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Initiation of antiretroviral therapy

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Abstract

Go to:

With the widespread availability of antiretroviral therapy, there is a dramatic decline in HIV related morbidity and mortality in both developed and developing countries. Further, the current antiretroviral drug combinations are safer and the availability of newer monitoring assays and guidelines has vastly improved the patient management. The clinician needs to evaluate several key issues prior to institution of antiretroviral regimen including the correct stage of starting the treatment and the kind of regimen to initiate. In addition to various disease related factors, it is also critical to assess the patient's general condition including nutritional status, presence of co-morbidities and mental preparedness prior to starting the therapy. The patients need to develop an overall understanding of the treatment and its benefits and the importance of lifelong adherence to the drugs. The presence of special situations like pediatric age, older patients, pregnancy, lactation and presence of opportunistic infections also require modification of the therapy. This review briefly summarizes issues relevant to the clinician prior to the initiation of antiretroviral therapy.

Keywords: Antiretroviral therapy, children, HIV, hepatitis B and C, pregnancy, serodiscordant couples, tuberculosis, viral load

INTRODUCTION

Go to:

The introduction of antiretroviral therapy (ART) has revolutionized the treatment and management of patients with HIV infection. New drugs have been approved including those that offer new mechanisms of action, improvements in potency and activity against multidrug-resistant virus, and a favorable safety profile.[1] Simplified regimens have been introduced in recent years, including those of the fixed-dose drug combinations, providing a lower pill burden and dosing frequency.[2] This review focuses on key issues relevant to the clinician including when to initiate ART, the choice of the drugs, indications to change the initial regimen as well as the recommendations for special group of children, pregnant and breastfeeding women.

Goal of treatment

Eradication of HIV infection cannot be achieved with available ART even when new, potent drugs are

added to a regimen.[3] The main goals of the treatment includes better control of HIV replication, restoring and preserving the immune system, improving survival and the quality of life, reducing HIV related mortality and morbidity along with decreasing the HIV transmission and preventing new infections.[4]

Considerations for starting the treatment

Before selection of an initial ART regimen, clinicians must make several decisions based on various factors. The first, and perhaps the most important in decision making, is to decide when to start the treatment and what regimen to initiate [Table 1]. There are various diseases as well as patient factors that need to be considered before taking the decision.

Secondly, it is also important to assess the patient's readiness prior to initiation of ART as well as prepare the patient for it. The patients need to develop an overall understanding of treatment and its benefits, the importance of lifelong adherence to drugs and the consequences of sub-optimal adherence (progression of disease, resistance, expensive second-line regimens) and only then should the treatment be initiated.[5]

Baseline evaluation

For every HIV patient, a complete medical history, physical examination, and laboratory evaluation should be done and counseling regarding the implications of HIV treatment given. These laboratory tests can be used to stage HIV disease and to assist in the selection of ART. In addition, other tests including screening for sexually transmitted infections and tests for determining the risk of opportunistic infections (OI) and the need for prophylaxis should be performed. In the case of previously treated patients who present for an initial evaluation, it is critical to obtain a complete ART history including drug resistance testing results, if available.

The CD4 T-cell count serves as the major laboratory indicator of immune function in HIV patients, determining both the urgency of ART initiation and the need for prophylaxis for OIs. It is also the strongest predictor of subsequent disease progression and survival.[6,7] Plasma HIV-1 RNA levels serves as a surrogate marker for treatment response and can be useful in predicting clinical progression.[8,9]

When to start treatment

There has been a persistent debate about when to start ART, particularly in asymptomatic treatment-naove patients, and upon which CD4 cell count and/or viral load thresholds, if any, to base this decision. One consistent and concurrent recommendation throughout all the guidelines has been recommended to treat patients with an AIDS-defining condition regardless of CD4 cell count or viral load.[10]

