societies will draw a training programme in such a way that training of manpower in all Govt. medical college hospitals in all six high prevalence States and up to district hospitals in States of Manipur and Nagaland is completed by December, 2004. ART teams from district hospitals in high prevalence states and medical colleges in other States would be completed by July, 2005. Once district training teams are in place in district hospitals, Medical Officers at Block level PHC/CHC should be trained in six high prevalence States by July 2006.

Training Tool Set

State AIDS Control Societies should make estimates for the requirements of training tool sets for their respective States and forwarded to NACO by 15th July 2004. The training tool set will consist of:

- WHO ARV treatment guidelines
- NACO/WHO guidelines for management of opportunistic illnesses
- Guidelines on management of HIV-TB co-infection.
- Guidelines on voluntary counselling and testing
- Implementation Guidelines for phased scale-up of antiretroviral therapy
- Training modules set

Monitoring and Reporting

State AIDS Control Societies are required to submit monthly reports to NACO. At the institution level the report will be prepared by the record keeper cum computer operator and will be submitted to SACS through HoD Medicine. The formats for the monthly reports are enclosed at Annexure VI, and VIII.

Supportive supervision and quality assurance

Project Directors and Addl. Project Directors, SACS should make frequent visits to the institutions to review the implementation of the ARV treatment programme and how it is being managed at local level. Efforts should be made from the very beginning to mainstream ARV treatment programme within the existing system of the institutions / hospitals. A check list should be prepared for programme Implementation and shared with the individual institution. Director of Health Services should also be mobilized to supervise the ARV treatment programme. They should focus on the following points during their visits:-

- Check list for programme implementation
- Status of delivery of ARV treatment
- Follow up and systems for monitoring adherence to anti-retroviral therapy

Estimation of drug needs and delivery

Project Directors, State AIDS Control Societies of six high prevalence states should convene a meeting of leading physicians both from public and private sectors to estimate the number of adolescents, adults, children and infants who would require treatment during the year 2004-2005 and 2005-06.. The requirement of ARV drugs should be

indicated hospital wise in the State. State AIDS Control Societies should make estimate of requirements of first line regimen ARV drugs for HIV/AIDS patients for their respective states.

Project Directors should inform NACO about the requirements of ARV drugs by September each year for the next year requirement as well as the status of logistic arrangements made for the effective delivery of ARV drugs.

Project Directors of SACS should also work out logistic systems that are effective and efficient for delivering goods to the point of use and ensure proper storage of drugs and that no gaps in supply occur. A reserve stock for four months should be available at all times.

Laboratory equipment and reagents

Project Directors should also make adequate provisions of funds in their annual action plans for procurement and supply of laboratory equipment/ reagents, drugs for treatment of opportunistic illnesses and ARV for post exposure prophylaxis. Basic laboratory monitoring requirement recommended for first-line ARV regimens are:

(a) Alanine Aminotransferse for hepatic toxicity
(b) CD4 counts at baseline (pre-therapy) and 6 monthly thereafter
(c) Hb, WBC, full blood picture (FBC)
(d) Pregnancy test
(e) Renal function test
(f) Serum amylase, lactic acid arterial blood gas analysis (at least in some centres)

For any investigations, PLHAS should not be prescribed hospital charges for investigation or any other service as care and treatment to PLHAs is an integral part of National control Programme as is the practice in other National health Programmes. In the north east (Manipur & Nagaland) the laboratory work up will include testing for Hep B & Hep C.

Logistics development

Project directors , SACS will request State Health Directorates for adequate infrastructure for the ART centres.

Material support for treatment must be available and properly managed at all levels. These supplies will include: condoms and other material for HIV prevention; syringes, dressings, reagents, diagnostics etc.

ANNEXURE I

TRAINING PROGRAMME

The training will include both the public and private sector partners so as to include physicians, pediatricians, gynecologists, microbiologists/ pathologists etc. Training should be organised separately for counselors, pharmacists, and laboratory technicians, NGOs, PLHAS.

Training of ART teams:

The National Trainers on ART will be deputed to train State level trainers. Besides, the trainers will also be used for supervision and monitoring of training programme conducted by State level trainers. They will also supervise the implementation of delivery of ART in medical college hospitals, district hospitals. A resource person from a Network of people living with HIV should also be selected as a trainer in order to bring forth the PLHA perspective on treatment.

