



**CLINICAL GUIDELINE FOR THE ELIMINATION
OF MOTHER-TO-CHILD TRANSMISSION OF
HIV AND **CONGENITAL SYPHILIS**
IN LATIN AMERICA AND THE CARIBBEAN**



**Pan American
Health
Organization**



*Regional Office of the
World Health Organization*



**Latin American Center for Perinatology
Women and Reproductive Health
CLAP/WR**



aecid
Agencia Española
de Cooperación
Internacional
para el Desarrollo



Clinical Guideline for the Elimination of Mother-to-Child Transmission of HIV and Congenital Syphilis in Latin America and the Caribbean



2011



**Pan American
Health
Organization**

*Regional Office of the
World Health Organization*



**LATIN AMERICAN CENTER FOR PERINATOLOGY
WOMEN AND REPRODUCTIVE HEALTH
CLAP/WR**



aecid
Agencia Española
de Cooperación
Internacional
para el Desarrollo



PAHO Headquarters Library — Catalog at source

González H, Serruya S ed.

“ Clinical Guideline For The Elimination Of Mother-To-Child Transmission Of HIV And Congenital Syphilis In Latin America And The Caribbean”.

Montevideo: CLAP/WR, 2011

(PAHO/FCH/HI/06-09.E)

ISBN: 978-92-75-12991-3

Title II. Series

- 1 Congenital Syphilis
 - 2 Sexually Transmitted Diseases
 - 3 Vertically Transmitted Disease
 - 4 Mother and Child Relations
 - 5 HIV Infections
 - 6 The Caribbean Region
 - 7 Latin America
- NLM WC161

<http://www.paho.org/iniciativadeeliminacion>

Website CLAP/WR: <http://www.new.paho.org/clap>

VHL - WOMEN MATERNAL AND PERINATAL: <http://perinatal.bvsalud.org>

Latin American Center for Perinatology / Women and Reproductive Health - CLAP/WR

Pan American Health Organization / World Health Organization - PAHO/WHO

P.O. Box 627, 11000 Montevideo, Uruguay

Telephone: +598 2 487 2929, Fax: +598 2 487 2593 postmaster@clap.ops-oms.org

CLINICAL GUIDELINES FOR THE ELIMINATION OF MOTHER TO CHILD TRANSMISSION OF HIV AND CONGENITAL SYPHILIS IN LATIN AMERICA AND THE CARIBBEAN

“GUÍA CLÍNICA PARA LA ELIMINACIÓN DE LA TRANSMISIÓN MATERNOINFANTIL DEL VIH Y DE LA SÍFILIS CONGÉNITA EN AMÉRICA LATINA Y EL CARIBE”.

Scientific publication CLAP/WR 1570-02

2011

The Pan American Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full.

Applications and inquiries should be addressed to the VIH/AIDS Unit, Pan American Health Organization, Washington, DC, USA, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and reprints and translations already available.

© Pan American Health Organization, 2011

Publications of the Pan American Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights are reserved. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the Pan American Health Organization concerning the status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the Pan American Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The opinions expressed in this document are the sole responsibility of its authors.

The secretariat and consultants have made all the efforts possible to ensure that the indications and doses stated in this document are correct, and generally recommended by the health authorities and medical literature.

Nevertheless, readers are suggested to consult the recommendations and information regularly provided by the authorities and manufacturers.

Editors

Raúl González Montero, PAHO

Suzanne Jacob Serruya, CLAP/WR/PAHO

Coordinators

Ricardo Fescina, CLAP/WR/PAHO

Kathleen Israel, HI/FCH/OPS

Listing of the Group of Latin American and Caribbean Experts for the Adaptation of the Regional Guidelines (GELAC) (in alphabetical order)

Dulce Almonte,

Mónica Alonso,

Tania Corpeño Olivas,

Bremen De Mucio,

Marie Deschamps

Hernando Estrada,

Carlos Falistocco,

Odalys García,

REDOVIH/REDLAT, Dominican Republic

PAHO

MINSA, Nicaragua

CLAP/WR/PAHO

GHEISKO, Haiti

Heres Salud I.P.S., Colombia

Medical advisor, National Program Against Human Retroviruses, Argentina

Ministry of Health, Honduras

Perry Gomez	MOH, The Bahamas
June Holdip,	CFNI/PAHO/WHO
Yira Ibarra	Head of the National Program Against HIV/AIDS, Panama
Beryl Irons	CAREC/PAHO
Noreen Jack	PHCO/PAHO
Andre Jolicoeur,	UNICEF
Osvaldo Lorenzo,	DIGECITSS, Dominican Republic
Denis Padgett,	IHSS/UNAH, Honduras
Russel Pierre	UWI, Mona, Jamaica
Leah-Mari Richards	UNFPA
Maria Dillion Remy	Tobago Regional Health Authority, Trinidad and Tobago
Margaret Ann St. John	MOH, Barbados
Omar Sued,	PAHO
Mauro Texeira,	GCTH, Brazil
Victor Vallejo Sandoval,	COPRECOS, Peru
Patricia Vasquez	San Juan de Dios Hospital, CONASIDA Advisory Committee, Chile
Ana Visconti	Ministry of Health, Uruguay

We thank Dr. Jorge Lattner, an expert on infectious diseases at the Fernández Hospital, Argentina, for the initial review of the draft version of this document and Dr. Bilali Camara for its initial coordination.

All the contents in the guideline were updated in May 2009, and the prevention of congenital syphilis was integrated as a joint strategy. This work was conducted by:

José Ramón Espinoza	UNICEF
Bertha Gómez	PAHO
Raúl González Montero	PAHO
Noreen Jack	PHCO/PAHO
Cecilia Sánchez Bodas	TACRO/UNICEF
Suzanne Jacob Serruya	CLAP/WR/PAHO
Omar Sued	PAHO

INDEX

Contents

1. INTRODUCTION	9
1.1. Epidemiology & Background	9
1.2. Objectives of the clinical guideline	14
1.3. Goals, indicators and program objectives of the “Initiative for the Elimination of Mother-To-Child Transmission of HIV and Congenital Syphilis in Latin America and the Caribbean”	15
2. OPERATIONAL DEFINITIONS	16
3. INTERVENTIONS FOR THE PRIMARY PREVENTION OF HIV AND SYPHILIS	20
3.1. Perinatal Electronic System	20
3.2. Primary prevention of HIV and syphilis in pregnant and non pregnant women	22
3.3. Preventing unwanted pregnancies	22
3.4. Pre Conception Counseling in HIV+ women	23
4. DIAGNOSIS.....	25
4.1. Diagnosis of maternal syphilis	25
4.1.1. Clinical	25
4.1.2. Laboratory tests for the diagnosis of syphilis.....	27
4.2. Diagnosis of congenital syphilis.....	30
4.2.1. Clinical	30
4.2.2. Serological Diagnosis.....	32
4.3. Diagnosing the mother’s HIV infection.....	32
4.3.1. Clinical Diagnosis	33
4.3.2. Serological Diagnosis.....	33
4.4. Diagnosis of HIV infection in children	34
4.4.1 Polymerase Chain Reaction for the detection of viral DNA	35
4.4.2 Viral RNA detection	36
5. CLINICAL MANAGEMENT	37
5.1. Syphilis	37
5.1.1. Treatment of maternal syphilis	37
5.1.2. Treating children with congenital syphilis	39
5.2. HIV INFECTION.....	40
5.2.1. Clinical and immunologic evaluation of HIV+ pregnant women: indication to start ARVT.....	40
5.2.2. Women that get pregnant while on ARVT.....	43
5.2.3. Antiretroviral MTCTP prophylaxis.....	45
5.2.4. Type of delivery and indication of caesarean section	49
5.2.5. Recommendations on how to feed the newborn.....	51
5.2.6. Safety of ARVT in pregnant women and children	53
5.2.7. Drug resistance following HIV MTCP	58

6. CHILD MONITORING	62
6.1 Systematic immunizations of the HIV-exposed child within the first months of life	64
6.1.2 BCG immunization (187)	65
6.2 Follow-Up Schedule	66
7. SPECIAL CONSIDERATIONS	71
7.1. Pregnant women with HIV and active tuberculosis	71
7.2. Pregnant women with HIV and hepatitis.....	72
7.3. Pregnant women with HIV and anaemia.....	73
7.4. Treating IDU pregnant women.....	73
7.5. Women with primary HIV-infection during pregnancy	75
8. ANNEXES	76
9. BIBLIOGRAPHY	87

ACRONYMS & ABBREVIATIONS

A3TC	Lamivudine
ABC	Abacavir
AC	Antenatal Care
AFASS	Affordable, Feasible, Acceptable, Sustainable and Safe. Acronym used by the WHO to describe under what circumstances milk formula can be recommended to replace breastfeeding.
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
ARVT	High Efficacy Combined Antiretroviral Therapy
ATV/r	Atazanavir / ritonavir
AZT	Azidotimidine (zidovudine)
CAH	Child & Adolescence Health
CDC	Centers for Disease Control and Prevention
CLAP/WM	Latin American Center for Perinatology, Women & Reproductive Health
CS	Congenital Syphilis
CSF	Cerebro Spinal Fluid
D4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic Acid
du-NVP	Single dose nevirapine
ECS	Elimination of Congenital Syphilis
EFV	Efavirenz
ELISA	Enzyme Linked Immunoabsorbent Assay
fAPV/r	Fosamprenavir / ritonavir
FTA-Abs	Fluorescence Treponemic Absorption of Antibodies
FTC	Emtricitabine
GUS	Genital Ulcer Syndrome
HALY	Handicap-Adjusted Life Years
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immune Deficiency Virus
IDV	Indinavir
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IU	International Units
LAC	Latin America and the Caribbean
LB	Live birth,
LPV/r	Lopinavir / ritonavir

MCH	Maternal & Child Health
MDGs	Millennium Development Goals
MHA-TP	MicroHaemagglutination Assay for Antibodies to <i>Treponema pallidum</i>
MSM	Men that have sex with men
MTCT	Mother-to-Child Transmission
MTCT	Prevention of Mother-To-Child Transmission of HIV
NFV	Nelfinavir
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
ORT	Opiate Replacement Therapy
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PECS	Program for the Elimination of Congenital Syphilis
PI	Protease Inhibitor
PVL	Plasma Viral Load
RIF	Rifampin
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reaginine
SQV/r	Saquinavir / ritonavir
SRH	Sexual & Reproductive Health
STI	Sexually Transmitted Infections
TB	Tuberculosis
TDF	Tenofovir
TPHA	<i>Treponema pallidum</i> haemagglutination assay
TP-PA	<i>Treponema pallidum</i> particle agglutination
UNGASS	United Nations General Assembly Special Session on VIH/AIDS
UNICEF	United Nations Children's Fund
USR	Unheated serum reagin
VDRL	Veneral Disease Research Laboratory
VT	Vertical Transmission
WHO	World Health Organization

1. INTRODUCTION

1.1. Epidemiology & Background

The HIV (Human Immune Deficiency Virus) pandemic is one of the most serious global health crises. Over 25 million people have succumbed to AIDS since the occurrence of the disease. Of the 33.4 million people with the HIV virus globally as of December 2008, almost 2 million lived in Latin America and the Caribbean, ⁽¹⁾.

HIV infection is accountable for a significant increase in morbidity in LAC ⁽²⁾. The Caribbean sub-region is second to Africa, with a prevalence between 0.1 to 2.2% ^(3,4,5). In Latin America, the mean prevalence of HIV infection is 0.5% ⁽⁶⁾. During 2008 there were more than 11 million births in the region; less than 54% of the pregnant women receiving an HIV test, with a great disparity among the various countries within the region. In 2007, ARV prophylaxis of MTCT in HIV-positive pregnant women was 54%⁽⁹⁾.

Women and children bear an important burden of the disease and in many places they still represent the group with the highest rates of new infections, and HIV-related mortality. The 2007 estimates indicated that there were 55,000 children under 15 years with HIV in the region⁽⁸⁾, and 6,000 of them died due to HIV in that year⁽⁹⁾. Most of these children got infected through MTCT, which may occur during pregnancy, childbirth or breastfeeding. By preventing HIV positive mothers from breastfeeding, the risk of transmission ranges from 15 to 30% and it rises to 20-45% when those mothers breastfeed their children ⁽¹⁰⁾. The risk is reduced to less than 2% as a result of the implementation of measures such as the administration of antiretroviral prophylaxis to HIV+ women during pregnancy and childbirth and to the young infant during its first weeks of life, obstetric interventions such as scheduled cesarean section (planned before the onset of labor and the rupture of membranes) and the avoidance of breastfeeding by HIV+ mothers.

Syphilis is still a serious public health issue; it is calculated that every year there are over 12 million new infections by *Treponema pallidum*, and more than 2 million occur in pregnant women. It is important to highlight that the LAC region exhibits the highest maternal syphilis rate in the world; the WHO estimated it reached 3.9% between 1997 and 2003. That figure suggests that there may be approximately

459,108 gestational cases in the Americas, (not including the USA and Canada), thus causing from 164,222 to 344,331 cases of congenital syphilis (CS) yearly ⁽¹¹⁾. In most cases, the infection is transmitted to the fetus (typically between pregnancy weeks 16 and 28) and it is fatal in 30-50% of the cases ^(12,13). The prevalence of maternal syphilis varies significantly across the countries in the region. For instance, in 2005-2006 it was 1.4% in Argentina, 5.75% in Haiti ⁽¹⁴⁾ and 5% in Bolivia ⁽¹⁵⁾.

Given the increasing prevalence of congenital syphilis and the apparent lack of awareness by health care professionals and community as a whole, the “XXIV Pan American Health Conference” called for the elimination of congenital syphilis (ECS) as a public health problem in the Americas in 1994. This led to the development of the “*Plan of Action for the Elimination of Congenital Syphilis*” at PAHO’s 116th Executive Committee’s Meeting in 1995 ⁽¹⁶⁾. That document established the definitions of congenital syphilis (CS) and the need to eliminate it as a public health issue, as well as the strategies and methods agreed to meet those objectives.

In 2004 PAHO included the ECS in its 2004-2005 working plan, and called for technical consultation to identify the recommendations needed to implement this initiative; those recommendations are compiled in the document “*Elimination of congenital syphilis in Latin America and the Caribbean. Reference Framework for its Implementation*”⁽¹⁷⁾.

These policies are reinforced by the resolutions adopted by the 59th World Health Assembly, held in May 2006, where they acknowledge the importance of surveillance of STIs and their complications, including the potential interventions for the control of CS ⁽¹⁸⁾. The Assembly adopted a strategy for the prevention and control of STIs that links prevention and control efforts with family planning, maternal health and the prevention and care of HIV, contemplating integrated interventions, especially targeting the young, to include comprehensive information, life skills training, education and care. This strategy was published as the “*2006-2015 Global Strategy for the Prevention and Control of Sexually Transmitted Infections*” ⁽¹⁹⁾.

The WHO recently published another document providing the rationale and the national and international strategies for the ECS, known as the “*Global Elimination of Congenital Syphilis: Rationale and Strategy for Action*” ⁽²⁰⁾. The strategy follows four guidelines that should be adapted to each country’s settings, to be integrated horizontally into M&CH programmes and services, including: a) to ensure the political commitment and visibility of the problem; b) to improve access to a quality mother and child health service; c) to screen all the pregnant women and to treat all

those affected, and d) to establish epidemiological surveillance systems, monitoring and evaluation. When this strategy was compared with several national programs, the most frequent barriers became apparent, as did the need to work with governments to improve women's access to serology testing, to develop recommendations or specific national technical guidelines and to improve the surveillance systems, to be successful in ESC ⁽²¹⁾.

In recent years there has been an unprecedented political and social mobilization in response to the HIV pandemic, with new funding opportunities and a public health approach, including the programs for the prevention of mother-to-child transmission (MTCT). These programs have proven to be feasible and cost-effective, even in most low- and medium-income countries that have not reached the objectives adopted by the United Nations General Assembly's Special Session on HIV/AIDS (UNGASS) in June 2001 (which includes reducing the rate of HIV-infected infants by 50% by 2010).

Together with other UNAIDS co-sponsoring agencies, the WHO produced a document published in 2003 describing a global strategy ⁽²²⁾ based on four pillars to prevent MTCT:

a) Primary prevention of HIV infection

Avoiding HIV infection in women will considerably contribute to the prevention of HIV transmission to infants and children. Hence, HIV prevention programs need to target women at risk and their couples, especially aiming at young women;

b) Preventing unwanted pregnancies

The women that are aware of their HIV positive status must receive key care and support services, including family planning and other reproductive health services, to allow for appropriate informed decision-making;

c) HIV Mother-to-Child Transmission Prevention

A specific intervention package has been identified to prevent the HIV-infected mother from transmitting the infection to her child. It includes the use of antiretroviral drugs, the election of a safer type of delivery, as well as advice on child feeding;

d) Care, therapy and support to women living with HIV, their children and families.