Until recently, the World Health Organisation (WHO) 2010 guidelines recommended the initiation of ART in treatment-naove HIV-infected patients with a CD4 cell count equal to or less than 350 cells/ml, regardless of symptom status.[11] This was based on results of observational cohort data as well as randomized control trials showing decreased risk of disease progression, death, and reduced vertical transmission when initiating ART at CD4 count thresholds of less than 350 cells/ml.[12,13,14,15] However, the latest WHO recommendations expand the eligibility for ART initiation to a CD4 count threshold of 500 cells/mm^3 or less for adults, adolescents and children (five years and older), while prioritizing symptomatic patients, those with advanced disease or CD4 cell count of 350 cells/mm^3 or less.[16] This new recommendation is supported by the results of a systematic review of 21 observational studies and 3 randomized controlled trials that show reduced morbidity and mortality[17] and reduced HIV transmission[18] on early initiation of treatment. Also, cost effectiveness models have showed that expanding ART eligibility to ≤500 cells/mm^3 may result in substantial health benefits and be cost effective

in most epidemic settings.[19] In totality, early initiation of ART reduced the risk of death, progression to AIDS and/or death, tuberculosis, development of a non-AIDS-defining illness and increased the likelihood of immune recovery.

However, there is insufficient evidence to recommend initiation of ART at CD4 cell count over 500 cells/mm^3 or in men having sex with men, transgender people, people injecting drugs, and sex workers; HIV-infected individuals who are 50 years of age and older; and those who are co-infected with HIV-2 or hepatitis C virus (HCV). The recommendations for these patients should follow the same general principles as for other adults and adolescents with HIV.[16]

However, for some patients, the potential risks of short or long-term drug-related complications and non-adherence to therapy in asymptomatic patients may offset possible benefits of earlier initiation of therapy.[17,18] Regardless of CD4 cell count, the decision to initiate ART should always include consideration of any co-morbid conditions, the willingness and readiness of the patient to initiate therapy, and the availability of resources.

OVERVIEW OF ART DRUGS

Go to:

Which regimen to start?

The main principle of ART is a ‘combination therapy’ with at least three effective drugs from two classes to achieve full viral suppression with immune reconstitution and prevent development of immune resistance. The recommendations for preferred and alternative first-line antiretroviral (ARV) drugs have evolved considerably over the past 17 years based on factors including efficacy, safety, and convenience.

It traditionally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone in combination with a third ‘cornerstone’ ARV drug that consists of either a ritonavir-boosted protease inhibitor (PIr) or a nonnucleoside reverse transcriptase inhibitor (NNRTI). More recently, raltegravir and maraviroc, have been studied in combination with a dual-NRTI backbone and are approved for use in treatment-naove patients.[2,4]

The essential principle of constructing an effective second/third-line regimen is to combine at least two or preferably three fully active drugs. These drugs should ideally include one from a new class (e.g. PI/r if NNRTI based first-line regimen) or those drugs from the same class of drugs with the least likelihood of resistance as determined by genotypic resistance testing (GRT). Choosing an active drug using GRT has better outcomes than based on expert opinion alone.[20,21] Genotypic resistance testing has to be performed when the patient is on or within two weeks of discontinuation of a failing regimen.

Early identification of second-line regimen failure is critical to preserve effective ARV options. CCR5 inhibitors, second generation NNRTIs and entry inhibitors are available in resource rich settings to construct salvage regimens.[22,23,24]

Alternative regimens

The alternative regimen list includes effective and tolerable options but have potential disadvantages compared to preferred regimens. For some patients, based on individual factors, an alternative regimen can be a preferred option. The acceptable list includes third-line regimens that can be selected but are not as satisfactory as preferred or alternative options and those regimens fall under the category where there is a lack of sufficient data required for its placement into a higher category.[2]

ART regimens to avoid

Over a time period, information has accumulated on which ARV drugs should not be used in combination due to suboptimal efficacy or drug interactions that result in heightened toxicities or other unwanted effects [Table 2].[2]

