Second Arab Congress of Clinical Microbiology and Infectious Diseases

May 24-26, 2012.

Tunisian recommendations on ART : process and results

M. BEN MAMOU
UNAIDS
Email: BenmamouM@unaids.org

M. CHAKROUN
Department of infectious diseases.
University Hospital. Monastir, Tunisia.
Email: mohamed.chakroun@rns.tn

Outline

- Process of elaborating ART national recommendations
- Presentation of national recommendations content

ART national recommendations :

1- **Elaboration process**

Introduction

- The prevalence of HIV infection is low in general population: 0,06 %; **concentrated in key populations** :13 % MSM, 2.5 % IDUs (2011).
- The reported annual number of new cases varies from 50 to 70.
- Reported cases (2010): Heterosexual transmission is the most frequent (49%) followed by drug use by injection (30%) and sexual transmission among men (6%).
- Prospective MoT study (2012) : future of the epidemics dominated by transmission through unprotected sex between men.

Background of ART in Tunisia

- **Free and universal ART** introduced in Tunisia in October 2000 + immuno-virological monitoring (all eligible patients on clinical and laboratory criteria).
- Therapeutic management and biological monitoring of PLHIV : **4 departments of infectious diseases** including 2 laboratories of Virology and Immunology.
- Number of **people under ART : 379 (2010) ; 483 (2012).**
- Sequence resistance testing on routine basis since August 2009 ; **68.3 % mono-resistance**.

Background of ART in Tunisia

- Since 2000 : **Agreement on first-line protocols** led by National committee of ART, care and psycho-social support of PLHIV.
- 2006-2009 : **Shortcomings, mismatch between orders, prescriptions, stocks of ARVs and treatment needs of patients.**

➔ **Need to organize, harmonize, standardize and coordinate ART**

Infectious diseases practitioners, lab specialists & pharmacists

National AIDS Programme managers

Process of elaborating ART national guidelines

- **October 2009 :** national workshop on ART counseling : need to develop **national guidelines** that take into account the specific Tunisian context & international requirements.
- **November 2009 : WHO updates ART recommendations** and encourages countries to adapt these generic guidelines to their national context**.**
- **November 2009- January 2010 : Advocacy of STPI** for ART national guidelines.
- **February 2010 : National task force*** mandated by Tunisian health authorities to develop and lead a national processes to produce national guidelines for antiretroviral therapy.

**Tunisian Society of Infectious Diseases (STPI), DSSB (NAP), national committee of ART, care and support of PLHIV, HIV reference lab CoMaLI NGO, UNAIDS.*

Expected results of the process

Expected outcomes :

- ART fulfill international requirements and matches epidemiological situation of HIV resistance.
- ART prescriptions are consistent with a public-health approach.
- ART management is harmonized and coordinated both at central and regional levels.

Expected product : consensus document of ART recommendations based on a public health approach, combining the situation of HIV resistance to the national and international recommendations.

Methodology

Recommendations for clinical practice (professional practice guidelines) and not consensus methodology.

Area : antiretroviral therapy

4 working groups :

Group 1: First line ART.

Group 2: Management of treatment failure.

Group 3: Management of side effects.

Group 4: ARV prophylaxis.

Each group : a coordinator + 6 to 10 members including university hospital and private infectious disease specialists, virologists and pharmacists.

Methodology

Rating the recommendations :

A : Randomized comparative trials, or randomized trials meta-analyses

B : Non randomized trials ; cohorts or case-control studies

C : Descriptive studies, expert opinions

Recommendations criteria :

- Evidence level
- Balance between positive & side effects
- Acceptability
- Cost and financial implications
- Feasibility

Key steps of the process

- **3 & 12 February 2010** : Task force : discussions and concept note on work methodology.
- **2 March 2010 :** extended meeting with national experts & stakeholders
- **April 2, 2010 :** meeting to present and discuss unpublished local data on antiretroviral resistance
- **March-April 2010 :** each group members work and exchange information by email, coordinator role.
- **Early May 2010 :** first draft reports provided by the 4 groups to reading committee
- **12 -13 May 2010 :** national workshop : discussions and consolidation the various recommendations specifying the strength and grade, inclusion of PLHIV. *(WHO + French experts)*
- **May-July 2010 :** Finalization of recommendations document