The reinforcement of linkages between the programs aimed at preventing HIV MTCT, the care and support services for HIV-infected women, their children and families will ensure that women have access to the services they need. Likewise, the improvement of the mothers' survival and quality of life will result in their children's benefit.

HIV and syphilis elimination interventions target the same population of women in child-bearing age and their couples, as well as all pregnant women. Consequently, both strategies can be integrated for the primary prevention of both conditions. Apart from integrating the screening tests into prenatal care and immediate therapy of syphilis, it requires providing timely prophylaxis and anti-retroviral therapy.

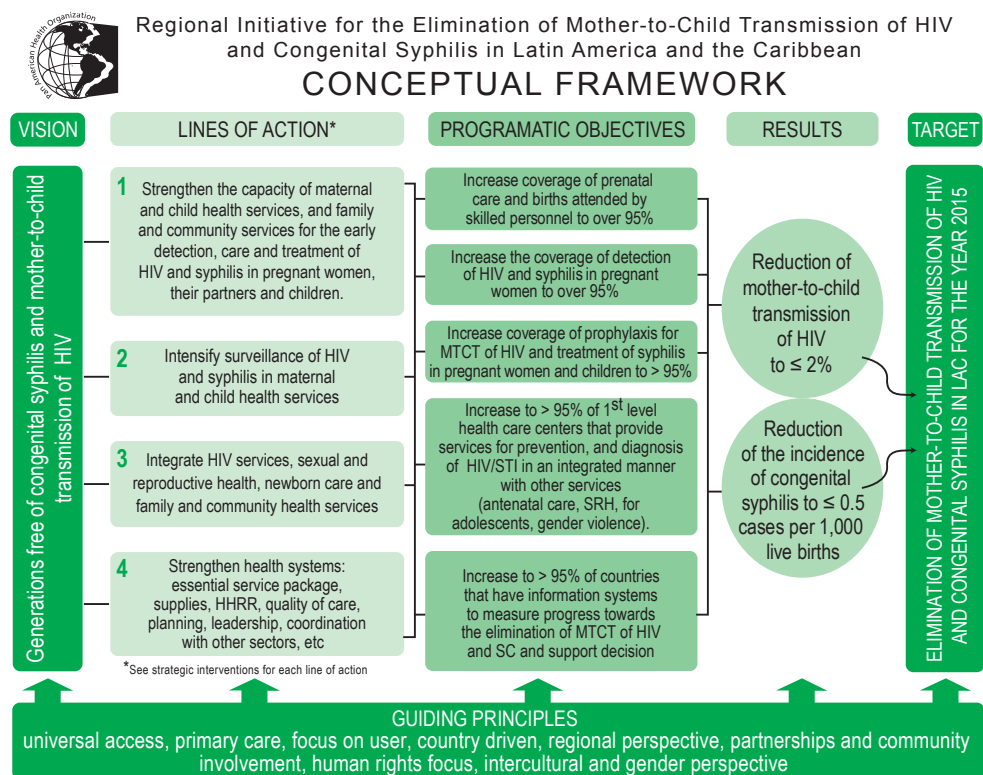
Despite the great heterogeneity of the health services observed in the Region, LAC has succeeded in improving most of the indicators of quality maternal care. Antenatal interventions contribute not only to reduce the risk of MTCT of several infections, but also to reduce maternal mortality, contributing to the improvement of the whole set of indicators of increasing women's life expectancy and contributing to the overall progress in health of the population.

The percentage of women that receive at least four antenatal visits has steadily increased in the Region, exceeding 50% in several countries. The percentage of childbirths that received care by skilled professionals has increased in recent years, reaching up to 88.5% in 2008. The maternal mortality rate was reduced from 180 to 89.2 cases/100,000 childbirths between 1990 and 2007, despite the big differences among the countries in the Region (in Haiti the rate was 630 deaths per 100,000 live births (LBs), while Chile reported a rate of 18.1/100,000). These differences are usually due to inequality with the poorest 20% contributing 50% of maternal deaths, while only 5% of those deaths occur among the wealthiest 20%. There is also an inequity in the distribution of human resources, with a shortage of doctors and skilled staff to provide care to childbirths occurring within the most socio-economically vulnerable settings.

PAHO/WHO and UNICEF have proposed the “*Initiative for the elimination of mother-to-child transmission of HIV and congenital syphilis in Latin America and the Caribbean*”, assuming that the integration of both actions will yield better outcomes than if each were addressed separately. The conceptual framework of the Initiative is described in the document: *Regional Initiative for the Elimination of Mother-To-Child Transmission of HIV and Congenital Syphilis in Latin America and the Caribbean. PAHO. September 2009 (184).*

The master lines are shown in Figure 1.

Figura 1.



The “Elimination Initiative” seeks to integrate antenatal care with the prevention of the transmission of HIV and congenital syphilis and other vertically transmitted diseases, improving access to SRH, the systematic provision of counselling and HIV and syphilis screening to all pregnant women, the use of ARVT to prevent MTCT to all women with HIV, ARV prophylaxis to the child during the first weeks of life, early and adequate therapy to women with syphilis identified during pregnancy and provision of child nutrition advice and support, recommending the replacement of breastfeeding for milk formula when the AFASS conditions are met.

1.2. Objectives of the clinical guidelines

This document provides guidance on the interventions for the elimination of mother-to-child transmission of HIV and congenital syphilis in Latin America and the Caribbean, and it intends to assist the health care workers and decision-makers in charge of public health to integrate the programmes and services for the detection and treatment of syphilis and HIV in pregnant women. HIV-negative women also warrant special attention especially during pregnancy and breastfeeding, since there are certain biologic and behavioral factors that may enhance their risk of getting infected in those periods and should be provided with access to primary prevention services,(24).

The main objectives of the guidelines are:

- To expand coverage and to achieve earlier and more frequent use of the existing services for pregnancy care, in order to improve access to quality antenatal, childbirth and postpartum care, and the services that provide nutritional guidance and support for the mother and the child;
- To attain an integrated management for the prevention of the transmission of HIV and congenital syphilis by standardizing therapy;
- To promote the rational use of tests, medications and interventions aimed at the prevention of congenital syphilis and the transmission of HIV.

1.3. Goals, indicators and program objectives of the “Initiative for the Elimination of Mother-To-Child Transmission of HIV and Congenital Syphilis in Latin America and the Caribbean”

Goal:

- To eliminate congenital syphilis and mother-to-child transmission of HIV in the Americas by 2015.

Output Indicators ⁴:

- Mother-To-Child Transmission of HIV is reduced to 2% or less;
- To reduce the incidence of congenital syphilis to ≤ 0.5 cases per 1,000 live births (including stillbirths).

Programmatic targets:

- To increase the coverage of antenatal care and skilled attendance at birth to 95% or more by 2015;
- To increase coverage of HIV and congenital syphilis screening in pregnancy to 95% or more;
- To increase coverage of HIV prophylaxis and syphilis therapy in pregnant women and children to over 95%;
- To increase to over 95% the number of first level health care centers that provide services for the prevention and diagnosis of HIV and STIs in an integrated manner with other health services, including antenatal care, SRH, care services for adolescents and gender violence;
- To increase >95% the number of countries in the region with information systems that enable them to monitor and evaluate progress towards the elimination of mother-to-child transmission of HIV and SC and to support decision making.

The successful implementation of the Initiative for the Elimination of Mother-To-Child Transmission of HIV and Congenital Syphilis will contribute to meeting the United Nations Millennium Development Goals (MDGs), reducing child mortality(MDG4), improving maternal health (MDG5) and combating HIV/AIDS, (MD G6).

4 Caribbean countries consider one third output indicator: reducing the incidence of HIV mother-to-child transmission to 0.3 cases per 1.000 live births or less,

2. OPERATIONAL DEFINITIONS

Adherence to therapy

Adherence implies taking the drugs at the dosages and intervals prescribed by the health care professional.

Antenatal care

Interdisciplinary and evidence-based care of pregnant women, applying a humanized vision of the women and their families, ensuring universal access to care, which should be provided early (initial visit before the 12th week of pregnancy), periodical (4-5 visits), comprehensive (covering the key interventions) and in an integrated manner, **also promoting the regular inclusion of the sexual partner at the visits.**

Basic, integrated and good quality antenatal care is a key strategy that contributes to the reduction of maternal and neonatal morbidity and mortality, and it should be considered a right of all pregnant women. Several studies have shown that five visits (the first being before the 12th week), suffice to provide good quality of care, as long as each includes the key interventions proposed^(25,26).

Plasma viral load

The PVL refers to the detection and quantification of HIV viral RNA in plasma. It is usually expressed as number of copies/ml.

Co-infection

Co-infection implies the presence of another relevant infection in a person with HIV; usually tuberculosis, syphilis or chronic viral hepatitis. There is a set of infections transmitted in the perinatal period; for further information refer to the CLAP/WM handbook on **perinatal infections transmitted from mother to child**⁽¹⁸⁵⁾.

Serological Testing

Establishing the diagnosis of an infection based on the presence of specific antibodies in plasma.

Serological Testing for Maternal Syphilis

Based on serological criteria, all the tests that react will be considered positive, regardless of the titers and of the usage of the treponemal test (rapid test or FTA-Abs) or a non treponemic test (VDRL or RPR).

From the programmatic and epidemiological perspective, all positive serologies will be considered presumptive diagnoses (or possible diagnoses) to ensure an early therapy.

Virological Testing

Establishing the diagnosis of an infection based on the presence of part of or the entire virus in plasma, in the peripheral blood cells or in other specimens. The techniques most commonly used for HIV are:

- o PCR-DNA, which detects the genome of the virus transcribed to the DNA and incorporated to the genome of the mononuclear cells;
- o RNA viral load, that detects and quantifies viral particles;
- o Viral culture: Culture of the virus in cell lines;
- o Detection of antigen p24, which detects that antigen in plasma.

Elimination

Elimination is the reduction of the mother to child HIV transmission to 2% or less and the reduction of the incidence of congenital syphilis (stillbirths included) to 0.5 cases or less than 1,000 births.

Antiretroviral Drugs

Drugs specifically designed to inhibit the replication of HIV in the human body.

Milk Formula

Preparations primarily obtained from cow milk and manipulated to mimic the nutrients and oligo elements present in human milk. They are used to feed the newborn when breastfeeding is either not possible or contraindicated.

Discordant Couples

Couples with serological mismatch; that is with member is HIV (+) and the other is HIV (-).

Primary Infection or acute infection

In adults, the term primary infection refers to the period going from the moment the causative organism enters the human body until complete seroconversion. In the case of HIV infection, it is especially relevant because it is a period of very high viral replication and consequently it is the time when transmission is more likely to occur.

Resistance to antiretroviral drugs

The loss of effectiveness of an antiretroviral drug usually secondary to one or more mutations in the viral genome.

CD4 lymphocyte count

It expresses the number of lymphocytes with the CD4 marker on its surface/ml. It is used to evaluate a person's immunological status.

Maternal or gestational syphilis

Any woman during pregnancy or puerperium, or with a recent spontaneous abortion, that presents clinical evidence (for example: chancre, syphilitic roseola, flat warts) or serological evidence of syphilis.

Congenital Syphilis: any of the scenarios below

- o Newborn, stillborn or spontaneous abortion of a woman with maternal syphilis that had not received appropriate treatment;
- o Child with VDRL or RPR titers four times higher than maternal (equivalent to two dilutions, i.e. women 1 / 4, child 1 / 16);
- o Child with clinical manifestations suggestive of congenital syphilis and positive serology regardless of the titer;
- o Product of gestation or placenta with evidence of *T. pallidum* infection in histological studies.

ARVT: High efficacy combined therapy for HIV infection

Simultaneous use of at least three ARVs. At present, mono- or bi-therapy have no role in the therapy of HIV infection.

HIV

The human immune deficiency virus is an infectious agent that attacks the immune system, primarily the white blood cells (T lymphocytes) and causes the acquired immune deficiency syndrome (AIDS).

Value and degree of strength of evidence-based recommendations

The recommendations made in this document are based on the evidence obtained through controlled and randomized clinical trials; for the issues not related to therapies they are based on high quality scientific studies, data from observational cohorts, and when there is no evidence, or when the existing evidence is not enough, it is based on the opinion of experts. The value of recommendations is summarized in the Chart below:

Chart 1

Value and grade of strength of a scientific evidence-based recommendation

Level of recommendation	Level of evidence to support the recommendations
A. Recommended: Should be followed;	I. At least one randomized controlled trial with programmatic, laboratory or clinical assessment criteria II. At least one high quality study or several sufficient studies with programmatic, laboratory or clinical assessment criteria
B. To be considered: applicable in most situations;	III. Observational cohort data; one or more properly designed analytical or case-control studies. Assess cases and controls;
C. Optional	IV. Expert opinion based on the assessment of other tests.

Source: Adapted from: "The British HIV Association (BHIVA) treatment guidelines for 2005" Ro; Developing an evidence-based guide to community preventive services — methods (28); WHO Evidence Network(29); EBM guidelines: evidence-based medicine(30).

3. INTERVENTIONS FOR THE PRIMARY PREVENTION OF HIV AND SYPHILIS

3.1. Perinatal Electronic System

The Perinatal Clinical record is the most valuable source of data available to the health team, either to know the characteristics of the users, to evaluate the results of the care provided and to conduct a broad range of operational research. This requires user-friendly mechanisms that facilitate the rapid storage and retrieval of the data, so they can be used by the health care providers themselves.

To address those needs, CLAP/WR-PAHO/WHO has developed the Perinatal Electronic System (SIP), which contemplates all the above-mentioned issues. It consists of the Perinatal Clinical Record (PCR), the Perinatal Card (PC) and the Computerized System, with software designed to process the information.

In a single page, the PCR puts together a set of data on which there is universal consensus, summarizing the minimal information indispensable for the adequate care of the pregnant woman and her newborn. The PCR serves as a road map; it is inexpensive and user-friendly.

The page is broken down into several sections that contain the documentation on obstetric events and data on the newborn in the immediate neonatal period. Almost all the questions in the list only require closed answers. The layout seeks to facilitate the systematic and timely collection of data. The Instructions Manual (CLAP/WR Publication; 1563) ⁽¹⁸⁸⁾ helps ensure the uniformity of the records entered in all the cases.

The PCR contains the key data required for the management of most low-risk cases.

The way data are traditionally processed results in the development of annual statistics that are rarely available to the health care providers that generated the initial data in a timely manner. It is frequently the case that by the time those statistics finally reach them, the information contained there fails to meet the health care providers' needs, preventing them from benefiting from the "feedback" that is indispensable for the evaluation and improvement of their performance. The Perinatal Electronic System addressed this issue by developing data processing software that allows the staff at the center originating the data to use their own information.

The operator may enter the PCR data by filling the facsimile page that appears in the computer, not requiring specific or extensive training. That will enable the Center itself to process and analyze its own data, and the health staff will be able to access the information when it is needed, facilitating the evaluation of care and decision-making.

The processed data result in a set of documents that summarize the center's activity in a given period, and they may also be elements to be used for further research.

The most salient characteristics of the system may be summarized in the items below:

- The local processing of data with these programs strengthens the self-evaluation capacity of perinatal care through the analysis of the data at the same health care center;
- It creates awareness among the staff on the importance of having comprehensive documentation of the health-related actions and observations;
- It facilitates intra- and extra-institutional communications, favors compliance with standards, records the legally relevant data and facilitates auditing;
- It serves as the basis for the planning of care, providing the data required to identify the population, evaluate care, categorize the problems and conduct the operational research.

The databases can be consolidated and analyzed at a national level to describe the status of various indicators in time per geographical areas, service networks or other characteristics of the specific populations, making the SIP a very useful instrument for the surveillance of maternal and neonatal events and for the evaluation of programs at a national level.

To facilitate these processes, CLAP/WM-PAHO/WHO has prepared a practice guideline to manage the Perinatal Electronic System to strengthen the capacities of the staff at the health care centers to make the most of the data available: <http://www.paho.org/clap>

3.2. Primary prevention of HIV and syphilis in pregnant and non pregnant women

The efforts for the prevention of HIV and congenital syphilis are more effective if they are fully integrated into the existing mother and child and family planning services. The mother and child services must be capable of implementing interventions to prevent the transmission of syphilis and HIV from the mother to the newborn ⁽³¹⁾.