Monitoring ART

There are no definitive standards for laboratory monitoring of ART. The key goals are to assess the immune as well as virological response to treatment and to detect drug toxicities. In patients on ART, the CD4 cell count is used to assess the immunologic response to ART and the need for initiation or discontinuation of prophylaxis for opportunistic infections.[6,7] Viral load monitoring provides an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation of drug-resistance mutations and improving clinical outcomes and also helps to discriminate between treatment failure and non-adherence.[8,9,25,26,27,28] However, the utility of virologic monitoring has been debated and trials have not shown much advantage in using viral loads to monitor treatment response (especially disease progression and mortality) as compared to immunological and clinical monitoring.[29,30,31] Genotypic resistance testing of the virus strain should be performed wherever facilities are available especially in cases with treatment failure. Clinical trials have demonstrated that consultation with specialists in HIV drug resistance improves virologic outcomes.[32] The frequency of monitoring other parameters is driven by the specific reasons, drugs used and individual patient considerations and as per clinical signs or symptoms [Table 3].

CO-INFECTIONS

Go to:

HIV and tuberculosis

The HIV pandemic has fueled a rise in both TB incidence and mortality, particularly in population with limited resources. In addition to being the most common co-morbidity, TB is also the leading cause of death in HIV-infected patients.[33] An increase in incidence of multidrug-resistant TB as well as extensively drug resistant TB has also been observed in these patients.[34]

The optimal time to initiate ART in those on anti-tubercular therapy (ATT) is not defined. Survival is improved when ART is started early following the initiation of ATT,[35,36,37] but a delay in initiating ART often was favored because of drug interactions, shared drug toxicities, immune reconstitution inflammatory syndrome (IRIS) and high pill burden and adherence issues.

As per the 2013 WHO guidelines, ART should be started in all TB patients including drug-resistant TB, irrespective of the CD4 cell count. ATT should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. The HIV-positive TB patients with profound immunosuppression (CD4 cell counts less than 50 cells/mm^3) should receive ART immediately within the first two weeks of initiating ATT.[16]

The treatment of active TB disease in HIV-infected patients follows the general principles guiding treatment for individuals without HIV. However, Efavirenz should be used as the preferred NNRTI in patients starting ART while on ATT.[16]

Current guidelines recommend a 6-month rifampicin-based regimen for treatment of pulmonary TB regardless of HIV status. However, this has been linked to higher probability of relapse.[38,39] A recent meta-analysis of randomized, controlled trials and cohort studies found that at least an 8 months duration of therapy, daily drug dosing during the initial phase of treatment, and concurrent ART are associated with improved outcomes in HIV-associated TB.[40]

HIV and hepatitis B and C

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure.[41,42] In individuals co-infected with hepatitis B virus (HBV) and/or HCV, ART may attenuate liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.[43,44] Although, ARV drugs do not inhibit HCV replication directly, HCV treatment outcomes improve when HIV replication is controlled or CD4 cell counts are increased.[45] The WHO 2010 guidelines recommended initiating ART in all individuals co-infected with HIV and HBV with chronic active hepatitis, regardless of CD4 cell count or WHO clinical stage.[3] However, due to insufficient evidence on favorable risk-benefit profile to support early initiation of ART in all co-infected patients and increased risk of hepatotoxicity, IRIS and hepatic flare[3], the 2013 guidelines recommend providing ART to all people co-infected with HIV and HBV counts with evidence of severe chronic liver disease regardless of CD4 and those at greatest risk of liver disease progression and mortality.[16] The ART regimen should include drugs with activity against both HIV and HBV such as tenofovir, lamivudine and emtricitabine which improves viral load response and reduces development of HBV drug resistance.[16] For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.

For HIV patients co-infected with HCV, there are no clear guidelines for initiating ART and it is recommended to follow the same principles as in HIV monoinfection.[16] However, combined treatment of both HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities.