Lessons learned of ART recommendations development and implementation

Strengths :

- **Commitment and accountability of national experts** (whole process performed with minimal external technical support) : ownership and adaptation to specific context
- **Partnership** between multiple stakeholders (NAP, infectious diseases society, lab, pharmacies, technical partners)
- **Consultative and inclusive process**

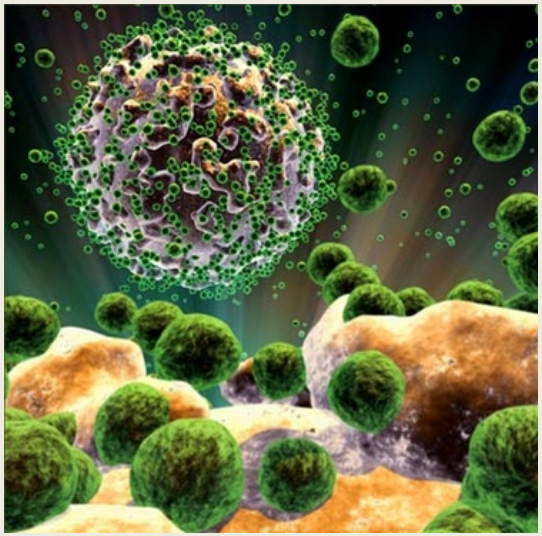
To be improved :

Linkages with and structure/organization of **ARV Procurement and Supply management system**

ART national recommendations :
2- Presentation of the content

La trithérapie antirétrovirale
Recommandations de pratique clinique

2010



ONUSIDA
PROGRAMME COMMUN DES NATIONS UNIES SUR LE VIH/SIDA
HCR UNICEF PAM PNUD UNFPA ONUDC OIT UNESCO OMS BANQUE MONDIALE

DSB
DIRECTION DES SOINS DE SANTE DE BASE

Tunisian recommendations

- Infection in adults
- PMTCT
- Infant infection

When to start ART?
Primary infection

ART is highly recommended (Strong recommendation, grade A) in :

Patients with severe symptoms, especially neurological, and / or sustainable symptoms, and / or opportunistic infections.

When CD4 count < 350/mm^3 at diagnosis

And during pregnancy

- Treatment may be considered if the CD4 count is between 350 and 500/mm^3, especially if the VL > 10^5 copies/ml. Without treatment, these patients should be closely monitored.
- The treatment is not recommended for patients with few symptoms and CD4 count > 500/mm^3.

When to start ART?
Chronic infection

ART is highly recommended (Strong recommendation, grade A) in :

Symptomatic patients

Asymptomatic patients with CD4 count < 350/mm^3

Initiation of ART may be recommended if **CD4 count is between 350 and 500/mm^3 with high VL** (> 10^5 copies/ml) and / or **rapid decrease in the CD4 count** (> 50-100/mm^3/year) or **age > 50 years** or **high cardiovascular risk.**

When to start ART?

Co-infection HIV/HCV or HVB

Co-infection HCV / HIV: ART should be initiated before HCV therapy.
If CD4 count > 500/mm^3, it is possible to treat VHC before initiating ART

(Strong recommendation, grade C).

Co-infection HIV / HBV: ART is recommended when there is indication to treat VHB, regardless to CD4 count

(Strong recommendation, grade C).

Preparation to therapy

It is recommended to :

- Prepare the patient for treatment to optimize compliance.
-Achieve a clinical and laboratory assessment in all patients before initiating ART (physical examination, CD4 count, VL, biological and serological test, etc.)

(Strong recommendation, grade C).

How to treat ?

Primary and chronic infection : first line

Primary infection : 2 NRTIs + 1 PI/r (lopinavir/r) is preferred

(Strong recommendation, grade A).

Chronic infection : 2 NRTIs + 1 PI/r or 1 NNRTI

AZT + 3TC or FTC + Lop/r or ATZ /r or EFV

Alternatives :

- TDF or ABC and ddI if intolerance.
- d4t is not recommended : neurological toxicity .