In the context of the mother-to-child transmission of HIV and syphilis, primary prevention should specifically address the areas below:

- Advocacy to highlight the existing relation between the activities of primary prevention (or their absence) and the occurrence of infections in the newborns;
- Promotion of the information and education on HIV and syphilis among the young women and men including counseling at centers that provide family planning services, antenatal care and child care services. Services should ensure supply of condoms and the prevention and treatment of sexually transmitted diseases;
- Increase access to counseling services and HIV testing, as well as screening for syphilis in men and women in child-bearing age, particularly during pregnancy, establishing appropriate mechanisms for referral;
- Primary prevention should also be available for the population at higher risk, such as sexual workers, migrants and mobile populations.

3.3. Preventing unwanted pregnancies

Family planning counseling must be integrated in all the phases of therapy and care of HIV, including pre- and post-testing and long-term follow-up. Women with

HIV must receive counseling, to enable them to choose the contraceptive methods that best suit their status and needs, taking into account the stage of the disease and therapy, as well as their personal preferences lifestyle. Regardless the method chosen, the information on the transmission of HIV and STIs and the dual protection required should be highlighted during the family planning counseling.

The consistent use of condoms should be promoted among all women with HIV. The programs must have data available to guide women with HIV on the best contraceptive choices, to be used in combination with the condom, based on the best scientific evidence available. This information must contain the recommendations below:

- Women at child-bearing age with HIV can use IUDs for contraception, ut always associated with condoms;
- Hormone-based contraceptives are not restricted, including combined oral contraceptives, pills containing progesterone alone, combined injection contraceptives, medroxy-progesterone acetate patches, combined patches and vaginal ring. In all cases, potential drug interactions must be borne in mind.

3.4. Pre Conception Counseling in HIV+ women

In the case of women planning to get pregnant, pre-conception counseling should include counseling on an adequate nutrition, replacing efavirenz when there are reasonable alternatives available and the viral load has become undetectable. Counseling and support must be provided to prevent the transmission to the sexual partner in the attempt of getting pregnant, especially in the case of discordant couples. The risk of HIV transmission is between 0.001 and 0.03^(32,33) per unprotected intercourse. The risk drops if the subject with HIV has an undetectable viral load resulting from the use of ARVT; however, the risk is not completely eliminated, since a significant number of organisms may be present in the genital fluids.

There are handbooks containing recommendations for the management of fertility in men and women with HIV⁽³⁴⁾. For couples with serological mismatch in which the male partner has HIV, sperm washing or insemination from a donor are recommended whenever available. Insemination from a negative HIV donor eliminates any risk of transmission during conception, but it also eliminates the opportunity of an HIV+ man achieving genetic fatherhood. Unprotected intercourse should be discouraged in the case of discordant couples with an HIV positive female; these couples should be instructed about the self insemination technique on the fertile days of the

woman's cycle. When both members of the couple are HIV (+), re-infection with different strains is also a concern; consequently, unprotected intercourse should be discouraged to prevent this risk.

4. DIAGNOSIS

4.1. Diagnosis of maternal syphilis

4.1.1. Clinical

Syphilis is an infectious disease caused by *Treponema pallidum*; it is transmitted sexually and across the placenta; its course is chronic and it is distributed worldwide. At present the transfusion-related route is almost nonexistent. Sexual transmission occurs when the causative agent is inoculated through disruptions (abrasions) of the skin or mucosa resulting from the micro trauma that may occur during the sexual intercourse; those disruptions will subsequently lead to erosions and finally, to ulcers. If the disease is not treated during the acute phase it turns into a chronic condition, with potentially serious manifestations.

Clinical picture Clinical manifestations of syphilis are grouped into periods based on their time of occurrence:

a) Primary syphilis:

The hallmark of this period is the so-called “chancre”, which appears after an incubation period of approximately 3 weeks (10-90 days). The chancre is the initial manifestation of syphilis, and it is located at the site of inoculation of the treponema. It is a painless and clear-cut erosion, with round or oval raised rims and an indurated base. In women it may be difficult to detect because the initial lesion is usually located internally. When the chancre is located in the genital area it is associated with changes in the groin lymph nodes, which can be enlarged, hardened and slightly painful on palpation. If untreated, the chancre resolves and heals within 2 to 6 weeks.

b) Secondary syphilis

This stage occurs 3 to 12 weeks after the chancre. Its most salient feature is the presence of papular lesions and other skin lesions known as syphilitic roseola. The syphilitic roseola consists of a rash with roundish, copper-red patches from 5 to 12mm in size, that tend to predominate on the chest, arms and abdomen, and involving palms and soles in 50 to 80% of the cases. They can be easily missed when the roseola is not too apparent.

Those lesions may last from a few days to weeks, and they finally resolve spontaneously; in up to one fourth of the patients, however, they may recur several times throughout the first year. Condyloma latas are another manifestation of secondary syphilis; they can be found in the perianal area, groins, genitalia, and axilla; in general terms they tend to occur on any folds where there is moisture and maceration; lesions are also found in the oral mucosa (red or off-white well-defined patches). Not infrequently does it present associated with a general malaise, muscular pain, appetite loss or gastrointestinal disorders, hoarseness, slight weight loss and mild rise of the body temperature. Glomerulonephritis has also been reported. The lesions will spontaneously disappear within 2 to 6 weeks, but the bacteria persist, giving rise to the latent phase, which is followed by tertiary syphilis.

c) Latent period

It is characterized by an asymptomatic period that may extend from 5 to 50 years until the patients show any evidence of tertiary syphilis. During this phase the diagnosis can only be made through serology. This period is broken down into an early latent syphilis (infection extending for less than one year), late latent syphilis (extending for over one year) or undetermined duration. If the patient is not treated, from one third to one fourth of the patients will develop manifestations of tertiary syphilis during follow-up. The risk of sexual transmission during the latent phase is low, but not inexistent, and it should be considered in the pregnant women.

d) Tertiary or late syphilis

Late syphilis occurs several years after the onset of the infection, and it affects up to 40% of the cases that receive no therapy. It includes a range of clinical manifestations, the most common being the cardiovascular complications, gummas and the neurological lesions.

Cardiovascular complications are the most frequent; they occur 10 to 30 years after the initial infection, and they may manifest as an aneurism of the aortic arch, coronary artery ostitis, and aortic regurgitation, among others.

Gummas usually appear from 3 to 15 years after the initial infection, and they start as several painless subcutaneous nodules. Although they may be seen anywhere in the body, they are more frequent on the face, scalp and trunk. Their surface reddens and gets ulcerated, and then they may give rise to scars that can ulcerate, then they may scar, or form ulcers, fall of the palate or the nasal septum, etc.

Involvement of the nervous system may be already present during early syphilis as a result of vascular impairment; this may be evidenced as meningitis, seizures, myelopathy, cranial nerve impairment or eye disease.

Late neurosyphilis represents the manifestations associated with chronic syphilis, and it includes dementia, tabes dorsalis, paresis, sensorial ataxia, sphincter dysfunction, etc

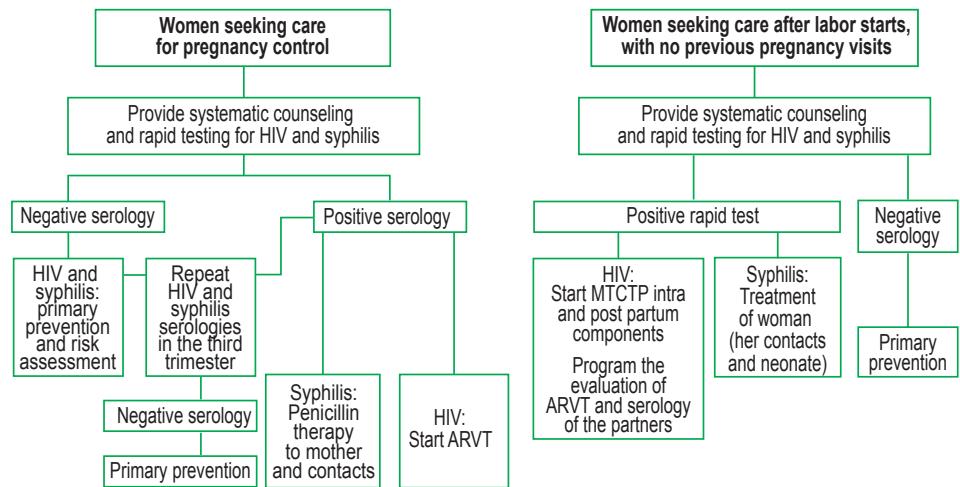
4.1.2. Laboratory tests for the diagnosis of syphilis

a) Serological Testing

All pregnant women should undergo serology screening at their first antenatal visit; if the test is negative, it must be repeated during the third trimester and upon childbirth or puerperium, prior to discharge (Figure 2). Women with increased risk of exposure may be tested more frequently. Serological testing is also recommended for sexual partners and any sexual contacts, if appropriate. If the mother has a positive serology, then her sexual partner should receive therapy too. The health care system that is treating the pregnant woman must also be responsible for the care treatment and follow-up of the couple. Those data must be recorded in the mother's clinical record. During pregnancy, the pregnant woman's therapy is just as important as her sexual partner's. Failure to treat the couple is the main source of re-infection during pregnancy.

Counseling should be provided at all visits to reduce the risk of acquiring syphilis or HIV during pregnancy.

Figure 2. Algorithm for the diagnosis and management of HIV and syphilis infection



CLAP/WM-PAHO/WHO has incorporated the possibility of recording two controls for the screening of syphilis in the Perinatal Clinical Record, consistent with the best evidence available and in keeping with most standard guidelines in the region. The first test must be performed upon the patient's initial presentation, at the first visit, (before Week 20), and the next should be at the third trimester. Figure 3.

Figure 3
Diagnosis and therapy file in the Perinatal Clinical Record

SYPHILIS- Diagnosis and Treatment											
Test						Treatment				Treat. partner	
no treponémic			treponémic			no	yes	n/d	n/a	no	yes
-	+	n/d	-	+	n/d	no	yes	n/d	n/a	no	yes
☐	☒	☐	☐	☒	☐	☒	☐	☒	☐	☒	☐
<20 wk											
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
≥20 wk											
☐	☒	☐	-	+	n/d	no	yes	n/d	n/a	no	yes
☐	☒	☐	☐	☒	☐	☒	☐	☒	☐	☒	☐
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

The serological diagnosis of syphilis is based on treponemic and non treponemic tests.

- Non treponemic tests include VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma reagin). A positive non treponemic test may indicate current infection, an infection treated recently or an untreated infection, but it may also be a false positive. False positive results occur in 1 to 3% of the general population, and they tend to show low titers. Tests may be negative at initial phases of the infection, or when the titer is very high (known as the prozone phenomenon) and they tend to turn negative or to drop to very low titers after therapy. In properly treated cases, the VDRL tends to turn negative with time, although in exceptional cases it may stay positive much longer, or even for good. False positives may be seen in autoimmune diseases, tuberculosis, mononucleosis, endocarditis and in pregnancy itself;
- Treponemic tests are specific, more complex and costly tests; they include TPHA (Treponema pallidum haemagglutination assay), TPPA (Treponema pallidum particle agglutination), MHATP (micro haemagglutination assay for antibodies to Treponema pallidum) and FTA Abs (fluorescent treponemal antibody absorption). They are used to confirm the result of a non treponemic test. The most frequently used techniques are MHA-TP and FTA-Abs.

These tests remain positive regardless of therapy, and false positives may be seen (less than 1%) in other disease caused by spirochetes (leptospirosis, Lyme's disease, rat-bite fever). In these cases there is usually a history suggesting the epidemiological agent. Hence, if a treponemic test is positive and there is no report of a previous therapy and/or the above-mentioned conditions are not met, then the patient should be treated;

- "Rapid tests" are simple tests that may be used and the results are available in minutes, making it possible to start therapy right away. They are usually based on reactive strips impregnated with treponemic antigens that turn positive (giving a color reaction) when in contact with serum, plasma or blood of a patient with syphilis antibodies. They tend to be ready for reading rapidly (within 30 minutes) and they are included in the treponemic tests. There are over 20 tests available globally, but they have different degrees of sensitivity and specificity, and there are some comparison studies and studies that measure their cost-effectiveness. They are especially useful when no standard treponemic tests are available. When the rapid tests are positive, the patient must undergo non treponemic tests that allow the evaluation of the response to therapy by quantifying that response.

b) Other laboratory testing for the diagnosis of syphilis

Under special circumstances, there are other techniques that may be useful as well; although they are usually more complex and less easily available at health care centers. These include the dark field examination with immunofluorescence of the exudates in the lesions, histology or PCR.

Chart 2. Result and interpretation of the serology testing

Result	Interpretation
NT(-) T(-)	Absence of infection. If exposure is very recent, it is recommended to repeat the tests;
NT(+) T(+)	Active infection, especially when the non treponemic test titers are high (>1/8). Low titers may reflect an old syphilis that was already treated;
NT(-) T(+)	Usually an old inactive syphilis that was already treated. Exceptionally it may be a false positive treponemic test;
NT(+) T (-)	It is recommended to repeat testing using a different treponemic method; if it is still negative, then the result of the non treponemic test is a false positive and the conclusion is that there is no infection.

NT: Non treponemic test. T: treponemic test.

4.2. Diagnosis of congenital syphilis

4.2.1. Clinical

Treponema pallidum is present in blood at early stages and it can be transmitted to the fetus. Passage through the placenta usually occurs between Weeks 16 and 28 of pregnancy, although there are cases reported as early as on Week 9.

A pregnant woman's odds of transmitting the disease to the fetus depends on the phase of infection, being 90% during the first year of the disease when there has been no therapy, and then dropping at later stages. The prognosis of children infected with syphilis in uterus is not well established, but the rate of negative events is estimated to range from 50% to 80%, including abortion, stillbirth, low birth weight, prematurity and neonatal infection ^(35,36,37,38).

All the children born to mothers that presented with syphilis during pregnancy must be tested to determine whether they show evidence of the disease.

The procedures below are recommended in all cases:

- Pathological examination of the placenta;
- Complete physical examination to include the active search of the lesions discussed further on;
- Serological testing;
- Dark field examination of the child's secretions;
- In the cases that meet the definition of congenital syphilis, the recommended testing includes a lumbar puncture to evaluate the VDRL, cytology and physico-chemical test of the cerebrospinal fluid (CSF). This should be done when the appropriate conditions for the procedure are met. If the lumbar tap is not feasible and there is a suspicion of neurological involvement, the child must be treated as if it were a case of neurosyphilis;
- Other tests should be considered based on their availability and on the clinical suspicion (e.g. long bone radiographs, or chest X-rays, liver function tests, neurological ultrasound evaluation, etc.)

Manifestations strongly suggesting an early congenital syphilis

The clinical manifestations of congenital syphilis are varied and they include the manifestations below:

- Prematurity;
- Intrauterine growth retardation;
- Pneumonitis (pneumonia alba);
- Enlargement of liver and spleen;
- Generalized lymph node enlargement;
- Haematological manifestations: anaemia, leucopaenia, leucocytosis, thrombocytopaenia;
- Mucocutaneous manifestations: purpura, palmo plantar pemphigus, maculo papular rash, condyloma latas, rhagades, petechias;
- Bone lesions, osteochondritis, periostitis;
- Kidney manifestations: nephrotic syndrome;

- CNS manifestations: aseptic meningitis, Parrot's pseudoparalysis;
- Eye manifestations: chorioretinitis, retinitis;
- Other findings: fever, hemorrhagic rhinorhea, pancreatitis, jaundice, inflammation of the gastrointestinal tract, hypopituitarism, myocarditis;
- Hydrops fetalis.

Manifestations suggesting late congenital syphilis

- Hutchinson's teeth;
- Interstitial keratitis;
- Saddle nose; olympian forehead;
- Gummas on feet;
- Involvement of the SNC: mental retardation, hydrocephalus, seizures, deafness and blindness;
- Osteoarticular lesions: Clutton's joints, saber tibia, bone gummas, bell-shaped scapula;
- High palate, protruding mandible, micrognathia, perioral fissures.