The training in States will be conducted in three phases:

(i) Phase I - In this Phase, 27 institutions across six high prevalence states and Delhi have been trained. These institutions are:-

Karnataka:-

1. VIMS, Bellary, Bangalore,
2. Vani Vilas Hosp., Bangalore, Karnataka
3. Indira Gandhi Instt. of Child Health, Bangalore
4. Bowring & Lady Curzon Hosp., Bangalore
5. Mysore Medical College, Karnataka
6. Karnataka medical College, Hubli, Karnataka

Andhra Pradesh:-

7. Osmania Medical college, Hyderabad
8. Guntur Medical college, Guntur, Andhra Pr.
9. Andhra pr. Med. College, Vishakhapatnam

Tamil Nadu:-

10. GHTM, Tambaram, Tamil Nadu

11. Stanley Medical College, Chennai
12. Madras Medical College, Chennai
13. Govt. Medical College, Namakkal
14. Kilpauk M. C., Chennai
15. CMC, Vellore

Maharashtra

16. JJ Hospital, Mumbai
17. Sion Hosp., Mumbai
18. KEM Hospital, Mumbai
19. Nair Hosp., Mumbai
20. Govt. Medical College, Sangli
21. B.J. Medical college, Pune

Manipur

22. RIMS, Manipur

Nagaland

23. Naga Hospital, Kohima

Delhi

24. AIIMS, Delhi
25. LNJP Hosp., Delhi
26. GTB Hosp., Delhi
27. RML Hosp., Delhi

The remaining medical colleges will be trained in the IInd phase of the training. The following four APEX institutions have been identified for conducting training for State level ART teams i.e. teams from Medical colleges all over the country.

- Sir J. J. Hospital, Mumbai, Maharashtra
- Govt. Hospital for Thoracic Medicine, Tambaram, Tamil Nadu
- Christian Medical College, Vellore, Tamil Nadu
- Regional Institute of Medical Sciences, Imphal, Manipur

ART team: In each of the institutions, The Principal/ Dean will identify a "State trainers team on ART" comprising of a Physician (from the Department of Internal Medicine or Infectious Diseases), Community Medicine specialist, Paediatrician, Obstetrician and Gynaecologist, Chest/ TB Physician, Psychologist/ Psychiatrist, Microbiologist, STD Specialists Senior Staff nurse and two Private Practitioners nominated by the Indian Medical association [total 10].

The main functions of the team are:

i) Delivery of treatment services to HIV/AIDS patients
ii) Training of other physicians in their respective institutions
iii) Training of district teams for ART

Curriculum

A Short Course-Training Program for Trainers in Clinical Management of HIV/AIDS patients.

Program objectives and goals

With the introduction of highly active antiretroviral therapy (HAART), a better understanding of mechanisms of the action of ARV drugs and experience gained in their use has resulted in significant reductions in HIV-related mortality and morbidity. However, major challenges still remain. These include appropriate choice of drug regimens, ensuring continuous drug availability, understanding and recognizing the drug toxicities and interactions and managing them, ensuring adherence and preventing/ treating drug resistance. All these consideration weigh heavily on the mind of a HIV physician in making decision regarding HIV drug treatment.

This interactive course, examines the issues which impact on HIV management, and we expect participating physicians to gain insight into the unmet medical needs, which arise from current treatment strategies. The faculty will lay stress on the clinical management of HIV/AIDS patients. It is our intention that participants will be able to understand the scientific rationale of ART and learn about their efficacy, safety, toxicities and drug interaction. The need for affordable and efficacious regimens shall be highlighted. Clinical handling of HIV patients in special situations shall also be addressed.

It is expected that participants will enrich the proceeding by their own experience and the faculty will be able to clear many doubts they may have about the clinical management, as also many misconceptions that are prevalent in the community at large.

During this interactive programme National Guidelines based on WHO guidelines will also be discussed with the hope that uniform regimen are adopted all over the country, which will also help in containing the drug resistance to some extent.