How to treat ?

Special situations

Anemia : TDF is preferred
HBV : TDF+ (FTC or 3TC) is preferred + PI / r or NNRTIs

HCV : TDF or ABC + (3TC ou FTC) + LPV/r.

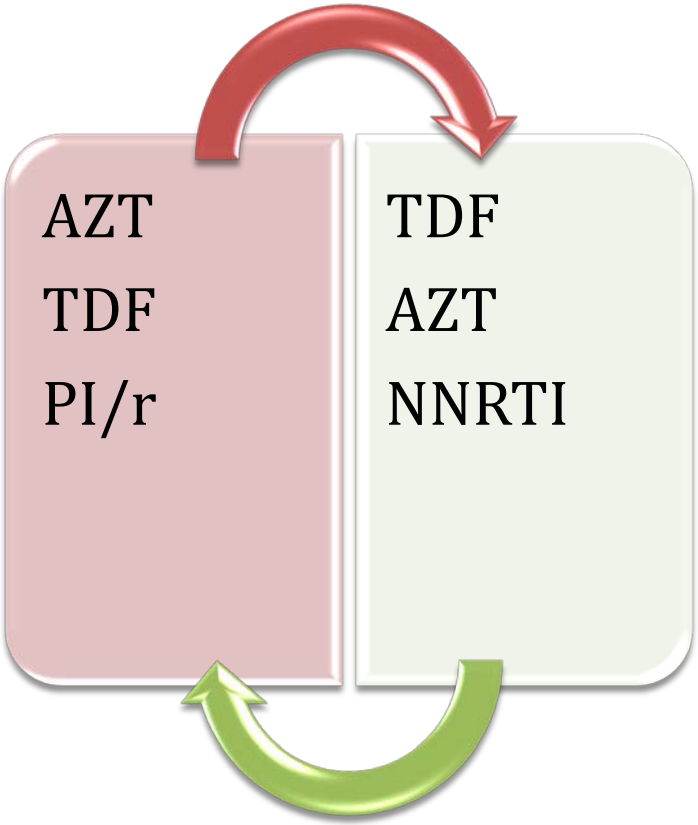
TB : AZT or TDF + 3TC or FTC + EFV.
PI/r is recommended when using rifabutin

High cardiovascular risk: Prefer ATZ / r due to a better lipid profile.
ABC should be avoided if VL > 10^5 copies / ml

Some ARV associations should be avoided because lack of power or toxicity: TDF + ddI , d4t + 3TC , AZT + ddI , TDF + ABC + 3TC.

Second and third line of ART

- Failure of a first-line treatment ➔ we should focus on strengthening compliance and switching to a second-line treatment.



If necessary : use
ABC or ddI

Third line : 2 NRTIs (at least one not used on first or second line) + Darunavir/r or Etravirine or Raltegravir

Preventing transmission of HIV from infected women to children. What ART regimen to initiate ?

First line regimens

Tunisian recommendation 2010	AZT + 3TC+ Lop/r EFV can be used from the second trimester. The combination of 3 NRTIs should be avoided during pregnancy because of the additive risk of mitochondrial toxicity in the fetus.
WHO recommendation 2010	AZT (TDF) + 3TC (FTC) + NVP(EFV)
EACS recommendation 2009	2 NRTI + PI/r NVP shouldn't be prescribed, but can be continued if started before pregnancy
French recommendation 2008	AZT + 3TC + PI/r