4.2.2. Serological Diagnosis

As IgG antibodies go through the placenta, both treponemic and non treponemic tests can be positive when mothers have syphilis. In these cases it is recommended to conduct a simultaneous assessment of VDRL or RPR to mother and child (the use of cord blood should be avoided because of the potential contamination with maternal blood) and to consider positive any child whose titers are four-fold their mothers' (for example, a titer of 1/8 in the mother and 1/32 in the child)^(40,41,39,40); it is however important to remember that lower titers do not fully rule out the diagnosis of congenital syphilis.

4.3. Diagnosing the mother's HIV infection

Counseling and HIV testing are a critical component of the MTCTP programs and they are key for the identification of the women that require medical care and ARVT or MTCT prevention interventions. Pregnant women must also receive information and counseling on the syphilis and HIV tests. All pregnant women must undergo serological screening at their first antenatal visit. If they are negative, they must be repeated in the third trimester and at childbirth.

When the test results are not available before delivery (for instance, because they did not receive antenatal care), counseling and HIV testing (ideally a rapid test) during delivery or immediately after childbirth, facilitate the provision of the intrapartum and postpartum components of the MTCTP interventions⁽⁴¹⁾ and the rapid syphilis test permits the neonate's early therapy.

Hence the need to reinforce the capacity to offer systematic counseling and HIV and syphilis tests at all centers that provide care to pregnant women and women at child-bearing age, even at the time of delivery. Special care must be given to the women presenting with negative serologies, providing them primary prevention services, particularly during pregnancy and lactation^(26,27). If the results are positive, the woman's sexual contacts should be offered counseling and serological testing. HIV tests should always be performed with counseling, respecting confidentiality and only after obtaining the person's consent.

4.3.1. Clinical Diagnosis

HIV infection may be asymptomatic for several years following the infection by the virus. AIDS symptoms occur when the CD4 counts drop and pave the way for an opportunistic infection. Most pregnant women with an HIV infection that seek antenatal care are asymptomatic, and they may not be aware that they have an HIV infection⁽⁴²⁾.

4.3.2. Serological Diagnosis

HIV tests detect antibodies or viral markers produced during HIV infection in blood or body fluids. Most HIV tests rely on the detection of antibodies in blood and they do not detect the virus itself. This means that at times, people recently infected may be reported as HIV (-), because of this period known as the "window period". Therefore, negative tests need to be repeated 6 weeks after the exposure.

Serological tests that detect HIV antibodies are usually broken down into two categories: screening and confirmation tests:

a) Screening tests

Screening tests are highly sensitive, but they may occasionally present false positive results, hence requiring confirmation.

- Enzyme Linked Immunoabsorbent Assay: ELISA is the test most frequently used test to detect HIV antibodies. The format has been gradually improved since its introduction. Fourth generation HIV tests permit to detect both viral antibodies and antigens;
- Rapid HIV tests: these are simple tests that do not require specific equipment; their sensitivity and specificity are similar to ELISA for the serological diagnosis of HIV infection. These tests permit to obtain the results in a few minutes.

b) Confirmation tests

Confirmation tests are designed to provide a higher sensitivity than the screening tests

- The Western Blot (WB) is used as a confirmation test and it is considered the gold standard to confirm the presence of antibodies against HIV. The combination of ELISA and WB are considered the algorithm for the serological diagnosis of HIV⁽⁴³⁾;
- There are several confirmatory tests, such as LIA or IFI;

See algorithm for the diagnosis and management of HIV and syphilis infection in fig. 2, page 28

4.4. Diagnosis of HIV infection in children

The diagnosis of HIV infection in the newborn needs to be done within the first weeks of life, so ARVT can be started early. WHO/PAHO recommends starting ARVT in all children under one year infected by HIV regardless of their clinical or immunological status, due to the high risk of progression to AIDS or death ⁽⁷⁾.

The laboratory serology tests typically used for the diagnosis of HIV infection (ELISA, WB, IFI) detect the presence of IgG antibodies against the viral proteins. These techniques are not useful in the newborn because of the presence of anti-HIV antibodies transferred by the mother. As a result, the diagnosis in children under one year of age must be done using virological tests.⁽⁷⁾

The virological tests preferred for clinical use for the diagnosis of HIV infection in children under 1 year of age are viral load, HIV RNA and DNA PCR. These tests imply the detection of part of the HIV's genome as they are definitive for the diagnosis of HIV infection.

The culture of HIV or the detection of antigen p24 are more costly procedures and they entail higher risks to the laboratory staff, so they are not recommended other than in the research contexts.

It is to note that when children acquire the infection at childbirth, the HIV genome assay may be negative the first weeks of life. The virological diagnosis is recommended at 4-6 weeks of life, when the sensitivity of this test reaches 95%. To establish the diagnosis, positive tests require confirmation with a second viral test. The children exposed to HIV that had a negative test and were breastfed by the mother must undergo new virological tests 6 weeks after weaning.

For considerations on the diagnosis of children older than 6 months, see “*Antiretroviral Therapy of HIV Infection in Children In Latin America and the Caribbean: Toward Universal Access*” ⁽⁴⁴⁾.

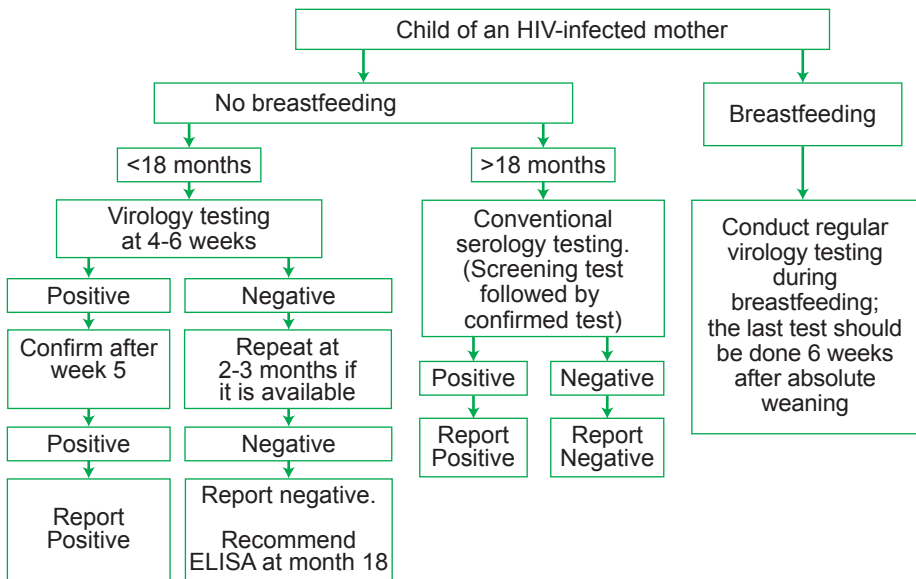
4.4.1 Polymerase Chain Reaction for the detection of viral DNA

This test detects the HIV's proviral DNA in the peripheral blood mononuclear cells and it shows that HIV has been permanently embedded into the child's lymphocyte genome. It requires the use of primers capable of amplifying the various subtypes of HIV. It will remain positive even after the mother and neonate receive combined ARVT. The sensitivity of a PCR test for the detection of the viral DNA (HIV DNA PCR) performed within the first 48 hours of life is <40%, but it increases up to >90% after 2-4 weeks. In other settings the first virological test is recommended at 2-3 weeks, to allow for an earlier diagnosis.

4.4.2 Viral RNA detection

This test detects the HIV RNA in plasma, directly reflecting the degree of viral replication and it is just as sensitive as the HIV DNA PCR for the early detection of HIV infection in exposed children. Its sensitivity is 25-40% the first week, but raises to 90-100% at the age of 2-3 months⁽⁴⁵⁾. The specificity has been reported to be similar to the DNA-PCR test in viremias with HIV-RNA that exceed 10,000 copies/ml, but this aspect should be interpreted with caution in children born to mothers that were on ARVT until the end of gestation and neonates that receive combined ARVT, because the viral plasma load (VPL) could be negative as a consequence of the antiretroviral therapy. The assessment should be conducted at least 1 week to 10 days after discontinuing neonatal antiretroviral prophylaxis.

Figure 5. Algorithm for the diagnosis of HIV infection in children



In the case of an incompatible result (for example, a negative result after a positive result or a positive result after a negative one) a new sample is required for confirmation.

5. CLINICAL MANAGEMENT

5.1. Syphilis

5.1.1. Treatment of maternal syphilis

The therapy of syphilis in the pregnant woman should be started immediately after obtaining the result of a positive screening test, preferably at the first level of care, unless the woman's status warrants a more complex level of care. For the purpose of prevention of congenital syphilis, it is considered adequate if it is done at least one month prior to delivery.

The treatment of primary and secondary syphilis and early latent syphilis consists of one single 2.4 million dose of intramuscular benzathine penicillin G (B-I).

The treatment of late latent syphilis or latent syphilis of unknown duration consists of 7.2 million units of benzathine penicillin G administered in three doses (one per week) 2.4 million dose of intramuscular benzathine penicillin G.

All the sexual contacts reported by the pregnant woman should be tested for syphilis, and all the positive contacts should be treated with 2.4 million dose of intramuscular benzathine penicillin G. Re-infection by the untreated sexual partner is one of the most important causes of congenital syphilis.

All treated women should be evaluated with quantitative serological testing at 1- to 3-month intervals. A four-fold increase of titers or higher is an indication of the need for a new therapy, considering that the therapy has failed, or re-infection or neurosyphilis, which also require the CSF examination (if the test is available).

Treatment administration must be supervised and recorded in the clinical records. **If there is no indication in the clinical record that the therapy was delivered, the newborn must be considered a case of congenital syphilis.**

The Jarish Herxheimer reaction consists of fever and poor general status, due to the release of antigens resulting from the death of the treponemas. When treatment is conducted on the second half of pregnancy, this reaction might exceptionally trigger labor.

Managing patients with a potential allergy to penicillin

There are no alternatives to penicillin with proven efficacy for the treatment of neurosyphilis, congenital syphilis, syphilis in pregnant women and HIV patients. On the other hand, repeating the administration of penicillin to a patient with previous history of allergy might cause severe and immediate reactions.

It is estimated that 10% of the people that report severe allergic reactions to penicillin continue to be allergic. With time, most of them will stop producing penicillin-specific E immunoglobulins. If it were possible to determine that the specific IgEs have cleared, these people could be treated with penicillin safely. There are skin tests with major and minor determinants for penicillin allergy that could effectively identify the people at a high risk of developing a reaction against penicillin.

Desensitization

The patients with a positive test to any of the penicillin determinants can be desensitized. The process is relatively safe, but cumbersome, and it may be done orally or intravenously (Chart 3); even when the two forms of desensitization have not been compared, the oral form seems to be safer and easier. Desensitization must be undertaken at hospital settings, since although they are rare, allergic reactions may occur. The procedure may be completed in four hours, after which the patient is administered the first dose of penicillin. Some authors recommend maintaining the daily penicillin doses low (500,000 IU per os) until the three weeks are completed. Desensitization must be done under medical surveillance and corticosteroids and adrenalin must be available in case there is a side effect.

This scheme must be repeated before every weekly injection dose.

If penicillin cannot be used, there are no effective alternatives for therapy. One possibility is erythromycin, at 500 mg/6h for 14 days (C- III), which may not be enough for the mother, who will require treatment with doxycyclin after delivery at a dose of 200 mg/day for 14 days. Erythromycin therapy of the pregnant woman is absolutely ineffective for treating the fetus, so the child will be given penicillin using the regimen described later.

Chart 3
Protocol for oral desensitization for patients with a positive skin test

Penicillin V suspension (*)	Amount(**) (IU/ml)	mll	IU	Accumulated dose (IU)
1	1.000	0.1	100	100
2	1.000	0.2	200	300
3	1.000	0.4	400	700
4	1.000	0.8	800	1.500
5	1.000	1.6	1.600	3.100
6	1.000	3.2	3.200	6.300
7	1.000	6.4	6.400	12.700
8	10.000	1.2	12.000	24.700
9	10.000	2.4	24.000	48.700
10	10.000	4.8	48.000	96.700
11	80.000	1.0	80.000	176.700
12	80.000	2.0	160.000	336.700
13	80.000	4.0	320.000	656.700
14	80.000	8.0	640.000	1.296.700

Observation period: 30 minutes before the parenteral administration of penicillin

Source: Wendel GO Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985;312: 1229-32.

(*) The interval between doses is 15 minutes; time elapsed, 3 hours and 45 minutes; accumulated dose 1.3 million units.

(**) The specific amount of penicillin is diluted in approximately 30 ml of water and then given orally.

5.1.2. Treating children with congenital syphilis

All the children with the features below:

- Clinical evidence of congenital syphilis;
- Asymptomatic but whose mother did not receive adequate therapy for maternal syphilis;

- Asymptomatic and whose mother was adequately treated, but who presents RPR or VDRL titers higher (4-fold) than the mother's;
- Asymptomatic, and whose mother was adequately treated but there are no quantified titers to compare with the mother's.

They must receive therapy with aqueous crystalline penicillin G: 50,000 units/Kg. every 12 hours (100,000/Kg/day) the first 7 days of age, continuing then with 50,000 units/kg every 8 hours (150,000/kg/day) until 10-14 days are completed. In the case of children that presented neurological manifestations, therapy must be maintained for 14 days. If neurosyphilis has been ruled out, an alternative therapy may be considered with IM procaine penicillin at a 50,000 u/kg dose at single daily doses for 10 to 14 days.

The asymptomatic children born from mothers with syphilis treated adequately and whose RPR or VDRL titers are similar or lower than the mother's should receive one single dose of benzathine penicillin G at 50,000 units/kg, regardless of the therapy received by the mother and without any further testing ⁽³⁶⁾.

5.2. HIV INFECTION

5.2.1. Clinical and immunologic evaluation of HIV+ pregnant women: indication to start ARVT

When a pregnant woman is found to be HIV+ her clinical status and CD4 count must be evaluated to determine the right moment to start therapy.

The viral load test is available in most countries in the region. It is not considered indispensable before starting therapy, but when it is available it provides significant information that will become relevant at follow-up. The viral load permits to evaluate the efficacy of therapy, and when it is higher than 1,000 copies/ml at the end of pregnancy, it supports the decision for delivery by elective cesarean section ^(46,47).

If the woman meets the clinical and/or immunological criteria to start therapy, she should be started on ARVT as soon as possible. If the woman is not eligible to initiate for therapy because of her own health, she should be started on ARVT as prophylaxis of MTCT of HIV as soon as possible after Week 14.

In pregnant women, ARVT protects the mother and hugely reduces the risk of MTCT, particularly in cases of advance disease. The issues that must

be taken into account when starting ARVT include the fetus's gestational age, the potential effects of intrauterine exposure to drugs and the adverse effects of ARVT in the pregnant woman. The objective of ARVT is to fully suppress the viral load to avoid the risk of transmission and minimize the risk of occurrence of ARV resistance.

The first-line guideline recommended for the pregnant women that require therapy and present with less than 250 CD4 cells/mm³ is based on two NRTIs (usually AZT + 3TC) with NVP.

It is to note that in women presenting with more than 250 CD4 cells/mm³, the use of NVP may be associated with a higher toxicity. Although there are several options available in that scenario, PIs are the preferred choice; other alternatives include using NVP under close monitoring of the patient the first 12 weeks of therapy, or to choose a regimen with 3 NRTIs. The 3 NRTI guideline has proven to be less effective, so its use must be limited to special situations.

a) Choosing the Nucleoside Reverse Transcriptase Inhibitors

The NRTI combination of choice in pregnant women is AZT + 3TC. AZT has been extensively studied in pregnant women and infants, and its safety and effectiveness in reducing the risk of MTCT have already been shown. Consequently, AZT should be included as part of the therapy in association with 3TC during pregnancy and whenever possible. Abacavir (ABC), didanosine (ddI) and stavudine (d4T) are other possible NRTIs. Before starting abacavir, and if the technique is available, consider assessing HLA-B* 5701, since its presence is predictive of the risk of occurrence of a hypersensitivity reaction. When the test is not available, patients must be monitored very closely.

d4T had been considered the drug of choice before AZT, because it requires a limited or no laboratory monitoring. However, it is the NRTI more consistently associated with lactic acidosis, fat atrophy and peripheral neuropathy ⁽⁴⁸⁾. That is why d4T is not among the NRTIs of choice in the first-line regimen. The d4T-ddI combination is contraindicated in pregnancy due to the increased risk of maternal death as a result of lactic acidosis and liver failure.