EDUCATIONAL OBJECTIVES

The intent of this program is:

1. To make the physicians aware of current issues in the diagnosis and treatment of HIV.
2. To emphasis the rational use of antiretroviral drugs.
3. To provide a better understanding of the possible strategies in the care and support for patients with HIV.
4. To develop consensus on training curricula.
5. To address stigma and discrimination at the treatment centers

COURSE DESCRIPTION:

The purpose of this course is to provide an up-to-date, state-of-the-art overview of the clinical care of patients with HIV infection for senior practicing clinicians and other health professionals. The course will include discussions on HIV epidemiology, clinical management and treatment of HIV and OIs. On hands training shall also be provided.

OBJECTIVES:

- To understand the epidemiological principles of HIV infection in order to gauge the extent and spread of HIV infection.
- To understand natural course and pathogeneses if HIV infection.
- To familiarize with principles and regimens of antiretroviral therapy for HIV infection.
- To learn how and when to initiate chemo-prophylaxis for opportunistic infections.
- To be able to diagnose and manage opportunistic infections of HIV infection.
- To recognize manifestations of tuberculosis in the context of HIV infection
- To be able to manage HIV/TB co-infection.
- To involve people living with HIV in their treatment in order to improve adherence

- To create a supporting environment to increase access to treatment

Overview of Training Curriculum

Objectives of the training:

1. To impart knowledge and skills on provision of HIV antiretroviral treatment
2. To sensitize health service providers on decreasing stigma and discrimination towards people living with HIV/AIDS
3. To impart knowledge and skills on improving treatment adherence to ART
4. To impart knowledge and skills in treatment monitoring, recording and reporting

Duration	Sessions	Specific Objectives	Content	Training methodology	Training materials
Module 0 Introduction and Administration					
Day 1					
9.00-9.30	Registration				
9.30-10.45	Welcome and Housekeeping Group norms Introduction and Ice breaking Pre-test Assessment Concurrent Training Evaluation Objectives of training Programme	Introduction of participants Orientation of trainees to the programme Establish baseline knowledge of trainees	Pre-Assessment forms Objectives	• Course coordinator/ game	• Questionnaire
Module 1 Introduction to public health issue on HIV/AIDS					
10:45-11:15	Submodule Government of India Initiative of HFM on HIV/AIDS	To understand the salient features of GOI initiatives in ART	Evolution of Initiative	Lectures Discussion	PPT. Slides

	Submodule • Epidemiology • Global, Regional and Indian • The impact of HIV/AIDS • The benefits of treatment	• To understand the epidemiological scenario in global, regional and Indian context • To understand rationale of ART as part of public health programmes	HIV Estimates from 1999 till date BSS (Behavioral Sentinel Surveillance) Impact of HIV/AIDS on households ART Success from other countries Cost for ART programmes	Lectures Discussion	PPT. Slides
11:15-11:30	Tea / Coffee				
11:30-12:00	Submodule Existing Health Infrastructure and HIV/AIDS Prevention and Care Policies	• To understand Health Care Delivery System of India • To make the participants aware of GOI POLICIES in context of HIV/AIDS • To familiarize the participants with existing HIV/AIDS services and access to ART	Health Care Delivery System of India National AIDS GOI Policies in context of HIV/AIDS	Lectures Discussion	PPT. Slides

12:30-1:30	Submodule NACO's ART Initiative	To understand the rationale of ART To understand the current strategies of ART and implementa-tion of ART programme	ARV Policy package Strategy framework for ARV drug delivery 3 target groups for ART Implementation plan	Lectures Discussion	PPT. Slides
1:30-2:30	Lunch				
Module 2 Entry points to HIV/AIDS treatment					
2:30-3:00	<u>Submodule</u> HIV/AIDS Counseling	To understand the concept of counseling including Pre-test and Post-test counseling	Principles of Counseling in HIV/AIDS	Lectures Role play	PPT. Slides
	Submodule VCCTC as Entry points to Treatment and linkages to PPTCT, RNTCP /STI and general health services	To understand the importance of VCT as a public health strategy to reduce HIV transmission and VCT linkages to PPTCT, RNTCP /STI and general health services	VCT, content of pre and post test, confidentiality, shared confidentiality, coping mechanisms, treatment preparedness and treatment adherence VCT and its linkages to healthy individuals, RNTCP, PPTCT, STIs	Lectures Visit to VCCTC	PPT. Slides