SPECIAL SITUATIONS

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HIV in children

In HIV positive children, mortality in untreated infants ranges from 20-25% in developed countries which accounts to 35% in infants and 53% by 2 years of age in resource-limited settings.[46,47] Infants are the most vulnerable as the natural progression of HIV can be rapid and independent of CD4+ cell count and viral load.[48,49] Disease progression in children aged >1 year is slower than in infants and correlates better with clinical, immunologic, and virologic criteria with the CD4+ values (CD4+ count and CD4+%) being the most important marker of mortality.[50] In children, the decision to start ART depends on age and immune maturation as well as other drug- and family-related factors [Table 1]. Early initiation of ART in HIV-infected infants greatly reduces mortality and progression to AIDS and growth catch-up.[51,52]

Latest WHO 2013 guidelines differ from the previous ones in recommending initiation of ART universally in all children less than 5 years of age, regardless of CD4 counts prioritizing the HIV-infected children 1-2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤750 cells/mm^3 or <25%, whichever is lower.[16] The course of HIV progression in children aged over 5 years is similar to that in adults, and traditionally adult treatment thresholds are applied. The current WHO guidelines have lowered CD4+ cell count thresholds for ART initiation for children aged >5 years to 500 cells/mm.[3,16]

Current guidelines of management of adult HIV and tuberculosis, Hepatitis B and C and other OIs can be extrapolated to children as well. However, with HCV co-infection in children less than 3 years of age, treatment is generally not recommended because of high spontaneous clearance (17-59%) in this age group.[53]

Metabolism, hepatic and renal function undergo rapid maturational change in the first 6 months of life,

explaining substantial differences in drug pharmacokinetics and dosing regimens in infants and young children. The recommended ART regimens differ in children as per age, and are tabulated in Table 4.

Pregnant and breastfeeding women

The availability of ART has driven the transmission rates of HIV from approximately 20% to 30% to <0.5% and has dramatically reduced the numbers of new cases of HIV infection in children.[54] In 2010, the WHO guidelines recommended life-long ART for pregnant women with CD4 cell count of 350 cells/mm^3 or less, and two complex prophylaxis options for those not yet eligible for ART^3. Option A provided twice, daily zidovudine to the mother from 14 weeks of gestation to the onset of labor, and single-dose nevirapine and twice, daily zidovudine and lamivudine given for seven days post-partum. Option B provided triple ARV therapy to the mother until her delivery or if breastfeeding was continued until one week after all infant exposure to breast milk had ended. Both prophylaxis options included four to six weeks of peri-partum nevirapine prophylaxis given to the infants.

In 2013, WHO recommends ART in one simplified regimen to all pregnant and breastfeeding women regardless of CD4 cell count during the period of risk of mother-to-child transmission (MTCT).[16] This continuation of life-long ART is recommended, particularly in generalized epidemic settings with high rates of fertility, and limited access to CD4 testing. This provides important programmatic and clinical benefits, including harmonization of the ARV regimen with that used in non-pregnant adults, ease of implementation and avoidance of stopping and starting drugs with repeat pregnancies and so provide early protection against MTCT in future pregnancies. Earlier ART may also reduce the high post-partum mortality, as well as offer protection from HIV transmission to the partner or spouse.[55]

A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized post-partum.[16]

In a well-resourced settings, the complete avoidance of breastfeeding has been a major factor in reducing transmission, and breastfeeding is not recommended for HIV-infected women (including those receiving ART), although it is not a feasible option in many low-resource settings. Continuation of ART during breastfeeding is important to decrease the risk of transmission to the infant.[55]

ART in serodiscordant couples

Lower plasma HIV-RNA levels are associated with decreases in the concentration of the virus in genital secretions.[56,57] Studies of HIV-serodiscordant heterosexual couples have demonstrated reduced risk of transmission of HIV when plasma HIV-RNA levels are lower.[58,59,60] Results of HPTN 052 study and other observational cohort studies along with modeling analyses show a decreased rate of HIV transmission in serodiscordant heterosexual couples following the introduction of ART, and demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs), which substantially reduces the risk of transmission of HIV.[18,61,62] Therefore, it is recommended that ART be offered to patients who are at risk of transmitting HIV to sexual partners regardless of CD4 count or symptoms.[16]

Use of ART for the infected partner and antiretroviral pre-exposure prophylaxis (PrEP) for the uninfected partner as HIV prevention is recommended for heterosexual discordant couples; especially couples who do not have access to assisted reproductive techniques and also those wishing to conceive in a natural way [

Table 5].