Given the lack of information on the use of TDF (nucleotide analog) in pregnancy and the concern over potential deleterious effects on the fetal

bones, TDF must be considered a component of the initial ARVT for pregnant women when other options are not available.

b) Choosing the Non Nucleotide Reverse Transcriptase Inhibitor

NVP is the NNRTI of choice for ARVT during pregnancy because of the considerable experience available of its use in pregnant women and its efficacy reducing MTCT. Special attention must be paid to its potential toxicity, especially hepatitis, in women that start ARVT with a lymphocyte count of over 250 CD4/mm³

When ARVT is started with NVP in a pregnant woman with a CD4 count higher than 250/mm³, it is advisable to monitor closely both clinical and laboratory parameters during the first 12 weeks of therapy. Moreover, the woman should be informed about the symptoms that warrant urgent care (jaundice, skin rash, fever or abdominal pain); scheduling more frequent visits during the first weeks of therapy (every two weeks) and assess the liver enzymes at baseline and during the first 12 weeks (for example at weeks 2, 4, 8 and 12), in case of occurrence of symptoms. If liver enzymes reach grade 3 or 4 (ALT or AST >5 times their upper normal limit) with no other potential cause, NVP should be discontinued permanently, changing it for another antiretroviral. NVP should also be discontinued if the patient shows symptoms of liver toxicity and there is no access laboratory tests , or if the patient presents with a severe skin rash.

EFV should not be used during the first trimester of pregnancy, except under exceptional conditions, when the benefit justifies the potential risk to the fetus, such as, for instance, when there are no other therapeutic options available and the woman meets the criteria for severe disease.

Recommendations for starting ARV therapy in women

- All pregnant women with ARV indication should receive ARVT (A-II);
- ARVT must be started as soon as the clinical or immunological indication has been defined (A-IV);
- Women not requiring ARVT for their own health will be started on ARVT regardless of their clinical status and immune count as soon as possible after week 14 of pregnancy as an HIV MTCT prophylactic measure (A-II);
- The first line ARVT plans preferred for pregnant women are: AZT + 3TC + NVP or AZT + 3TC + PI (LPV/r or SQV/r) (A-II);
 - Plan including PI;
 - Plan including NVP only if a close clinical and analytical testing can be assured for the next 12 weeks;
 - Plan with 3 NRTIs (*Guidelines with 3 NRTIs are less powerful than PI- or INNT-based plans*).
- Consider using TDF as a component of the initial ARVT only when there are no other alternatives available or when the existing ones are contraindicated (C-IV).

5.2.2. Women that get pregnant while on ARVT

The primary concern with women that get pregnant while on ARVT is to maintain their health status and to ensure they receive an adequate treatment. It is then necessary to evaluate the gestational age, the woman's clinical status, and the need to make adjustments to her therapy.

When pregnancy is detected in the first trimester, the potential risks and benefits of antiretroviral drugs both for the woman and the child's future (the risk of MTCT and those risks resulting from intrauterine exposure of ARVs) need to be considered. In the USA, the registry of mothers that received ARVT during pregnancy (*Antiretroviral Pregnancy Registry*) evaluated the risk of congenital malformations induced by the antiretrovirals, concluding that the prevalence of congenital malformations was not higher than that of the general population⁽⁴⁹⁾. The ARV medication that poses more concern is EFV. Significant congenital defects have been

reported in the central nervous system of monkeys exposed *in utero* to EFV concentrations similar to those reached in humans at the standard therapeutic dose. Additionally, there are four cases reported of children exposed to EFV during the first trimester that presented important neurological defects ^(50,51,52). Therefore, this drug should not be used in women of child-bearing age when the use of an effective contraceptive method cannot be assured, to prevent the risk of teratogenicity in case they get pregnant.

When pregnancy is detected during the first trimester in a woman on EFV, this drug should be replaced for Nevirapine (NVP), or a protease inhibitor (PI), or for another nucleotide, such as abacavir. When NVP is used to replace EFV, the patients must be closely monitored the first 12 weeks of therapy, particularly those women with a good immune response (CD4 >250 lymphocytes/mm³) to the EFV-based regimen. In these cases, the women should start directly with a dose of NVP of 200 mg twice a day, because the stepwise dosaging has been associated to subtherapeutic concentrations of the drug ⁽⁵³⁾.

When pregnancy is detected after the first trimester, some authors suggest that the woman can go on with her EFV therapy, because the high risk period is already over ^(54,55).

When pregnancy is detected in women receiving an ARVT with no EFV, they should continue the same therapy. Discontinuing it would lead to a rebound of the viral load (increasing the risk of MTCT) and a reduction of CD4 lymphocytes ⁽⁵⁶⁾, with the subsequent increase of the risk of complications to the mother^(57,58). Replacement is not recommended in the women that receive tenofovir in a second-line scheme.

In all cases, attempts should be made to include AZT in the regimen and program the intrapartum and postpartum components for mother and child for MTCT prophylaxis.

Recommendation for women with HIV that get pregnant while on ARVT

- Avoid the use of EFV in women at child-bearing age that do not use or that do not have access to an effective contraceptive method **(A-IV)**;
- Women that are receiving ARVT with EFV:
 - a) If pregnancy is detected during the **first trimester**:
 - Change EFV for NVP and monitor closely all the women with CD4 counts >250 cell/(mm³) because of the toxicity risk **(A-IV)** or
 - Replace EFV for a PI (LPV/r, SQV/r) **(A-IV)** or
 - Replace EFV for another NRTI (e.g.: ABC) **(B-IV)**
(The guidelines with 3 NRTIs are less powerful than those based on PIs or NNRTI)
 - b) If pregnancy is detected during the second or third trimester and the therapy has been effective, they should continue with EFV **(A-IV)**
- Women receiving TDF in a second line therapy: the benefits of maintaining it probably make up for the risk of toxicity in the child; replacement of this drug is not recommended **(A-IV)**;
- In every case:
 - a) Include AZT in the mother's therapy scheme **(A-IV)**;
 - b) Indicate the intra- and postpartum components of MTCTP **(A-IV)**;

5.2.3. Antiretroviral MTCTP prophylaxis

If the woman is not under ARVT and does not meet the clinical and/or immunological criteria to start ARVT, she should receive the most effective prophylaxis possible. Since the year 1994, when the PACTG study 076⁽⁵⁹⁾ was published, multiple studies have shown the benefit of antiretroviral interventions in the prevention of mother-to-child transmission of HIV ^(60, 61,62,63,64,65,66,67,68,69). The evidence available shows the greater efficacy of the regimens using triple therapy versus the other options ^(70,71,72,73) and many countries in the region have adopted this scheme as the standard PMTCT interventions^(50,52,74,75,76,77).

By implementing these guidelines, in addition to the replacement of maternal breastfeeding, and cesarean sections in the cases that require it,

the transmission rate has been reduced to under 2%.

Clinical scenarios: recommendations

- a) Women with HIV and with no ARVT and with no indication to receive it and seeking care early in pregnancy

The prophylactic regimen chosen for women with HIV infection is ARVT, starting on the second trimester and discontinuing after delivery. This approach reduces the effective risk of MTCT, with a low risk of occurrence of resistance, and preserving the options of care.

The regimen choices includes:

1) Prepartum component

AZT + 3TC, associated to NVP (use NVP only if the mother has less than 250 cell/mm³) or a PI boosted with ritonavir, lopinavir (LPV/r) or saquinavir (SQV/r),

The 3 NRTI option (AZT-3TC-ABC) is less powerful and hence it is not recommended because of the occurrence of NRTI mutations that may jeopardize future therapies.

Therapy should be started as soon possible after Week 14.

2) Intrapartum Component (Not utilized if ART is provided antepartum)

Starting with the onset of labor, or four hours before the cesarian section, the mother must receive a loading dose of intravenous AZT of 2 mg/ Kg, followed by a 1-hour continuous intravenous infusion of AZT at 1 mg/ Kg/hour until the expulsion period is completed. If no intravenous AZT is available, then the recommendation is 300 mg AZT orally or one tablet of AZT-3TC (300-150mg) at the onset of labor or 4 hours before the cesarean section and then repeat every 3 hours until birth.

3) Postpartum component

For the mother: if the mother has no indication of ARVT and exclusive milk formula feeding is ensured for the child, the regimen must be discontinued immediately after delivery. The women that received the AZT-3TC-NVP plan must continue therapy with AZT-3TC (300-150mg) every 12 hours for 7-10 days after delivery to reduce the risk of NNRTI resistance. In the case of the women that followed the guidelines with PI + 2 NRTIs, they

should be discontinued jointly after delivery.

For the child: administer AZT in syrup from 6 to 8 hours after childbirth, at dosages of 2 mg/kg every 6 hours for at least 6 weeks.

b) Women with HIV and naïve of therapy that present at the final stages of pregnancy and labor

The efficacy of the interventions is reduced when the woman does not have an adequate antenatal care. Women that present at the final stages of pregnancy must be immediately started on a combined prophylactic regimen and the cesarean section should be scheduled.

If the woman presents at childbirth, intrapartum and postpartum components must be administered, even if the opportunity to indicate the prepartum component has been missed. In the case of pregnant women that do not seek antenatal care, the rapid tests and the PMTCT intrapartum and postpartum components help prevent new infections and reduce the total health cost compared to not undertaking these two interventions ⁽⁷⁸⁾.

The **regimen of choice** includes:

1) Intrapartum Component

The woman should immediately start an intravenous loading dose of AZT at 2 mg/ kg, in 1 hour, and one 200 mg NVP. Continue with a continuous intravenous infusion of AZT at 1 mg/kg/hour until the time of childbirth. If labor has not started yet or if the mother has not ruptured membranes, childbirth should preferably be through scheduled cesarian section.

2) Postpartum Component

For the mother: If NVP was administered, continue with AZT-3TC (300-150mg) every 12 hours for 7-10 days for a week to reduce the risk of NNRTI resistance.

For the child: AZT + NVP with the guideline below:

- AZT syrup 6-8 hours after childbirth, at a dose of 2 mg/kg every 6 hours for 6 weeks;
- NVP; if the mother has not received this drug during delivery, administer one first 2 mg/kg dose (solution, 10 mg in 1 ml) within the first 12 hours of life and one second dose at 72 hours of life. If the mother received

Nevirapine during delivery, the newborn will have Nevirapine levels during the first 72 hours of life, so one single dose of the drug will be administered at 48-72 hours.

Some programs in the region consider the use of combined triple therapy with AZT-3TC-NVP in the presence of risk factors for transmission such as prematurity, membranes ruptured for more than 4 hours, genital tract infections and bleeding. See paragraph C.

Alternative regimen:

The minimum regimen that should be provided includes:

1) Intrapartum Component

Start immediately with oral AZT-3TC (300-150mg) and repeat the dose every 3 hours until birth.

2) Postpartum Component

For the mother: not indicated

For the child: AZT + NVP with the guideline below:

- AZT in syrup 6-8 hours after delivery at 2 mg/kg doses every 6 hours for 6 weeks;
- NVP: administer one first 2 mg/kg dose (solution, 10 mg in 1 ml) within the first 12 hours of life and one second dose at 72 hours of life.

Some programs in the region consider the use of combined triple therapy with AZT-3TC-NVP in the presence of risk factors for transmission such as prematurity, membranes ruptured for more than 4 hours, genital tract infections and bleeding. See paragraph C.

c) Neonate born to mother with HIV and who has not received any prophylaxis guideline for PMTCT

In this case, as the prepartum and intrapartum components have been interrupted, the odds for reducing the MTCT are limited to the post partum component in the child. These children should undergo virological testing as soon as possible (ideally taking the first specimen immediately at birth before starting prophylaxis, and the next one at 4 weeks) to rapidly determine the child's status and to assess the need for treatment. ARV prophylaxis in the child must be started as soon as the newborn can tolerate oral feeding and if possible within the first hours of birth. The recommendation for

these cases is to start the child on combined therapy with AZT-3TC-NVP, following the guideline below:

- First week: Administer NVP at 2 mg/kg/day, delivering the first dose as soon as possible, hopefully within the child's first 12 hours. After day 5, administer 4 mg/ kg/day;
- Second week: continue with a dose of 4 mg/kg/day from day 8 to day 14, interrupting therapy if the virological HIV testing (viral load, RNA or DNA PCR) is reported as negative;
- After interrupting NVP therapy, keep AZT and 3TC for 15 days, to reduce the possibility of developing NVP resistance.

The total duration of prophylaxis is 4 weeks; the first two weeks with: AZT+3TC+NVP and the last two with AZT+3TC. If available, it would be important to determine the HIV genome (DNA or RNA) within the child's first 48 hours of life, repeating this same test at 2 weeks and having the result in 24-72 hours, to determine the need for maintaining therapy. If the results of the first and second control are negative, Nevirapine can be discontinued. This is theoretically the most effective guideline although there are no studies to support this intervention.

One second choice is to use AZT + NVP, following the guideline below:

- AZT: syrup 6-8 hours after childbirth, at doses of 2 mg/kg every 6 hours for 4-6 weeks;
- NVP: administer one first 2-mg/kg dose (solution, 10 mg in 1 ml) within the first 12 hours of life and one second dose at 72 hours of life. The minimum choice would be AZT for 6 weeks, starting 6-8 hours after childbirth, as stated in plan ACTG 076. This option is less effective.

5.2.4. Type of delivery and indication of caesarean section

Universal precautions or measures should be implemented during all the procedure of delivery, including the use of apron, gloves, boots, cap and eye protection.

Furthermore, the recommendations below seek to reduce the risk of mother-to-fetus transmission and the accidental transmission to all the health staff:

a) Avoid:

- Unnecessary invasive procedures;

- The episiotomy, unless it is clinically indicated;
 - Artificial rupture of membranes;
 - Prolonged rupture of membranes;
 - Use of straight suture needles;
 - Use of scalpel to sever the umbilical cord;
 - Amniocentesis;
 - Amnioscopy;
 - Invasive monitoring
- b) Clamping and immediate cutting of the umbilical cord;
- c) Using gloves to manipulate the newborn;
- d) Bathing the child immediately with soap and water.

Indication for planned cesarean section

The planned cesarean section is the procedure performed before starting labor and before the rupture of membranes. It is associated with 50% reductions of the MTCT and up to 90% if the woman receive ARV for PMTCT^(79,80), which has resulted in a significant increase of its prescription in women with HIV.

When the procedure is programmed, it has shown to be effective, safe and cost-effective; however, it is to note that it is not free from risks and that it has a complication rate slightly higher than non elective cesarean section in the short term⁽⁸¹⁾. Other constraints of the procedure include the lack of information about the benefits of cesarean sections in women with a prolonged rupture of membranes and the cost-effectiveness in settings with limited resources where the complication rates may be higher^(82,83).

In women receiving ARVT, with a good compliance and presenting with an undetectable viral load or <1,000 copies/ml in the last trimester, the recommendation favors the vaginal delivery^(88,84). When managing uterine atonia, the use of methyl ergonovine must be avoided if the patient uses protease inhibitors or efavirenz, because this combination has been associated to an excessive vasoconstriction⁽¹⁹³⁾.

Recommendations on childbirth type in pregnant women with HIV

- Programmed cesarean section at Week 38 to the women:
 - Whose viral load has not been assessed at the third trimester of pregnancy **(A-I)**;
 - with a viral load >1,000 copies/ml **(A-I)**;
- Provide vaginal delivery to those women with no obstetric indication of cesarean section, on stable ARVT, good compliance and viral load performed on the last trimester of pregnancy <1,000 copies/ml **(A-IV)**

5.2.5. Recommendations on how to feed the newborn

Seeking to minimize the risk of HIV transmission to children, the group of experts in the Region of the Americas proposed reinforcing the strategy of suppressing breastfeeding of children borne to mothers with HIV. In that respect, PAHO/WHO recommends avoiding breastfeeding whenever this option is acceptable, feasible, affordable, sustainable and safe (AFASS). To that end, the group of experts acknowledges that countries must increase their efforts to meet these requirements, to allow them to offer this alternative to the women that need it. Nevertheless, there are reports claiming that milk formula is associated with greater morbidity and mortality for other causes, and that mixed breastfeeding (maternal breastfeeding plus milk formula) presents a higher risk of HIV transmission. As a result, when health professionals recommend avoiding breastfeeding, they should consider the local risks of presenting diarrhea and malnutrition, while ensuring the uninterrupted and safe supply of milk formula.

Consequently, apart from the above-mentioned conditions, when the exclusive use of milk formula cannot be assured for the first six months, then exclusive maternal breastfeeding should be considered until the “AFASS” conditions are met. Prolonging the exclusive maternal breastfeeding period beyond six months increases the risk of malnutrition. Mothers should receive counseling and support at least until the child turns two years of age, to ensure an adequate nutrition. Counseling is to include the risks and benefits of these alternative ways of feeding a child, the technique required to implement them, and the therapeutic methods to suppress the mother’s production of milk whenever necessary.