	Submodule ART and Living with HIV (Stigma, Discrimination, Confidentiality, adherence, Ethical legal issues)	To understand needs of PLHA	Living with HIV/AIDS Legal rights Discrimination Confidentiality Sexuality Attitude and PLHA experience with ART, VCT&Health care providers	Testimonies by PLHA Panel discussion Role play	PLHA Lawyers collective
	Submodule HIV Testing procedures	To understand HIV testing strategies	NACO HIV testing strategies HIV testing principles, (rapids, ELISA)	Lectures	PPT. Slides
	Field Visit to VCCTC		VCCTCs/ community centre		
Module 3 Principles of HIV/AIDS treatment					
Day 2					
9:00-9:30	<u>Submodule</u> Natural history of HIV Clinical manifestations WHO Clinical & lab staging	To understand HIV, its replication and clinical manifestations	Virology The natural course of HIV/AIDS infection WHO clinical and laboratory staging system	Lectures	Viral slides, interaction of virus with drugs
9:30-10:00	<u>Submodule</u> Antiretroviral drugs, clinical pharmacology	To understand ARV drugs and their interaction with HIV, effects, side effects,	Clinical pharmacology of ARV Mechanisms and sites of action ARV drug drug interaction ART drug interaction with other drugs (Chemotherapy of OIs) Recognition of ADR/toxicities and management	Lectures	PPT. Slides

	Submodule • Current strategies of ART	To understand how to initiate ART	Indications for ARV treatment (eligibility criteria) Preparation counselling (including adherence and family counselling) Baseline clinical assessment Baseline laboratory assessment Determining and initiating 1st line tx (deciding on treatment regimen) Drug naïve and drug experienced px	Lectures Case studies	• PPT. Slides
10:00-10:30	Submodule Follow up, adherence to ART and drug resistance	To understand how to maintain, monitor and switch ART from 1st line to second line therapy	Monitoring, follow up and adherence Drug failure (defaulting in treatment and drug resistance) (Side effects/ Severe adverse effects /Complications) Indications for switching ART 2nd line regimens (advantage and disadvantages)	Lectures Case Studies	• PPT. Slides
10:30-11:15	Submodule ART Logistics / Procurement Patient monitoring and recording/ reporting	To understand the concept of commodity management	Procurement Disbursement Storage Records Documentation Reporting to SACS Supervision	Lectures Discussion on ART formats	Monitoring checklist Recording and reporting forms
11:15-11:30	Tea / Coffee				
11:30-12:00	Submodule ART for special population groups	To understand administration of ART for special	Pediatric AIDS IDU, Hep C/B Mobile populations	Lectures Case Studies	PPT. Slides

		population groups			
12:30-1:30	Submodule Women and AIDS	To understand the importance of ART in HIV+ women	Importance of ART in HIV+ women	Lectures	PPT. Slides
12:00-12:30	Submodule Universal precautions and post-exposure prophylaxis	To acquire skills for Universal Precautions and Post Exposure Prophylaxis	Universal Precautions (UP) Post Exposure Prophylaxis (PEP)	Lectures	PPT. Slides
1:30-2:30	Lunch				
2:30-5:00	Bed side clinics				
Module 4 Diagnosis and management of opportunistic infections in children and adults					
Day 3					
9:30-10:30	Submodule ART Case Discussions Minimum 5 cases	To acquire hands-on skills in case discussions	HIV/TB HIV / candidiasis HIV / PCP HIV / Cryptococcal meningitis HIV / Diarrhea HIV / nutrition	Work-up with Lectures	PPT. Slides
10:30-11:15	Discussions		Toxoplasmosis Neurological involvement CMV(inlcuding retinitis) HIV associated malignancies Immunization in HIV	Lectures	PPT. Slides
11:15-11:30	Tea / Coffee				
11:30-12:30	Submodule STI and HIV		Etiological Management Syndromic Management STI/HIV co-infection	Lectures	PPT. Slides
12:30-1:30	Submodule		Correlation of HIV/TB	Lectures	PPT. Slides