HIV in older age group

Concerns about decreased immune recovery and increased risk of serious non-AIDS events favor initiation of ART in patients >50 years of age regardless of CD4 cell count. At present, there are no separate recommendations on ART regimens on basis of age. The choice of regimen depends on the patient's other medical conditions and medications. Frequency of monitoring parameters of ART effectiveness and safety for adults age >50 years are similar to those for the general HIV-infected population.[16] Complex dosing requirements, high pill burden, inability to access medications because of cost or availability, misunderstanding of instructions, depression, and neurocognitive impairment and poor adherence are key management issues in these patients.

General care for people living with HIV

In addition to ART, a good general care for people living with HIV goes a long way in promoting a general well being and a good quality of life for the patient along with reducing HIV transmission and prevention of infection. It includes overall assessment of the patient for past and current HIV related conditions, WHO clinical staging, nutrition and growth and development in children and adolescents. It also includes screening for OI, STI, other co-morbidities, mental illness and substance use. Counseling for disclosure, risk reduction and HIV prevention, psychosocial support and providing advice on family planning and contraception, prevention of mother-to-child transmission (PMTCT) and infant and child feeding is an integral component of the general care. It is also important to assess the patient's readiness prior to initiating ART as well as preparing the patient for it.[16]

Role of nutrition

Nutrition plays an important role in maintenance of immune system. An immune deficiency as a result of HIV/AIDS leads to malnutrition, and malnutrition further perpetuates immune deficiency, increases the risk of developing opportunistic infections, especially TB and also, contributes to more rapid progression to AIDS. It also results from the wasting syndrome, hypermetabolic states in acute infections and side effects of drug treatment. In many areas of the developing world, HIV infection and malnutrition co-exist.[63] Malnutrition should be detected early, treated and monitored, to improve the ability to respond to therapies as well as survival and quality of life. It is also an important consideration in the pregnant and lactating women as well as infants and the growing children, where providing an early and adequate nutrition support is one of the most important intervention.

Psycho-social support

In the context of ART, it is imperative to provide appropriate social, psychological, and instrumental support to the patient for his overall well being as well as to enhance optimal adherence. In addition to HIV associated mental health problems, numerous individual-level and structural-level factors account for poor adherence. The various factors include poor health literacy, non-adherence in asymptomatic stage and social factors like widespread stigmatization and discrimination.[64]

CONCLUSION

Go to:

Optimum management of HIV positive patient requires in-depth knowledge of available drugs, monitoring options, impact of OIs and other co-morbid conditions and an interdisciplinary approach with coordination with psychologists, nutritionists, counselors and social workers. Table 6 summarizes the issues to be considered prior to starting ART.

MCQS

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1. Leading cause of death in HIV infected patients is
    a. Tuberculosis
    b. Kaposi sarcoma
    c. Cryptococcal meningitis
    d. Hepatitis B
2. The HIV positive TB patients with CD4 count <50 cells/mm^3 should be started on
    a. ART after completion of AKT.
    b. ART immediately within 2 weeks of starting AKT
    c. ART only
    d. AKT only
3. Which is the preferred NNRTI for patients started on ART while on AKT.
    a. Nevirapine
    b. Efavirenz
    c. Delavirdine
    d. any of the above
4. First line ART recommended in pregnant & breast feeding women is
    a. AZT+3TC+EFV
    b. TDF+3TC+EFV
    c. D4T+3TC+EFV
    d. AZT+3TC+NVP
5. Infants of mothers who are receiving ART should
    a. Not be given prophylaxis
    b. receive AZT+NVP prophylaxis for 10 weeks
    c. Receive daily NVP prophylaxis for 6 weeks
    d. Receive daily NVP prophylaxis for 10 weeks
6. When to start ART in patients >50 years of age
    a. CD4 count <250 cells/mm^3
    b. CD4 count <350 cells/mm^3
    c. CD4 count <150 cells/mm^3
    d. Regardless of CD4 count
7. WHO now recommends initiation of ART in asymptomatic PLHA adults with CD4 count.
    a. <350 cells/mm^3
    b. <250 cells/mm^3
    c. <150 cells/mm^3
    d. <500 cells/mm^3