There are recent studies suggesting that maintaining the mother on triple therapy during the breastfeeding period significantly reduces the risk of HIV MTCT ^(85,86,87,186). Exclusive maternal breastfeeding with ARVT can be contemplated exceptionally in those cases where it is impossible to assure formula feeding in line with the AFASS conditions, even if the recommendation for an optimal prophylaxis is suppressing maternal breastfeeding and replacing it with milk formula.

Mixed breastfeeding (mother's milk and milk formula) poses a greater risk of transmission than the exclusive maternal breastfeeding or feeding exclusively with milk formula, and should always be avoided ^(88,89). In order to ensure that children will not receive mixed feeding, and for the mothers' convenience, the programs must ensure their access to counseling, support, and specific medication to suppress lactation when appropriate.

Recommendations for feeding the neonate born to a mother with HIV

- All the mothers should receive counseling and nutritional support to feed their children, **(A III)**;
- Replace maternal breastfeeding when the AFASS conditions are met **(A-II)**;
- Discourage mixed breastfeeding **(A-I)**;
- When replacement of maternal breastfeeding for milk formula is recommended, provide the medication required to suppress lactation **(A-IV)**;
- In the exceptional cases in which maternal breastfeeding cannot be replaced by feeding with adapted formula, the recommendation is to provide exclusive maternal breastfeeding, limiting it to the first 6 months, and extending the mother's ARVT as long as she breastfeeds her child, even if her own health does not warrant such therapy **(A-I)**

5.2.6. Safety of ARVT in pregnant women and children

Pregnancy and breastfeeding pose additional issues concerning PMTCT and the toxicity that may affect the choice of antiretrovirals. However, these issues must be approached in the context of ensuring the woman the optimum treatment for her health. All antiretrovirals are associated with some toxicity, which may be transient or permanent, and may affect both woman and child. On the other hand, the women that receive ARVT are at a lower risk of progression of their disease, death and MTCT of the HIV infection. The risk for the pregnant woman, fetus and newborn vary based on the stage of fetal development, the duration of exposure and the number of drugs the woman and child have been exposed to.

5.2.6.1 Antiretroviral safety in the treatment of the pregnant woman

The toxicity of ARVs during pregnancy is not greater than in non pregnant women⁽⁹⁰⁾. The ARVT guideline for adults developed by PAHO/WHO contains a more in-depth description of the toxicity of antiretrovirals. In this chapter we will specifically address the safety issues related to pregnancy.

a) Nucleoside Reverse Transcriptase Inhibitors

The NRTIs that have been used more extensively for pregnant women are AZT and 3TC; hence, those two drugs are considered the NRTIs of choice. The optional first-line NRTIs in the ARVT guidelines include ABC, d4T and ddI. The pharmacokinetic studies conducted in pregnant women indicate that no dose adjustments are required for AZT, 3TC, ABC, ddI, or d4T^(91,92,93,94). FTC has a similar structure to 3TC, although there is limited evidence of its safety in pregnancy. TDF is a nucleotide analog that has been included as an option in the ARVT guidelines as first line therapy of adults. The experience with TDF in pregnancy is limited. The studies in monkeys exposed to the drug in uterus show reduction of fetal growth and bone porosity^(87,88). Bone demineralization has also been reported in humans, in some infected children that received chronic therapy with TDF^(89,95,96).

The primary toxicity observed with AZT is hematological (anaemia and neutropaenia); pregnant women with a severe anaemia (hemoglobin < 7 g/dl) the use of AZT should be avoided, replacing it by other NRTIs, such

as ABC or d4T. The combination of ddI and d4T has been implicated in several reports of cases of lactic acidosis in pregnant women, some of which had a fatal outcome either for the mother or the fetus. All these women that had received this regimen since before conception and had continued it during pregnancy presented symptoms of lactic acidosis at the end of pregnancy^(97,98).

There are no reports of increased risk of congenital abnormalities among children exposed to AZT, 3TC or ABC during the first trimester, evaluated prospectively, considering that the number of cases evaluated would permit to detect a 1.5-fold increase, and for the case of ABC, the risk is twice as high⁽⁵³⁾. With regard ddI, malformations were observed in 13 cases of the 205 (6.3%) live-born exposed to the drug during the first trimester, versus 2 cases of 190 (1.1%) newborns exposed to ddI after the first trimester⁽⁵³⁾.

b) Non Nucleotide Reverse Transcriptase Inhibitors

NVP is the NNRTI of choice for the ARVT during pregnancy, as a result of the accumulated clinical experience and its efficacy to reduce MTCT^(69,99,100). The most frequent adverse events of NVP are hepatotoxicity and skin rashes. Although symptomatic hepatotoxicity or serious skin toxicity are rare, they are more frequent in women than in men and they tend to occur from 6 to 12 weeks after the treatment is started. Frequency is also higher among the women that start ARVT with a CD4 count over 250 lymphocytes/mm³, and in males with a count over 400 lymphocytes/mm³^(101,102,103). In an analysis including several studies with approximately 600 women with a variable range of CD4 counts, symptomatic hepatotoxicity was present in close to 10% of the cases, and a fatal hepatotoxicity was seen in 0.7% of the women with a CD4 count higher than 250/mm³ upon the start of NVP. When the CD4 count was lower than 250 cells/mm³, the frequency of symptomatic hepatitis was 1 to 2%, and no cases of lethal hepatotoxicity were observed^(106,108). Although some cases have been reported in pregnant women, it is not clear whether pregnancy predisposes women to these toxic effects even further^(95,104,105), despite the fact that a better immune status among pregnant women might increase their toxicity risk⁽¹⁰⁶⁾. The highest mortality (1.1%) was observed among women with a CD4 count over 400 lymphocytes/mm³. There is probably a toxicity risk gradient in women with CD4 counts over 250/mm³, with the highest risk being when the CD4 count gets closer to the normal parameters, as has been observed

in the women with no HIV infection that received prophylaxis following exposure to NVP⁽⁶⁵⁾.

Some studies conducted at sites with limited resources, predominantly including pregnant women, have concluded that the risk of NVP-related hepatotoxicity is lower than that reported in industrialized countries. These studies have reported 3- to 4 grade increases of liver enzymes in around 4% to 7% of the women with various CD4 counts^(70,76,111,107,108). Conversely, a study conducted in South Africa reported higher symptomatic and severe liver toxicity rates in non pregnant women with CD4 counts over 200 lymphocytes/mm³ (the mean CD4 count in patients with early hepatotoxicity was 406 lymphocytes/mm³)⁽¹⁰⁹⁾. The data from the Antiretroviral Pregnancy Registry have failed to detect any increases in the overall risk of congenital malformations following exposure to NVP within the first trimester⁽⁵³⁾.

With respect EFV (the alternative NNRTI for the first-line therapy), there is evidence suggesting it might be implicated in a higher risk of congenital malformations. Significant malformations have been observed in young monkeys exposed in uterus to a concentration of EFV similar to the therapeutic concentrations used in humans, such as anencephaly, anophthalmia and cleft palate ^(“o”). Six cases of central nervous system defects have been reported in children exposed to EFV during the first trimester (three of them with myelomeningocele and one with a Walker-Petimetre malformation)^(54,56,111).

In a prospective registry of pregnancy cases, which included women that did not know their pregnancy status or tests such as antenatal ultrasound, congenital malformations were observed in 5 of 228 (2.2%, 95% CI: 0.7-5.1) live-born infants exposed to EFV during the first trimester⁽⁵³⁾. None of the abnormalities reported in this study were similar to those observed in the animal studies or in the case reports. Despite the large number of live-born infant exposed to EFV that have been monitored, it has not been possible to conclusively detect a significant increase in the risk of congenital malformations. However, more exhaustive studies are required to evaluate the risk of specific congenital malformations, such as the defects of the neural tube, because the current prospective studies lack the power to draw conclusions about these risks ^(113,114).

The US Food and Drug Administration (FDA) ranks EFV as a category D drug, i.e., “Positive evidence of undesirable effects on the human fetus based on experimental or post-marketing data, even though the potential

benefits might be acceptable despite their possible risks”⁽¹¹⁶⁾. The use of EFV could be considered in pregnant women going through their second or third trimester and who cannot receive NVP (e.g., a pregnant woman with severe NVP-induced toxicity or with tuberculosis).

When a woman at child-bearing age is prescribed an EFV-based guideline, the treating professional must ensure that she is not pregnant and that she has access to counseling and effective contraceptive methods. In a recent study in Côte d’Ivoire, 548 women that received EFV with family planning counseling and hormone contraception methods, the annual incidence of pregnancy was 2.6%⁽¹¹⁵⁾.

c) Protease Inhibitors

The recommendations concerning the second line therapy in pregnant women are limited, as a result of the scantier experience with the protease inhibitors (PIs) in pregnancy. The most commonly used protease inhibitors, and for which there is more safety data for pregnancy available are saquinavir enhanced with low-dose ritonavir (SQV/r) and nelfinavir (NFV)^(75,116,117).

During pregnancy the drug distribution may change significantly; however, there seems to be no need to adjust the SQV/r dose⁽¹¹⁸⁾.

In the case of nelfinavir, the results have been contradictory, since several studies have shown that the concentration of this drug is extremely variable in pregnant women^(119,120). The capsule formulation of lopinavir enhanced with ritonavir (LPV/r) have also shown to associate to lower concentrations during the third trimester⁽⁵¹⁾. However, another study observed sufficiently high plasma concentrations in most women⁽¹²¹⁾. There are no data on the changes of the pharmaceutical form of LPV/ r in heat-stable tablets in pregnancy; hence, and until further data is available, the usual dose in targets should be used. The concentrations of indinavir (IDV) with no boosting are lower during pregnancy than in the post partum period^(124,122,123). There is no information available on the concentrations of atazanavir (ATV) or fosamprenavir (fAPV) in pregnant women, either alone or augmented with low-dose ritonavir; as a result, these drugs should be avoided until more data become available, unless they are the only option available.

There are contradictory data with respect the potential adverse effects of ARVT with PIs in pregnancy, especially with regard the risk of premature childbirth^(75,124,125,126,127,128). Observational studies conducted in environments

with limited resources, such as Côte d'Ivoire and Thailand, described similar rates of premature childbirths in the women that had received ARVT and those that received MTCT prophylaxis with one or two drugs ^(129,130). Some studies suggest that the use of PIs in pregnancy could be associated with a higher risk of gestational hyperglycaemia or diabetes, although this has not been shown in more recent studies. The role of the PIs in the development of pre-eclampsia is also under debate ^(131,132). In the case of the women that require a second line therapy and get pregnant while they were receiving PIs, or they need to switch drugs during pregnancy, the benefits of treatment to mothers outweigh the theoretical risks of an adverse outcome of pregnancy, and the treatment must be started or continued, as appropriate. There are enough observations of exposure to nelfinavir and ritonavir in the first trimester to detect a two-fold increase of the risk of general congenital malformations; not having detected this increase to date ⁽⁵¹⁾. The data available about the use of other PIs in pregnancy does not permit to draw conclusions.

d) Long-term effects of the child's intrauterine exposure to ARVs

The data on the long-term effects of the child's intrauterine exposure to antiretroviral drugs reported by the industrialized countries are contradictory. Reports on a large French cohort showed evidence of clinical symptoms of mitochondrial dysfunction in 0.26% of the non infected exposed children that had received antiretrovirals during pregnancy, associated to a 0.07% mortality rate ⁽¹³³⁾. The children presented mainly neurological symptoms, sometimes associated with a significant hyperlactatemia and an impairment of the function of the mitochondrial respiratory chain enzymes. However, these findings have not been confirmed in other cohorts in Europe and the United States ^(134,135).

There are reports describing asymptomatic but persistent hematological abnormalities in the non infected children with intrauterine exposure to antiretrovirals ⁽¹³⁶⁾. There is currently a long-term follow-up study underway on the exposed non infected children that received antiretrovirals, to evaluate the child's risk as a result of that exposure.

5.2.6.2 Safety of the antiretrovirals used as prophylaxis for the prevention of HIV infection in newborns

Short-term toxicity is infrequent, as revealed by the clinical studies on PMTCT, and with the guidelines that are used for the antiretroviral prophylaxis in most settings with limited resources⁽¹³⁷⁾. Several controlled trials with a prolonged follow-up, usage of AZT for MTCTP was not associated with significant clinical or laboratory toxicity^(63,138). In the French study, the association of AZT and 3TC administered to women for MTCTP from the beginning of the second trimester of pregnancy and the newborn for six weeks was associated to higher rates of anaemia and neutropenia in the child, as compared with the children only exposed to AZT⁽¹⁰⁴⁾. In settings with limited resources, exposure to AZT and 3TC during pregnancy and in the newborn typically lasts less, and severe hematological toxicity does not occur frequently^(66,73,142,139).

NVP has been associated to minimal toxicity in the clinical trials performed to date, with more than 1,600 women and children enrolled⁽¹⁴²⁾.

Hepatotoxicity and skin rashes were not frequent in the women and their children, and in the comparative studies they were not significantly different from the branch compared (placebo, AZT alone, or AZT and 3TC)^(58,59,140). Likewise, in the most recent studies addressing the association of du-NVP and the AZT or AZT and 3TC guidelines, there is no evidence of a significant maternal or child toxicity^(73,134).

A study on the prophylaxis of children with one NVP alone or associated with AZT showed evidence of transient and mild abnormalities (first degree) in blood and in the liver enzymes at six weeks of age in the newborns that had received one dose of NVP and seven days of prophylaxis with AZT, as compared with those that only received du-NVP^(141,142).

5.2.7. Drug resistance following HIV PMTCT

Background

The guidelines that fail to achieve a complete viral suppression favor the occurrence and the increase of the resisting virus over the non mutated virus due to the selection pressure. In the context of suboptimal therapies, resistance develops more easily for NVP and 3TC, because the occurrence of one single mutation causes high grade resistance^(143,144). In the case of AZT however, several mutations are required to provide high grade resistance, so resistance

is usually evidenced after several months of suboptimal therapy and in the people with advanced disease ^(145,146,147).

NVP has a prolonged mean life, with concentrations that can be detected up to 21 days after receiving NVP⁽¹⁴⁸⁾.

NVP resistance to EFV is detected with the usual test for antiretroviral resistance in 25 to 50% of the women that receive one single dose, although this figure increases to 60-89% if the most sensitive techniques are used, such as the real time polymerase chain reaction (PCR) ^(149,150,151,152)

It is interesting to observe that the mutations found in mothers are different from those found in the children infected. In children, up to 50% of the cases that get the infection will present resistance if the mother received NVP ^(33,34,155).

With respect 3TC, the risk of resistance correlates with the duration of the exposure ⁽¹⁵⁶⁾. A French cohort study revealed an overall resistance rate of 39% six weeks after delivery. This study did not show resistance in the 12 women that received the guideline for less than one month, while it was 20% in the group that received therapy for one or two months and 50% when the duration of therapy was greater than two months⁽¹⁰⁴⁾. In Petra, the multicentric study, 12% of the women that received AZT and 3TC before childbirth, intrapartum and postpartum presented resistance; however, no resistance was observed to AZT or 3TC when this association was administered only during delivery and up to one week later⁽¹⁴⁹⁾.

In a study that included 819 pregnant women of 4 countries in the region (Argentina, Bahamas, Brazil and Mexico), there were resistance mutations in 19 of 118 women (16%) with a resistance test available. It is difficult to extrapolate these results because 78% of these patients had received ARV earlier.⁽³⁷⁾

In Brazil, a study addressed the development of NFV resistance in women exposed to this drug for the MTCTP, conducting a resistance test at baseline and at 6 months from delivery. Thirty patients that received AZT-3TC-NFV were studied. At baseline, 2/25 ARV-naïve patients presented mutations of ARVs. At 6 months, 23% (4/17) of the women exposed to NFV developed some mutation associated with drug resistance to this drug (in two cases there were major mutations and in two cases they were minor mutations) and other 3 patients developed mutations to NRTI⁽¹⁵⁸⁾.

Prevention of NVP resistance

The risk of emergence of resistance to ARV drugs is especially associated with the plasma viral load and with the mother's CD4 count at the time of exposure. Consequently, the women at a higher risk of presenting resistance to NVP after receiving one du-NVP are the only ones that present more advanced HIV disease.