	HIV/TB		HIV/TB Management		
1:30-2:30	Lunch				
2:30-3:30	Submodule • Comprehensive HIV/AIDS Care a. Principles of HIV prevention, treatment b. Care continuum Chronic care delivery	To understand the comprehensive care,ongoing care and follow-up for HIV/AIDS patients	Ongoing care through referrals for Care continuum Chronic care such as day care center Drop In center, linkages Palliative Terminally III	Lectures Panel discussion Role play	PPT. Slides PLHA NGO Nurse Physician
3:30-3:45	Tea / Coffee				
3:45-5:30	Field visit /Bed side			Visit to hospital	
Module 5 Organization of HIV/AIDS care and treatment services within health care facility and community					
Day 4					
9:30-10:30	Submodule ART as a team tasks (physicians, nurses, counselors, pharmacists, PLHA groups)	To establish ARV treatment units and develop linkages for care	Roles and responsibilities of treatment units and persons Training Delivery of services Referral linkages with district hospitals, NGOs and PLHA groups Supervision and monitoring of ART in district hospital	Lectures Discussion	PPT. Slides

10:30-11:15	Submodule Role of civil society, PLHA networks, NGOs and other stakeholders in Treatment adherence and drug resistance	To acquire counseling and management skills to improve treatment adherence	Counseling PLHA Outreach/ home visit Packaging, provision of drugs Guardian Psychosocial support Family Counseling	Working groups Role play Case studies	PLHA UNICEF handbook
11:15-11:30	Tea / Coffee				
Module 6 Training of trainers					
Day 4 (cont'd)					
11:30-12:15	Submodule State level trainers	To understand roles and responsibilities	Roles and responsibilities	Discussion	
12:15-1:00	Submodule Principles of adult learning	To understand principles of adult learning	Training technology		
1:00-1:30	Post test Closing				Questionnaire
1:30 onwards	Lunch				

Annexure II

CONFIDENTIAL

NATIONAL AIDS CONTROL ORGANIZATION

INDIVIDUAL ARV IDENTITY CARD

Patient's name _____

ARV Registration Number _____

Age _____ Sex _____

Address _____

Guardian's name _____

Weight (kg) (at presentation) _____

Date of starting 1st line ARV therapy _____

Specify 1st line regimen _____

Indication for starting ARV therapy (stage III, stage IV, CD4 count<200, other)

_____

Next follow up date _____

Date if Starting alternative 1st line regimen_____

Reason for Starting alternative 1st line regimen _____

Date of starting 2nd line ARV therapy _____

Reason for 2nd line ARV therapy _____

Current Treatment Unit _____

Annexure III

NATIONAL AIDS CONTROL ORGANIZATION

Patient Master Record Card for ARV: Unique ARV Registration Number _____

Name _____ Age _____ Sex _____ Wt.(Kg) _____ Transfer in (Y/N) Source of referral _____

Address (physical/PO Box) _____ Name of identifiable guardian _____

Date of starting 1st line ARV regimen(Specify d4T/3TC/NVP formulation) _____ Reasons for ARV_____

Dated of starting alternative 1st line ARV regimen(specify) _____ Date of starting 2nd line ARV regimen (specify) _____

Month	Date	Wt. Kg	Outcome stage					Of Stage Alive			Ambulatory states				Side effects		No. of pills in bottle	ARV given	ARV not given	CD4 counts
			A	D	DF	Stop	T	Amb.	Re-engaged prev. work	Not employed	Ambulatory	Bed	Y	N	Y	N				
Jan																				
Feb																				
Mar																				
Apr																				
May																				
Un																				
Jul																				
Aug																				
Sep																				

Oct																			
Nov																			
Dec																			

A – Alive, D – Dead, DF – Defaulted, Stop – Stopped, T – Transferred out Y- Yes P – Peripheral Neuropathy

N – No J – Jaundice

Ambulatory – able to walk to the treatment unit and walk around at home unaided if yes : mention CH – Cutaneous hypersensitivity

Bed – unable to walk to the treatment units and spend most of the time in bed at home Lf – Life failure

Annexure IV

NATIONAL AIDS CONTROL ORGANIZATION

ARV QUARTERLY COHORT ANALYSIS FORM:

NAME OF TREATMENT UNIT_____COHORT [specify the year and the quarter]_____Total number of patients initially registered for ARV in the cohort_____ Year in which evaluation is taking place_____
Quarter in which evaluation is taking place [Q1,2,3,4]_____
Of total number registered in the cohort:
Number Alive and on ARV therapy_____
[Alive and on first line regimen_____
[Alive and on alternative first line regimen_____
[Alive and on second line regimen_____
Dead_____
Defaulted_____
Stopped_____
Transferred out to another treatment unit_____
Of these Alive:
Number Ambulatory_____
With work status = yes_____
With side effects = No_____
With pill count in bottle 8 or less_____

Note: Pill count in bottle 8 or less is equivalent to 95% adherence

Annexure V

NATIONAL AIDS CONTROL ORGANIZATION

ARV Cumulative Annually Cohort Analysis Form:

NAME OF THE TREATMENT UNIT _____

Cohort [specify the year and the quarter] _____

Total number of patients initially registered for ARV in the cohort_____

Year in which evaluation is taking place _____

Quarter in which evaluation is taking place [Q 1, 2, 3, 4] _____

Of total number registered for ARV since ARV therapy started:

Number Alive and on ARV therapy_____

[Alive and on first line regimen_____

[Alive and on alternative first line regimen_____

[Alive and on second line regimen_____

Dead_____

Defaulted_____

Stopped_____

Transferred out to another treatment unit_____

Of those Alive since ARV therapy started

Number Ambulatory_____

With work status = yes_____

With side effects = No_____

With pill count in bottle 8 or less_____

Note: Pill count in bottle 8 or less is equivalent to 95% adherence

Annexure VI

Monthly Progress Report on ART

S. No.	Activity performed	Month	Cumulative
1.	Number of Officers trained in ART programme according to National guidelines • Public sector • Private sector		
2.	Number of Nurses and paramedical trained in ART programme • Public sector • Private sector		
3.	Number of hospitals providing treatment for opportunistic infections • Public sector • Private sector		
4.	Number of hospitals providing ART as per National guidelines • Public sector		

	• Private sector		
5.	Number of hospitals providing tests for CD4/CD8 • Public sector • Private sector		
6.	Number of new patients received ART in public sector hospitals • Children under 15 years • Women • Others		
7.	Total number of patients received ART • Children under 15 years • Women • Others		
8.	Number of individual who picked up their ART treatment at: 0 month 3 months 6 months		

9.	Number of patients dropped out during the month on account of side effects or other reasons		
10.	Number of drugs regimens distributed to patients _____ (a) (b) (c) (d) (e)		

ANNEXURE VII

Time line for Training :

	Starting from	Instt.s to be trained
1. Phase I	28th-29th January,04	Sensitization/ Consultation Workshops for National Trainers on ART
2. Phase I	15th Feb.,04	All 25 Institutions mentioned on page _____
3. Phase II	25th August	All Medical Colleges in 6 high prevalent States
4. Phase III	1st Jan' 06	All Medical Colleges in the Country and District hospitals of 6 high prevalence States
5. Phase IV	1st June,06	All district hospitals

* Note: In each training batch of 30, there will be two participants each from Intersectorals i.e. SAIL, Railways, ESIC, DGAFMS and private practitioners .

Training material

All the participants at the training sites will be provided:

- Draft NACO/ WHO Guidelines on he use of ART in India [December 2003]
- NACO/ WHO Guidelines on managing HIV/TB co infection
- NACO/ WHO guidelines on the diagnosis and management of Opportunistic infections
- Treatment, Follow up Monitoring formats
- Laboratory guidelines for CD4/ CD8 machines QA (WHO)
- VCCT guidelines
- A set of slides
- A directory of Networks of people living with HIV in the country

NACO/ SACS will make the training material available at the training centers.

Annexure VI

Drug and Logistics Stock Register

Name of the drug _____

Date	Stock at the start of the day	Daily consumption	Stock at the end of the day

Total			

Monthly summary

Stock at the start of the month (A)	
Consumption during the month (B)	
Stock received during the month (C)	
Stock at the end of the month A-B+C	

Annexure VII

Monthly Treatment Unit Report

Name of the Treatment Unit :_____

Name of the Treatment Unit incharge :_____

Report for the month / year : _____

A. PERFORMANCE

No. of patients on ARV at the start of the month | |

No. of patients screened for ARV eligibility during the month | |

No. of patient who commenced ARV during the month **Male** | |

Female | |

Total | |

No. of patients who discontinued treatment during the month:

Died | |

Defaulted | |

Stopped by choice | |

No. of patients who took < 95% of their drug doses this month | |

No. of patients who did not collect drug packets this month | |

No. of patients prescribed the first line treatment in this month ☐

No. of patients prescribed the second line treatment this month ☐

B. Drug Stocks: Was there a drug stock-out this month? ☐ Yes ☐ No

Item	Stock on first day of month	Stock received during the month	Consumption during month	Stock on last day of month	Amount requested

C. Training conducted during the month

Category of staff trained during the month	Number trained

Annexure VIII

PATIENT VISIT RECORD

Part A

Body Weight _____kg Pulse _____bpm BP _____ Temp _____^{0}C Resp Rate_____

PHYSICAL EXAMINATION: (tick if normal, describe if abnormal)

☐ General	.....	☐ Skin	.....
☐ ENT	.....	☐ Lymph nodes	.....
☐ Heart	.....	☐ Resp	.....
☐ Abdomen	.....	☐ GU	.....
☐ Musculoskeletal	.....	☐ Extremity	.....
☐ Neuro	.....	☐ Other (describe)	.....

HIV-RELATED ILLNESSES: new and ongoing (If new, indicate Start Date)

Are there any new HIV-related illnesses at this visit? ☐ no ☐ yes if **yes**, specify

	START DATE		COMMENTS
☐ oral candidiasis	___/___/___	☐	_____
☐ oral hairy leukoplakia	___/___/___	☐	_____
☐ pruritic papular eruption	___/___/___	☐	_____
☐ lymphadenopathy (> 1 cm on both sides)	___/___/___	☐	_____
☐ other HIV related illnesses:			
_____	___/___/___	☐	_____
_____	___/___/___	☐	_____

BASIC LABORATORY RESULTS

Haemoglobin _ _ . _ g/dl WBC _ _ . _ _ 10^{3}cells/µl Platelets _ _ _ _ 10^{9}/l

Total lymphocyte count _ _ . _ _ 10^{3}cells/µl

Glucose _ _ _ _ mg/dl Creatinine _ _ . _ _ mg/dl

ALT/ SGPT _ _ _ _ U/l

CD4+ cells _ _ _ _ /µl HIV-1 RNA _ _ _ _ _ _ _ copies/ml

Other lab results (e.g. CXR, AFB, culture, serology)

_____ _____

_____

_____

WHO Stage: ☐ I ☐ II ☐ III ☐ IV

CDC classification: ☐ A ☐ B ☐ C Any disease progression ☐ no ☐ yes

NOTES/PLAN: _____

_____

_____

_____

Follow-up Date:_____

Annexure VIII

Part B - Treatment Plan:

- ☐ **Initial 2 weeks of therapy**
  - ☐ d4T 30 mg + 3TC 150 mg twice a day
  - ☐ d4T 40 mg + 3TC 150 mg twice a day
  - ☐ AZT 300 mg + 3TC 150 mg twice a day
  - ☐ NVP 200 mg once a day
  - ☐ EFV 600 mg once a day
- ☐ **Continuation phase of ARV (after initial 2 weeks)**
  - ☐ d4T 30 mg + 3TC 150 mg + NVP 200 mg twice a day
  - ☐ d4T 40 mg + 3TC 150 mg + NVP 200 mg twice a day
  - ☐ AZT 300 mg + 3TC 150 mg + NVP 200 mg twice a day
  - ☐ d4T 30 mg + 3TC 150 mg twice a day + EFV 600 mg once a day
  - ☐ d4T 40 mg + 3TC 150 mg twice a day + EFV 600 mg once a day
  - ☐ AZT 300 mg + 3TC 150 mg + EFV 600 mg once a day

- ☐ **Other ARVs:**
  - ☐ Cotrimoxazole
    - ☐ 250 mg once a day
    - ☐ 250 mg twice a day
- ☐ **OI Prophylaxis**
  - ☐ Flucnazole
  - ☐ INH
- ☐ ddI

- ☐ 400 mg once a day
- ☐ NFV 1250mg twice a day
- ☐ ABC 300mg twice a day
- ☐ TFV 300mg once a day
- ☐ LPV/r 3 tablets twice a day
- ☐ SQV/r 1000mg/100mg twice a day
- ☐ Other _____