1. a, 2. b, 3. b, 4. b, 5. c, 6. d, 7. d

Footnotes

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Figures and Tables

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Table 1

Regimen	Level of evidence
Preferred regimens	
NNRTI-Based Regimen	AI
EFV/TDF/FTC[a]	
PI-Based Regimens	AI
ATV/r+TDF/FTC[a]	
DRV/r (once daily)+TDF/FTC[a]	
INSTI-Based Regimen	AI
RAL+TDF/FTC[a]	
Alternative regimens	
NNRTI-Based Regimens	
EFV+ABC/3TC[a]	BI
RPV/TDF/FTC[a]	BI
RPV+ABC/3TC[a]	BIII
PI-Based Regimens	
ATV/r+ABC/3TC[a]	BI
DRV/r+ABC/3TC[a]	BII
FPV/r (once or twice daily)+ABC/3TC[a] or TDF/FTC[a]	BI
LPV/r (once or twice daily)+ABC/3TC[a] or TDF/FTC[a]	BI
INSTI-Based Regimen	
EVG/COBI/TDF/FTC[a]	BI
RAL+ABC/3TC[a]	BIII
Acceptable regimens	
NNRTI-Based Regimen	
EFV+ZDV/3TC[a]	
NVP+(ABC/3TC[a] or TDF/FTC[a] or ZDV/3TC[a])	
RPV+ZDV/3TC[a]	
PI-Based Regimens	

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Quality of evidence of recommended antiretroviral therapy regimen

Table 2

ARVs/regimens	Reasons
Mono, dual therapy	Sub-optimal potency and resistance development
3-4 NRTIs	Resistance, decreased potency
TDF+ddI+NNRTI	Higher risk of failure; drug interactions
TDF+ABC	Non additive, resistance
D4T+ddI	Additive toxicity
Unboosted PIs	Poor biovailability
Dual NRTIs	Increased adverse effects
D4T+AZT	Antagonist

NNRTI=Nonnucleoside reverse transcriptase inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor; ABC=Abacavir; D4T=Stavudine; ddI=Didanosine; TDF=Tenofovir; AZT=Zidovudine

Antiretroviral combinations to be avoided

Table 3

Test	Baseline	Subsequent
HIV serology	+	
CD4	+	q6m, at treatment failure
HIV-RNA levels	±	After 6m of ART initiation, annually thereafter, at treatment failure
HLA-B*5701testing	If considering ABC	
Tropism testing	If considering a CCR5 antagonist	
Tuberculosis screening	+	As per clinical indication
Screening for other STIs	+	As per clinical indication
HBsAg & Anti-HCV	+	
Pregnancy test	+	Before initiating ART (esp EFV)
Cryptococcus antigen	if CD4 count≤100 cells/mm^3	As per clinical indication
Haemogram	+	2wk, 4wk, 3m (esp AZT), q6m
Kidney function tests	+	q6m (esp TDF)
Liver function tests	+	As per clinical indication (esp NVP)
Lipid Profile	+	Annually & when changing regimen
Blood sugar	+	Annually & when changing regimen
Cervical PAP smear	+	Annually
Genotypic resistance testing	±	Indicated at ART failure

HIV–Human immunodeficiency virus; HCV–Hepatitis C virus; STI–Sexually

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Laboratory monitoring after initiation of antiretroviral therapy