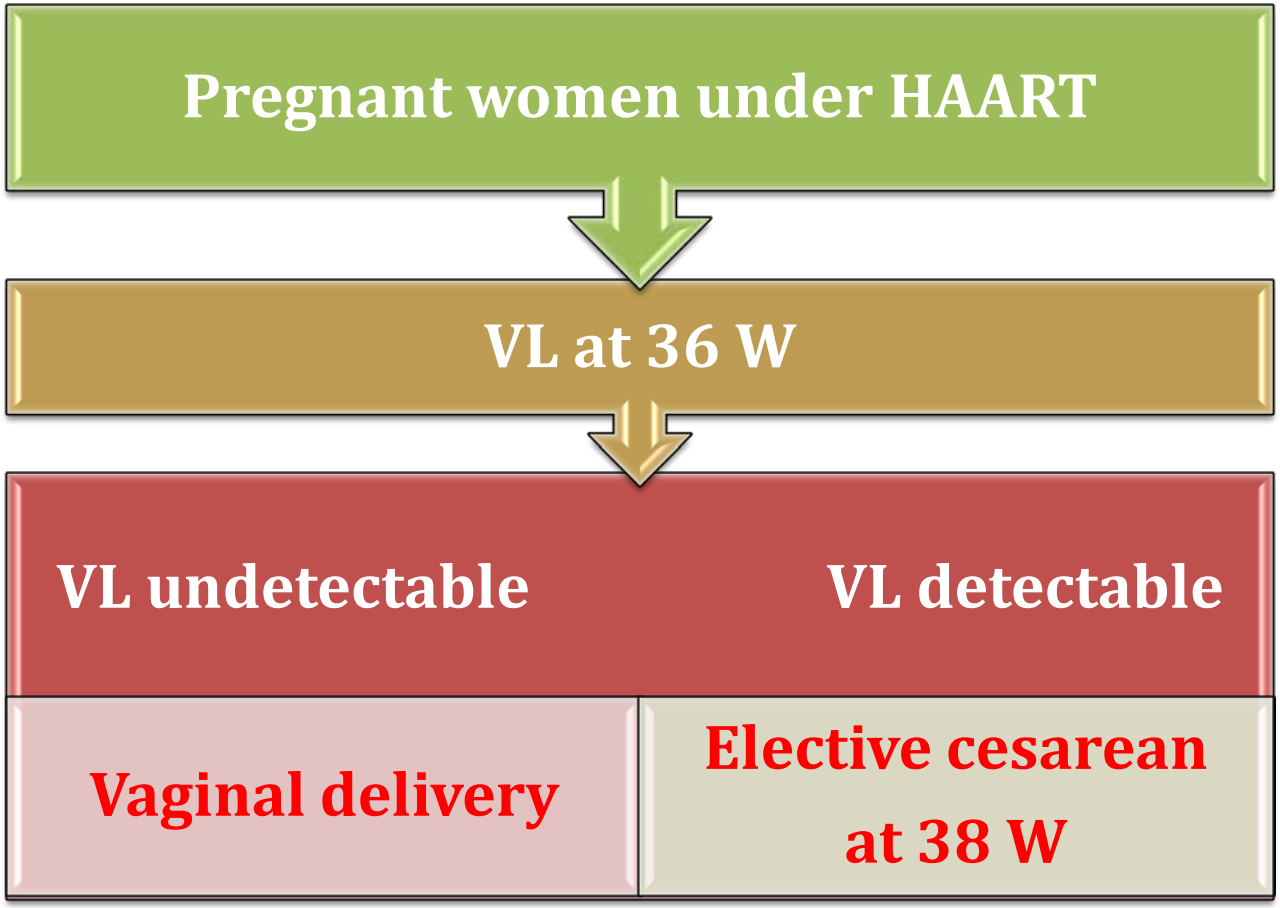
PMTCT

Clinical and laboratory monitoring

	M1	M2	M3	M4	M5	M6	M7	M8	M9
Clinical care HIV infection	+			+			+	36 W +	
Obstetrical care									
Fetal ultrasonography	+ 12 weeks			+ 22 weeks			+ 32 weeks		
CD4	+			+			+		
VL	+			+			36 W +		
Biological tests (Hemogram, glycemia, creat and others exams	+		+		+		+	+	+
	Should be based on the potential adverse reactions of the antiretroviral agents used.								
CMV PCR and Eye study	**If women with CD4 < 50/mm^3**								
Resistance testing	**Virological failure with residual viral replication under treatment.**								

PMTCT

Prophylaxis perpartum: mode of delivery.



PMTCT

Perpartum prophylaxis : other indications for cesarean.