☐ Other _____

Annexure

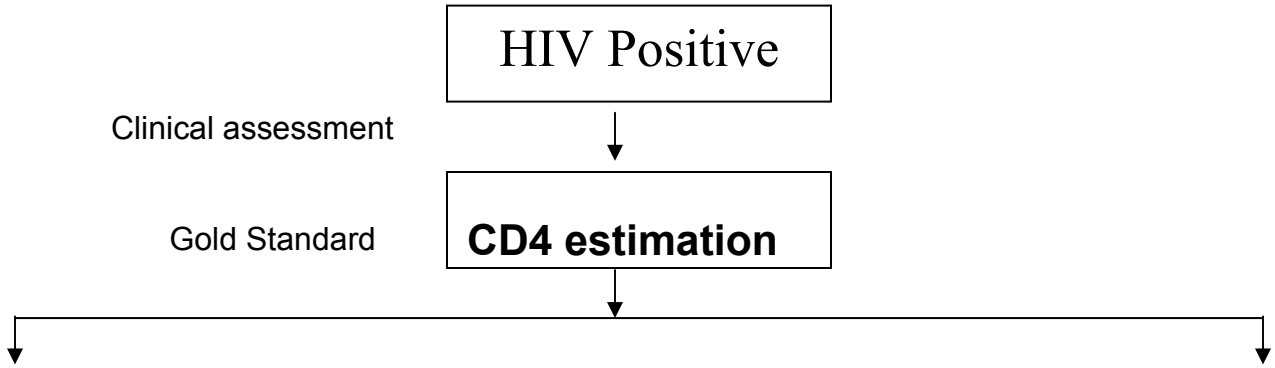
A list of CD4/CD8 Centers

1. Sir J.J Group of Hospitals, Mumbai
2. KEM Hospital, Parel, Mumbai.
3. B.J. Medical College, Pune.
4. Medical College, Panaji, Goa.
5. V. J. Medical College, Ahemedabad, Gujarat.
6. Gandhi Medical College, Bhopal, M.P.
7. Chaitram Hospital, Indore, MP.
8. Medical College, Guwahati, Assam.
9. J.N. Medical College, Imphal, Manipur.
10. Calcutta Medical College, Kolkatta, WB.
11. Instt. Of Thoracic Medicine, Tambaram, Chennai, TN.
12. Maduri Medical College, Maduri, TN.
13. Medical College, Thiruvananthapuram, Kerala.
14. Nizam Instt. Of Medical Sciences, Hyberabad, AP.
15. NIMHANS, Bangalore, Karnataka.
16. Govt. Medical College, Shimla, HP.
17. SMC, Jaipur, Rajasthan.
18. KG Medical College, Lucknow, UP
19. PGI Chandigarh

20. AIIMS, New Delhi.
21. NICD, Delhi.
22. RML Hospital, New Delhi.
23. Safdarjung Hospital, New Delhi.
24. Banaras Hindu University, Varanasi.
25. Lady Curzon & Bowering Hospital, Bangalore. (CII)
26. LNJP Hospital (CII)
27. Naga Hospital, Kohima (CII)
28. Osmania Medical college & Hospital Hyderabad. (CII)
29. C.M.C. Vellore. (WHO)
30. BYL Nair Hospital Mumbai (WHO)

NATIONAL AIDS CONTROL PROGRAMME

National Criteria for initiating Anti-Retroviral Therapy



If CD4 estimation facility available

- WHO Stage IV disease irrespective of CD4 cell count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary tuberculosis, recurrent invasive Bacterial infections, or recurrent/persistent mucosal candidiasis) with consideration of using CD4 cell counts < 350 mm3 to assist decision making.
- WHO Stage I or II disease with CD4 cell

If CD4 estimation facility not available

- WHO Stage IV disease irrespective of total lymphocyte count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic Diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary tuberculosis, Recurrent invasive bacterial infections, or recurrent/ persistent mucosal candidiasis) irrespective of total lymphocyte count
- WHO Stage II disease with a total lymphocyte

counts <= 200/mm3. count <= 1200/mm3

For WHO classification - refer to national implementation guidelines on ART