The most important method for the prevention of NVP resistance is not to use this drug in monotherapy ⁽¹⁵⁹⁾. Although in studies where women receive NVP in a combined guideline the resistant viral strains are also selected, the rate is lower. In a study conducted in Ireland with triple therapy that included NVP, the resistance rate was 15%⁽¹⁶⁰⁾, a rate similar to that observed in a Latin American multi-centric study ⁽⁶²⁾. In another study, the administration of AZT+3TC during labor, together with du-NVP, followed by AZT and 3TC between four to seven days after delivery, reduces the occurrence of NVP resistance from 60% to about 10%⁽¹⁵⁹⁾. When prophylaxis is administered only to the children exposed, the frequency is even lower ^(164,162). An effective suppression of the virus before discontinuing therapy and continuation for 7 days of AZT-3TC could protect the development of NVP resistance ⁽¹⁶³⁾.

a) Resistance surveillance

The mathematical models have suggested that in the future resistance will be majorly due to transmission, and it will probably continue to be lower than 5%, which will require the systematic study of resistance in sentinel studies ⁽¹⁶⁴⁾. To survey transmission, the WHO recommends a method that uses minimal resources and indicates the time when that transmission is relevant enough to be detected, and then to consider additional prevention and evaluation measures. The results may contribute to the decision-making on the best prevention strategies and the optimum ARVT regimens, based on the use of therapies for the pre- and post-exposure prophylaxis and for the prevention of mother-to-child transmission of HIV.

In LAC there are few consistent surveillance studies on the primary resistance in treatment-naïve pregnant women. Several studies in treatment-naïve patients have shown that the prevalence of resistance in the region is maintained at a moderately low level ⁽¹⁶⁵⁾, although it could reach 6.4% ⁽¹⁶⁰⁾, while in the United States up to 10% of the pregnant women present resistance to some of the drugs typically used in PMTCT ⁽⁶⁷⁾.

b) Implications of resistance

The actual impact of the occurrence of resistance on the monitoring of the exposed mothers has not been established yet. In recent studies in Africa, the authors observed that previous exposure to a du-NVP would not reduce the efficacy of this single dose in subsequent pregnancies ^(168,169). However, the virological response to NVP therapy in the mother may be lower if she was previously exposed to a single dose of NVP ⁽¹⁷⁰⁾.

6. CHILD MONITORING

The main elements to be considered in the follow-up of the child born to a mother with HIV or syphilis are related with the early diagnosis of both infections, feeding, growth and development, and the early identification of the potential side effects of antiretrovirals, either to be used with the mother or with the child as part of the prophylaxis of HIV infection. An issue that has to be addressed is the occurrence of resistance to some drugs used in the prevention schemes, especially to Nevirapine, both in the mother and the child, if it were ultimately infected. Moreover, it is important to evaluate the status of exposure to tuberculosis and to prescribe isoniazid when appropriate.

The adequate administration of ARV medication is essential for the success of PMTCT, so special care must be taken to provide counseling and promote adherence by caregivers.

The monitoring of the HIV-exposed child will be done in the context of postnatal and common child care, including the control of the well child, the diagnosis and therapy of the common childhood infections and the systematic immunizations.

Chart 12 summarizes the package of interventions that must be included in the follow-up of the child exposed to HIV:

Chart 12.
Package of interventions that should be included in the child's follow-up.

Delivering the antiretroviral prophylaxis regimen
Nutritional counseling and support for feeding
General care and monitoring growth
Systematic immunization
Early diagnosis of the HIV infection and the HIV-related conditions
Early diagnosis of congenital syphilis
Diagnosis and therapy of the infections common in childhood.
Diagnosis and therapy of TB and other opportunistic infections and prophylaxis with isoniazid when indicated
Prophylaxis with trimethoprim-sulfamethoxazole
Indication and surveillance of ARVT for the children infected with HIV
Counseling on support to compliance by caregivers
Monitoring potential side effects of antiretrovirals

An aspect that is especially important in the follow-up is the monitoring of the potential adverse effects. The potential consequences of the in utero and postnatal exposure to ARV in the child are not well known, thus demanding close monitoring in the short, medium and long term. A matter of great concern is the possible mitochondrial toxicity in the child exposed to NRTIs. There are reports of very severe mitochondrial disease, including two infants that died of an encephalopathy, which may manifest months after delivery ⁽¹⁷¹⁾. Non infected children exposed to NRTIs may present mitochondrial damage, as evidenced by the high prevalence of asymptomatic hyperlactatemia the first 3-6 months of life ⁽¹⁷²⁾. However, the spontaneous reversion suggests that this mitochondrial damage has no symptomatic clinical expression in the vast majority of children ^(173,174). It is important to know that the risk of symptomatic mitochondrial disease is scarce, but somehow larger than that in the general population, and that a high degree of suspicion is required to diagnose it because of the lack of specificity of the clinical symptoms.

Another common occurrence in children exposed to NRTI is anaemia, particularly frequent with AZT, and which could increase with the association of 3TC. It tends to be mild and self-limited, and it usually does not require treatment. In the first months of the child's life, the controls performed for the confirmation diagnosis or exclusion of HIV infection usually include hemoglobin assays. However, they might not be necessary, due to the mild and self-limited course of the anaemia.

The child's monitoring must be conducted in the context of an integrated care to the family and newborn that contemplates the pool of interventions indicated in Chart 12. The different interventions, such as counseling, immunizations, clinical evaluations, laboratory sampling, etc., should be as concentrated as possible, both in time and site of care, optimizing the number of visits and thus improving care and reducing the losses to follow-up.

The section below shows a schedule for care. Ideally, as it has been recommended throughout this document, the syphilis and HIV serological status of the mother should be known before delivery, to enable the planning of pre and intrapartum care and counseling on the decisions that need to be taken after delivery. It is especially important to talk with the mother about the decisions concerning the feeding of the newborn in case the child is HIV positive.

6.1 Systematic immunizations of the HIV-exposed child within the first months of life

The immunogenic response to vaccines is good during the first year of life, but subsequently, and due to immuno-suppression, the response to the vaccine antigens is diminished, so it is important to start vaccination early. At present, an early ARVT can maintain the HIV child in an almost immuno-competent status, and it is possible that the vaccines administered in accordance with the usual schedule may elicit an adequate immunity after the age of one year. It is to be noted that even when the systematic immunization is safe, some vaccines, such as those containing live attenuated organisms, cannot be administered if the child is immunosuppressed.

The immunization schedule applied to the HIV exposed child in the first months of life does not differ from the schedule of the non exposed child, except for some considerations on the polio vaccination, and in a greater extent, to the application of BCG.

In theory, the attenuated polio vaccination should not be administered orally for the theoretical possibility of transmission to people infected with HIV and living in the same household, but there are many studies that have shown for years that this risk is exceptional.

6.1.2 BCG immunization ⁽¹⁸⁷⁾

Ultimately, the decision on BCG immunization at a national level is based on a number of factors determined locally:

- Prevalence of tuberculosis in the general population;
- Potential exposure to tuberculosis;
- Prevalence of HIV infection;
- Coverage and efficacy of the interventions to prevent the mother-to-child transmission of HIV;
- Exclusive and mixed maternal breastfeeding;
- Capacity to implement the monitoring of the vaccinated children;
- Capacity to conduct virological testing the first months of life.

The risk of vaccinating an HIV-infected child with the BCG is to cause a severe and potentially fatal disease, as a result of the spreading of the Calmette-Guérin bacillus infection.

Guidance to facilitate decision-making at a local and national level on the use of the BCG immunization of the children at risk of presenting HIV infection:

- a) In general, the populations with a high prevalence of HIV infection, also have the highest infection rate of tuberculosis, so that the children not infected with HIV in this population may especially benefit of the use of BCG immunization;
- b) If the local prevalence of TB is high, especially in the case of multiresistant TB, the benefits of administering BCG immunization to children born to HIV+ mothers, but whose (the child's) HIV infection status is unknown, and with no obvious signs or symptoms suggesting HIV infection, would exceed the risks;
- c) However, the risks of vaccinating with BCG the children known to be infected with HIV, with or without signs or symptoms of HIV, exceed the benefits of that immunization. **These children must not be immunized;**

- d) The risks entailed by BCG immunization are generally higher than the benefits in neonates born to HIV+ mothers and whose HIV infection status is unknown, but who have presented signs or symptoms suggestive of HIV infection. **These children must not be immunized.**

All the above has led to the following recommendations:

- a) Delay the BCG vaccination of the child born to a mother with HIV until the child's negative status can be confirmed;
- b) Delay the BCG vaccination of the child born to a mother with no HIV testing until the mother has undergone screening;
- c) Children confirmed as HIV positive must not receive BCG immunization;
- d) Children with a suspected symptomatic HIV infection (even if not confirmed) must not receive BCG immunization;
- e) In areas with a high prevalence of multiresistant tuberculosis, and when it is possible to diagnose the BCG disease in the child, and there is the capacity to treat the BCG disseminated disease, the child born to a mother with HIV must receive BCG immunization. Notwithstanding, even in this context, if the child is confirmed as HIV+, or if the child is suspected to have an HIV symptomatic infection, the child must not be immunized;
- f) Children confirmed as not infected with HIV may receive BCG immunization.

6.2 Follow-Up Schedule

a) Birth

- Clinical examination and general care of the newborn; hepatitis B immunization in accordance with national guidelines;
- Confirmation of the mother's HIV and syphilis serological status:

If the mother has an HIV(+) serology:

- o Counseling on feeding. If the AFASS conditions are met, the recommendation is to replace maternal breastfeeding for milk formula. When those conditions are not met, then exclusive maternal breastfeeding is recommended;
- o Start prophylaxis with ARV before the first 6 to 8 hours of life, as soon as the newborn can tolerate feeding and oral medication;

- o Do counseling to reinforce adherence to therapy.
- Normal clinical examination; there is no clinical evidence of infection:
 - o Postpone BCG immunization to confirm the absence of HIV in the first virological diagnosis;
 - o A complete blood count should be obtained, to determine the baseline hemoglobin level;
 - o Monitor in 7-14 days.
- Abnormalities in the clinical examination; clinical suspicion of symptomatic HIV infection (very rare, this would indicate intrauterine infection):
 - o Rule out/confirm other conditions, including performing blood count and blood chemistry as necessary;
 - o HIV diagnostic virological testing;
 - o BCG should be avoided until the HIV infection has been ruled out;
 - o If there are no associated problems requiring to start other therapies, schedule a follow-up visit in 7-14 days.
- Mother with syphilis (+) for syphilis:
 - o Follow the diagnosis and therapy algorithms described in sections 4.2 and 5.1.2;
 - o If there is no HIV (+) serology, the indications for BCG and hepatitis B immunization do not differ from the general population;
 - o In the absence of a positive HIV serology (+), breastfeeding will be recommended as the first-line choice for the child's nutrition and development;
 - o All the children born to mothers with syphilis must undergo screening tests in parallel with their mothers, using a non treponemic test for subsequent tracking.

b) 7-14 days of age

- General child care, check weight and nutritional status;
- Counseling on feeding; if the child is fed with a milk formula, ensure that the formula is appropriate with regard concentration, cleanliness and technique in the case of children born to a mother with HIV, as exclusive feeding;
- If the child is on ARV prophylaxis for PMTCT:
 - o Confirm and stress adherence to treatment;

- o Evaluate the presence of side effects, especially signs and symptoms related with anaemia and mitochondrial toxicity;
- o Adjust dosage to weight.
- If an HIV serological test was conducted at birth, report the results; if it is positive:
 - o Confirm with a second virological test;
 - o Obtain a specimen for viral load, genotyping for the study of ARV resistances (if the technique is available and in accordance with national guidelines) and CD4 count;
 - o Plan ARVT.

c) 4-6 weeks old

- General child care, check weight and nutritional status;
- Counseling on feeding; if the child is fed with a milk formula, ensure that the formula is adequate and in the case of children born to a mother with HIV, check that is the child's exclusive feeding;
- If the subject is on ARV PMTCT prophylaxis:
 - o Check the absence of side effects, especially the signs and symptoms related with anaemia and mitochondrial toxicity;
 - o Terminate prophylaxis.
- Start prophylaxis of pneumonia by *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole;
- Immunize against hepatitis B following the national guidelines;
- If no virological testing has been conducted for HIV, conduct the test;
- If an HIV serological test was conducted at birth, report the results; if it is positive:
 - o Conduct a second serological virological test for confirmation;
 - o Obtain a specimen for viral load, genotyping for the study of ARV resistances (if the technique is available and in accordance with national guidelines) and CD4 count;
 - o Plan ARVT.
- If there is a second positive virological test for HIV:
 - o Counseling to report the results with a multidisciplinary approach; weigh the need to assess the psychological support;

- o Counseling on the start of ARVT. Special emphasis on compliance to therapy;
- o Start ARVT.

d) 2 months of age

- General child care, check weight and nutritional status;
- General immunization schedule following the national standards;
- Counseling on feeding; if the child is fed with a milk formula, ensure that the formula is adequate and in the case of children born to a mother with HIV, it should be exclusive feeding;
- If the subject is + or has taken ARV, check for the absence of side effects, especially signs and symptoms related with anemia and mitochondrial toxicity;
- If an HIV serological test was conducted, report the results if available; if it is positive:
 - o Conduct one second virological test for confirmation;
 - o Obtain a specimen for viral load, genotyping for the study of ARV resistances (if the technique is available) and CD4 count;
 - o Plan ARVT.
- If a positive virological test confirms diagnosis:
 - o Counseling to report the results with a multidisciplinary approach; weigh the need for psychological support;
 - o Counseling to start ARVT. Special emphasis on adherence to therapy;
 - o Start ARVT.
- If the mother's syphilis serology was positive and the non treponemic test was done to the mother at the time of birth, the same test can be done to the child now to assess the course of titers.

e) 3 months of age and older

During the first year, the recommendation is a monthly follow-up, checking the child's general care, weight gain, growth and nutritional status. Counseling on feeding must be provided; if the child is fed with a milk formula, ensure that the formula is adequate and in the case of children born to mothers with HIV, make sure it is being used as exclusive feeding, with no breastfeeding ("mixed" feeding).

If the subject is on ARVT, make sure the following are checked in every visit:

- o Absence of side effects, with special care to signs and symptoms related to mitochondrial toxicity;
- o Check that the medication is being taken adequately;
- o Adjust the dose to the child's changing weight;
- o Stress the adherence to therapy;

For the aspects specifically related with ARVT for children, see the 2008 PAHO Guidelines *Antiretroviral Therapy of HIV Infection in Children in Latin America and the Caribbean: Toward universal access*.

All children with positive serology for syphilis at birth (or the children whose mothers were seroreactive) must receive postnatal monitoring with clinical examinations and non treponemic serological tests every 2-3 months until the test becomes negative or until the titer has been reduced in four dilutions. The antibody titers should decrease at 3 months and they should turn negative at the age of 6 months if the child was not infected (that is, if the positive result of the test was caused by the passive transfer of maternal IgG antibodies) or was infected, but was treated adequately. The serological response may be slower in the children treated after the neonatal period. If these titers remain stable or if they increase after the 6-12 months, the child should be re-evaluated.

7. SPECIAL CONSIDERATIONS

7.1. Pregnant women with HIV and active tuberculosis

All women presenting with an episode of cough lasting 2 to 3 weeks must undergo screening tests to detect active tuberculosis. In pregnant women with active tuberculosis treating the tuberculosis is a priority, even when with an adequate follow up, the treatment of the HIV infection may also be conducted at the same time. The best time to start ARVT depends on the CD4 count, tolerance to the TB therapy and other clinical factors, but it has been recommended from 2-8 weeks after the start of the TB therapy. Drug interactions between some antiretrovirals and rifampin make the choice of ARVT more complex in active tuberculosis.

The first-line therapy recommended for women with tuberculosis and HIV is based on EFV, but this therapy can only be considered in the pregnant women that are already in their second or third trimester of pregnancy, and who can assure they will follow an effective contraceptive method after delivery. There is no experience to recommend the simultaneous use of Nevirapine and rifampin in pregnant women. Other choices include the three NRTI regimen, such as combining AZT + 3TC + ABC.

The use of protease inhibitors while on that therapy should be avoided ⁽¹⁷⁶⁾. Its use with SQV/r (1000 mg/100 mg twice a day) has been associated with a severe hepatotoxicity ⁽¹⁷⁶⁾, although under certain circumstances (presence of a resistant virus, failure of first-line therapy, etc.) this scheme may be required. When applied, it should be done under close monitoring. Other options include using LPV with high doses of ritonavir (400mg/400 mg twice a day) or SQV/r (400 mg/400 mg twice a day), only if a possible to keep a close clinical and laboratory monitoring.