- Obstetric indication.
- AZT Monotherapy.
- Late treatment
- Co-infection HIV-HCV if positive HCV-VL

IV infusion of AZT is recommended when the mother VL is detectable :
2 mg/kg in 1 hour from the onset of labour and maintaining dose of 1 mg/kg/ h until cord clamping or throughout the duration of caesarean section.

PMTCT

Post-exposure prophylaxis in the newborn and breastfeeding.

Low risk

Optimal maternal prophylaxis with undetectable or low VL (<1,000 copies/ml) associated with an uncomplicated delivery (caesarean or vaginal).

Intermediate risk

Mothers whose VL remains detectable (between 1,000 and 10,000 copies / ml) under treatment at the 8th month and for which the cesarean was not possible.

Important risk

Mothers who did not receive prevention during pregnancy and / or delivery.
Difficult conditions of delivery.
A high maternal VL at delivery (> 10,000 copies / ml) despite ART during pregnancy.

Breastfeeding should be avoided and should be replaced by an artificial milk from birth.

PMTCT : main situations.

Tunisian recommendations ART 2010

Clinical situation	Drug regimen
Woman starting a pregnancy on ART	
• VL undetectable	• Continue the same treatment
• VL detectable	• Evaluate compliance, if possible repeat the VL before possibly changing the initial treatment
• In both situations	Stop or avoid prescription of : • EFV during the first trimester. • Associations : d4T + ddI and d4T+3TC.
Woman starting a pregnancy without ART	
• In maternal indication for ART.	• Start ART from 12 weeks or as soon as possible.
• If no maternal indication for ART.	• Start ART from 14 weeks or as soon as possible in women who consult late in pregnancy.

PMTCT : main situations.

Tunisian recommendations ART 2010

Clinical situation	Drug regimen
Pregnant women not followed and untreated and / or whose diagnosis of HIV infection has been delayed	
• Late diagnosis between the 8th and 9th month of gestation or before labour.	• Rapid initiation of ART. • Elective Caesarian. • Strengthening of the newborn treatment (AZT+3TC).
• Diagnosis very late at labour	• Infusion AZT + NVP single dose and AZT +3TC for a week. • Caesarean or vaginal delivery according to the progress of labour. • Intensive of the newborn treatment (triple therapy).

Children infection : When to start ART ?

- It is recommended to start treatment at an early stage before the severe immune deficiency.
- In children under 12 months : A systematic early ART is initiated upon the confirmation of the diagnosis of HIV infection even in the asymptomatic children.
- In children from 1 to 5 years : ART is recommended in all symptomatic child in category B or C (CDC classification) and/or % CD4 < 25 from 1 to 3 years and % CD4 < 20 beyond 3 years.
- No treatment is recommended if the child is asymptomatic or slightly symptomatic (category A of CDC classification) and % CD4 > 30 from 1 to 3 years or % CD4 > 25 beyond 3 years with VL < 10^5 copies/ml.
- In children over 5 years : same indications as adults.

What to start ?

Regimen for first-line ART on Paediatric infection

Regimen for first-line ART : 2 NRTIs + 1 PI/r or 1 NNRTI.			
	NRTI	PI/r	NNRTI
Tunisian recommendation 2010	AZT, 3TC, ABC.	LPV/r.	EFV from 3 years.
WHO 2010	AZT, 3TC, ABC, d4t	LPV/r or fosamprenavir/r	NVP or EFV from 3 years.
French recommendation 2008	AZT, 3TC, ABC.	LPV/r.	EFV from 3 years.

Ovoid AZT if severe anemia or neutropenia.
The choice of PI/r is justified by the low genetic barrier of NNRTIs in the context of frequent difficulties in adherence at baseline. Preferred if Exposed to NVP (maternal or infant treatment or PMTCT). The choice of INNTI if assurance of a good compliance from the baseline or TB.

Conclusion

- Recommendations on antiretroviral therapy is an interesting initiative in Tunisia.
- They are intended to standardize requirements and improve the management of ARVs.
- Two years later, it is desirable to measure their impact on quality of care.