Table 4

When to initiate ART (ARV-naïve individuals)			
Population	**Target population**	**2010 ART guidelines**	**2013 ART guidelines**
Adults and adolescents	HIV-infected individuals	CD4 cell count ≤350 cells/mm^3 or WHO clinical stage 3 or 4 regardless of CD4 cell count	CD4 cell count ≤500 cells/mm^3 or WHO clinical stage 3 or 4 regardless of CD4 cell count
	HIV-infected pregnant and breastfeeding women	CD4 cell count ≤350 cells/mm^3 or WHO clinical stage 3 or 4 regardless of CD4 cell count	Regardless of CD4 cell count or WHO clinical stage
	HIV-infected partners in serodiscordant couple relationship(s)	No recommendation established	Regardless of CD4 cell count or WHO clinical stage
	HIV/TB co-infection	Presence of active TB disease, regardless of CD4 cell count	No change
	HIV/HBV co-infection	Evidence of chronic active HBV disease, regardless of CD4 cell count	Evidence of chronic HBV disease with severe liver disease (e.g., cirrhosis), regardless of CD4 cell count
Children	HIV-infected children≥5 years old	CD4 cell count ≤350 cells/mm^3 or WHO clinical stage 3 or 4 regardless of CD4 cell count	CD4 cell count ≤500 cells/mm^3 or WHO clinical stage 3 or 4 regardless of CD4 cell count
	HIV-infected children 1-5 years old	1. Between 12 and 24 months of age, regardless of CD4 cell count or WHO clinical stage 2. Between 24 and 59 months of age with CD4 cell count of ≤750 cells/mm^3 or CD4% ≤25, or whichever is lower, regardless of WHO clinical stage	Regardless of CD4 cell count and WHO clinical stage
	HIV-infected infants <1 year old	All infants, regardless of CD4 cell count and WHO clinical stage	No change
What ART regimen to start with (ARV-naïve individuals)			
Adults and adolescent	HIV-infected individuals HIV-infected pregnant and breastfeeding ARV-naïve women HIV/TB co-infection HIV/HBV co-infection	AZT or TDF+3TC (or FTC)+EFV or NVP AZT+3TC+NVP or EFV AZT or TDF+3TC (or FTC)+EFV TDF+3TC (or FTC)+EFV	TDF + 3TC (or FTC)+EFV(as a fixed-dose combination)
Adolescents	Weighing <35 kg		ABC (or AZT or TDF)+3TC+EFV
Children	≥3 years old <3 years old**		ABC (or AZT or TDF)+3TC+EFV ABC (or AZT)+3TC+LPV/r (regardless of PMTCT exposure)

FI=3TC=Lamivudine; ABC=Abacavir; EFV=Efavirenz; FTC=Emtricitabine; LPV/r=Lopinavir/ritonavir; NVP=Nevirapine; TDF=Tenofovir; AZT=Zidovudine

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Comparison of WHO recommendations on when to start ART and choice of drug regimen between 2010 and 2013

Table 5

M+F-serodiscordant couples
Risk reduction approaches
1. Infected partner on ART with suppressed viral load (or on effective regimen for 6 months)
2. Daily oral PrEP with FTC/TDF for the uninfected partner until pregnancy achieved
3. Sex without condoms limited to peak fertility

F+M-serodiscordant couples
1. Infected partner on ART with suppressed viral load (or on effective regimen for 6 months)
2. MMC
3. Daily oral PrEP with FTC/TDF for the uninfected partner until pregnancy achieved
4. Sex without condoms limited to peak fertility

PrEP=Pre-exposure prophylaxis; FTC=Emtricitabine; TDF=Tenofovir; MMC=Male medical circumcision

Recommendations for mutually disclosed serodiscordant couples who choose to attempt conception through intercourse and have completed baseline fertility and preconception evaluation(s)

Table 6

When to start
Severity of HIV disease and risk of progression-determined by:
Age
Symptoms/clinical stage
CD4+cell count and CD4+%
Viral load
Acceptance by the patient & family
Special situations-pregnancy, lactation
Pre/Post Exposure prophylaxis
What to start
Available drugs
Children-formulations, Palatability
Previous ART exposure
Drugs
Potency
Frequency of dosing
Fixed dose combinations availability
Side effects
Resistance
Drug interaction (with other medications taken by patient)
Co-morbidities:
TB
Hepatitis B, C
Other opportunistic infections
Chronic illnesses (liver, renal, cardiovascular, diabetes)

ART=Antiretroviral therapy; HIV=Human immunodeficiency virus; TB=Tuberculosis

Consideration prior to starting the combination antiretroviral therapy