7.2. Pregnant women with HIV and hepatitis

Coinfection with HCV

The co-existence of HIV and HCV in a pregnant woman further complicates the management of therapy. Studies on the effect of HCV on the clinical progression of HIV have yielded controversial results, but some research suggests that people with HIV-HCV co-infection experience a slower immune recovery with ARVT (recovery of the CD4 lymphocytes)⁽¹⁷⁷⁾. HCV co-infection is associated with a greater risk of ARVT-induced hepatotoxicity.

Likewise, patients with that co-infection have a higher HCV viral load and experience a faster progression to liver fibrosis than those patients on HCV monoinfection⁽¹⁷⁸⁾.

Mother-to-child transmission of HCV is high in pregnant women with HIV (from 5% to 20%). At present there are no interventions available to prevent mother-to-child transmission of HCV. The use of ribavirin and pegylated interferon is contraindicated in pregnancy. In planned pregnancies, the treatment of hepatitis C should be completed before planning conception⁽¹⁷⁹⁾.

Due to the high risk of HCV infection in newborns of mothers with HIV-HCV co-infection, the newborn should be monitored, keeping track of both infections⁽¹⁸⁰⁾.

HBV Co-infection

There is no evidence suggesting that HBV may have a negative impact on the course of HIV infection; however, the liver damage caused by HVB may enhance the toxicity of the ARVs.

Any woman with HIV should undergo routine screening for the HVB surface antigen (HBsAg). Pregnant women with HIV-HVB co-infection should be started on an ARVT combination that includes 3TC, which is effective against both viruses. The mother-to-child transmission rate of HVB may be reduced through the suppression of the viral replication.

When the mother is HBsAg-positive, the newborn should receive a dose of the vaccine against HVB and 0.5 ml IgHB within the first 12 hours of birth. These children may then receive the regular immunization plan against HVB (0, 1 and 6 months). Newborns weighing less than 2000 gr should receive four doses of the HVB vaccine (at birth, 1,2-3 and 6-7 months). HBsAg testing should be done at 9 and 18 months of age to all children born to HBsAg positive mothers.

7.3. Pregnant women with HIV and anaemia

Anaemia is more frequent in pregnancy, and it may be also increased in settings with limited resources. HIV infection, malnutrition, malaria in certain areas, or parasitic diseases can interact and further exacerbate the effects of each separate disease. Prevention, diagnosis and therapy of anaemia are key components of the usual prenatal care in settings with limited resources. As part of a strategy to prevent anaemia and its adverse effects, the WHO recommends the usual consumption of iron and the administration of folate supplements to all the pregnant women living in areas with a high prevalence of iron deficiency. The administration of iron supplements is also recommended during postpartum. Moreover, prevention and treatment are important in cases of malaria, to reduce the anaemia of the pregnant women living in regions where malaria is endemic.

Women with an indication of a rapid start of ARVT and a severe anaemia (Hb < 7 g/dl) should be started on an AZT-free regimen and treatment of their anaemia. The treatments of choice are d4T and ABC.

In the case of women with HIV infection but with no indications to receive antiretrovirals, the priority is to treat the severe anaemia. The AZT-containing prophylactic regimens should only be started after the severe anaemia has been corrected (Hb > 7 g/dl).

7.4. Intravenous Drug Use in pregnant women

Intravenous drug consumption is an important means of HIV transmission in many countries in Europe, Asia and Latin America. Although intravenous drug use is considerably lower in Latin America, and almost negligible in the Caribbean other routes are used to some extent to consume cocaine and crack. Those situations require a special care, to meet the needs of the HIV-infected drug users, especially during pregnancy.

The pregnant women that use drugs are at a higher risk of medical complications. For therapy to be effective, these people need to be persuaded to seek care at the health services at an early stage of pregnancy. The care should be provided by a multidisciplinary team: antenatal care, care of HIV, management of drug dependence and psychosocial support.

These women's access to health care is usually hindered by various issues. The stigmatizing attitude of health care professionals and the lack of coordination

between obstetricians and experts in drug dependencies and the damage reduction programs are some of the factors involved.

The national programs should aim at ensuring an environment that may be friendly to female HIV+ intravenous drug users at the centers that provide antenatal, labor and postpartum care.

These women require counseling on the effects of alcohol and the other drugs in the fetal growth and development and on the benefits of the damage reduction services. An ongoing integrated care is required throughout pregnancy and in the postpartum period, to address the issues posed by the treatment of the HIV infection, the gynaecological and obstetric needs and those deriving from the use of IV drugs, to include specific medication, improvement of medication and referral mechanisms.

Counseling is a key component in the management of HIV+ pregnant drug users, stressing the aspects below:

- The risk of the impact of drugs on the fetus and neonate;
- Interaction between illicit or social drugs and ARV;
- The importance of ARV adherence and clinical monitoring.

The neonatal withdrawal syndrome consists of the signs and symptoms presented by newborns abruptly separated from their mothers after a prolonged exposure to drugs during pregnancy. Initially, this term was used to describe the opiate withdrawal, but at present the definition consists of manifestations of withdrawal of cocaine, amphetamines and alcohol. The neonatal withdrawal syndrome occurs in close to 60% of all the fetuses exposed to these drugs, usually within the first 72 hours of life. The clinical manifestations of neonatal withdrawal vary depending on the substance implied, the metabolism and excretion of the drug and its metabolites. Symptoms include gastrointestinal disorders such as increased or ineffective suckling, vomits, excessive regurgitation and diarrhea; cardiorespiratory syndromes like tachycardia, tachypnea, cyanosis; neurological like shaking, hypotonia, hypertonia, hyperreflexia, irritability, agitation or seizures, and general symptoms like fever, diaphoresis, high-pitched crying, sleep disturbances and failure to thrive. The diagnosis requires a high degree of suspicion and the management usually includes fluid and electrolyte balance and nutritional support⁽¹⁸¹⁾

In general, the same principles for the clinical and immunological evaluation of the HIV positive pregnant women apply for pregnant IDUs. Drug interactions may be an issue in the case of pregnant women that were already receiving ARVT.

For pregnant IDUs with HIV not eligible for ARVT, the regimen of choice is the same as the prophylaxis therapy used for MTCTP in non IDU women ⁽¹⁸²⁾. The use of drugs is one of the main factors that hinder ARVT, so drug users require psychosocial support and close monitoring of their compliance.

Most drug users fail to seek antenatal care, and they only go to the health services for labor. In these cases the health staff must be ready to evaluate the use of drugs, offer counseling and HIV testing, to provide therapy in case of withdrawal, and counseling on the effect of the drugs on the newborn.

7.5. Women with primary HIV-infection during pregnancy

Many women may present a negative serology test the first trimester, but they may continue to be at risk of acquiring the infection, either because their usual partner has HIV or because she is experiencing an acute infection. During the acute infection, the transmission rates are higher than during the established infection because of the higher concentrations of the virus that circulate at this stage. This also applies in the setting of MTCT.

In New York, 1.4% of the pregnant women with detected HIV infection had a negative test at the early stages of pregnancy ⁽¹⁸³⁾. This highlights the critical importance of counseling and providing HIV testing to the male partners, to reduce the risk of new infections and to detect serological discordant sexual partners. In addition, repeating the HIV test towards the end of pregnancy (around 32 weeks) to the women that had a negative test in the first trimester allows identification of the women with a recent HIV infection and permits their access to PMTCT interventions and to health care.

This strategy has been used in pregnant women in areas of high prevalence and in pregnant women in place with a low prevalence but with a higher risk of HIV exposure (e.g., personal history of sexually transmitted infection, sexual workers and intravenous drug users and pregnant women with an HIV positive sexual partner)

8. ANNEXES

ANNEX 1. ALGORITHMS TO BE APPLIED IN THE VARIOUS SETTINGS

ANNEX 2. MEDICATION DOSAGES

ANNEX 3. DRUG INTERACTIONS

ANNEX 4. VERTICAL MOTHER-TO-CHILD TRANSMISSION OF INFECTIONS SCREENING AND SYSTEMATIC INTERVENTIONS

ANNEX 5. GLOBAL MEASURES TO PREVENT INFECTIONS DURING PREGNANCY

Annex 1. ALGORITHMS FOR THE DIFFERENT SCENARIOS

Annex 1.1

Options for the antiretroviral therapy of pregnant women with a CD4 count over 250 cells/mm³ and ARVT prescription

Option	Advantages	Disadvantages
Use a PI-based guideline (1);	• Lower risk of hepatotoxicity;	• Limits the choices of second line therapy;
Start an NVP-based therapy under close surveillance the first 12 weeks (2);	• Keeps PIs for the second line guideline; • Compatible with the current recommendations	• Potential risk of serious hepatotoxicity;
Start a guideline with 3 NRTIs;	• The PI is kept for the second line guideline; • Lower risk of hepatotoxicity	• Less powerful than guidelines with NNRTI or PI; • The use of TDF is not recommended because of potential toxicity still undefined

Annex 1.2

Guidelines for the prophylaxis of ARVT-naïve women with HIV with no indication for ARVT, and seeking care at early stages of pregnancy

Recommendation level	Pregnancy	Labor	Postpartum	Advantages	Disadvantages
Recommended A-I	AZT -3TC- NVP after week 14;	AZT-EV	- Mother: Discontinue NVP and continue 7-10 days AZT-3TC* - Child: AZT 4-6 weeks;	Very effective guideline;	- Risk of toxicity in women with CD4 counts 250 cell/mm3;
Recommended A-I	AZT-3CT-PI (LPV-r/SQV-r/) after week 14;	AZT-EV	- Mother: Discontinue* - Child: AZT 4-6 weeks;	Very effective guideline;	- Higher cost. The use of PI may jeopardize its future use as 2nd line therapy
Optional C-III	AZT-3TC-ABC after week 14	AZT- EV	- Mother: Discontinue* - Child: AZT 4-6 weeks;	Easy dosaging in combination with a fixed dose	- Lower virological efficacy; - Risk of NRTI resistance; - Risk of ABC hypersensitivity
#. Discontinue if the mother does not have an indication for starting ARVT.					

Annex 1.3

Guidelines for the prophylaxis of therapy-naïve women with HIV that seek care at labor

Recommendation level	Labor	Postpartum	Advantages	Disadvantages
Recommended B-II	du-NVP+AZT i.v up to childbirth;	- Mother: AZT/3TC × 7-10 days; - Child: AZT 4-6 weeks + NVP (1 or 2 doses; see text). Assess triple therapy depending on risk factors (see text);	Permits to reduce the MTCT rates closer to combined therapy; Easily implemented;	- AZT/3TC must be administered to prevent the occurrence of NNRTI resistance ;
Recommended A-I	AZT-EV	-Mother: Discontinue* -Child: AZT 4-6 weeks;	Very effective guideline;	-Higher cost. The use of a PI may hinder its future use as second line therapy;
Note: see dosages in Annex 2 # There are limited data available on the efficacy of a 4-week AZT for the child.				

Annex 1.4

Guidelines for antiretroviral prophylaxis of children born to mothers with HIV that received no prophylaxis

	Postpartum	Advantages	Disadvantages
Recommended B-II	Child: triple therapy AZT-3TC-NVP for 4 weeks;	Greater theoretical efficacy;	There are no studies supporting this evidence; Virological testing should be conducted before starting therapy;
Option B-II	Child: NVP (2 dose, The first immediately after childbirth) + AZT × 6 weeks	NVP + AZT is more effective than du-NVP alone or AZT alone.	Toxicity risk; Risk of NVP resistance if the child was infected during delivery
Note: see dosages in Annex 2			

Annex 2. MEDICATION DOSAGES

Annex 2.1 Medication for mothers

Medication	Dosage	Strengths
Zidovudine	300mg/12 hours	Tablet x 300mg Tablet x 100mg
Lamivudine	150mg/12 hours	Tablet x 300mg
Zidovudine/Lamivudine	300mg/150mg/12 hours	Tablet x 300mg AZT/150mg 3TC
Nevirapine	200/mg/12 hours	Tablet x 200mg
Lopinavir/Ritonavir	400mg/100mg/12 hours	Tablet x 133.3mg/33.3mg
Stavudine	30-40 mg/12 hours	Tablet 30mg
Benzathine Penicillin	2.400.000 IU	Ampoule 2.400.000 UI

Annex 2.2 Medication for children

Medication	Dosage	Strengths
Zidovudine	2mg/Kg/cada 6 hours	Bottle 50mg/5ml x 240ml
Lamivudine	2mg/Kg/12 hours	Bottle 50mg/5ml x 240ml
Nevirapine	2mg/Kg/day	Bottle 50mg/5ml x 240ml
Benzathine penicillin	50.000 UI/Kg.	Ampoule 2.400.000 IU
Procaine penicillin	50.000 UI/Kg/day (IM)	Ampoule
Aqueous crystalline penicillin G	100.000 – 150.000 IU/kg/8-12 hours (i.v)	Ampoule
Trimetoprim/sulfamethoxazole	2.5 ml/day	Bottle 40mg/200mg/5ml

Annex 3. DRUG INTERACTIONS

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) or Nucleoside Analogs (NA)

	Contraindications	Potential interaction	No relevant interactions	Comments
FTC	3TC	Cidofovir: ↓ 3TC and FTC clearance	TDF, AZT, ABC, ddl, d4T, IP: all, Maraviroc, NVP, EFV, Raltegravir, Elvitegravir, Enfuvirtide, Etravirine (TMC-125), Famcyclovir	
3TC	<u>Trimetoprim-sulfamethoxazol</u> : a dosis elevadas aumenta el riesgo de ototoxicidad Foscarnet FTC Ganciclovir	Cidofovir: ↓ 3TC and FTC clearance	AZT, d4T, ddl, IP: all, Maraviroc, NVP, EFV, Enfuvirtide, Etravirine, Ranitidin	
AZT	d4T	<u>Ganciclovir</u> : hematological toxicity. Caution with others hematotoxic drugs, such as TMP-SMX, dapsone, Pirimetamin, ribavirin or amphotericin. <u>Interferon</u> : may ↑ AZT levels <u>TPV</u> : might ↓ levels AZT <u>Valproate</u> : ↑ 79% AZT <u>Fluconazole</u> : ↑ 74% AZT <u>Probenecide</u> : ↑ 80% AZT Cidofovir: recommend ↓ AZT by half	3TC, ABC, Acyclovir, Atovaquone, Azithromycin, ddl, EFV, Elvitegravir, Enfuvirtide, Etravirine, Foscarnet, FTC IP: all Maraviroc, Megestrol, NVP, Paracetamol, Ranitidine, Rifampin, Rifabutin	
Ddl	Allopurinol: doubles ddl Ribavirin ² TDF ³ levels	ATV ↓ 87% levels of ddl if buffered tablets (not with enteric capsules). Separate 1-2 hours (and with IDV and TPC) Avoid drugs that induce neuropathy: dapsone, isoniazid, etc.	3TC, Dapsone, EFV, Elvitegravir, Enfuvirtide, Etravirine, Foscarnet, FTC, Isoniazid, Loperamide, Maraviroc, Metoclopramide, NVP, Raltegravir, Ranitidin, Rifabutin, AZT	Potential interaction with all the IPs D4T ⁴
TDF	ATV not enhanced ddl ³	Potential nephrotoxicity associated to cyclosporine or tacrolimus or aminoglycosides, cidofovir, foscarnet, amphotericin b deoxicolate	AZT, 3TC, FTC, ABC, D4T, EFV, NVP, ATV/r IP: all ⁵ Maraviroc, Raltegravir, Elvitegravir, Enfuvirtide, Etravirine, Famcyclovir, Ribavirin, Rifampin	Non recommended starting therapy: TDF/3TC/ABC/TDF/3TC/ddl Potential interaction with LPV, ATV
D4T	ddl ³ AZT	Ribavirin ³ Avoid drugs that induce neuropathy: <u>dapsone</u> , <u>isoniazid</u> , etc.	3TC, FTC, TDF, EFV, NVP, Enfuvirtide, Etravirine IP: all Maraviroc, Raltegravir, Elvitegravir, Foscarnet, Ganciclovir, Clarithromycin	
ABC		Avoid <u>TPV/r</u> could ↓ 44% ABC levels	NVP, EFV PIs: all ⁶ Maraviroc, Elvitegravir, Enfuvirtide, Etravirine	<u>Avoid combining with:</u> TDF/3TC TDF/FTC <u>Caution</u> When starting NRTIs NNRTI because the hypersensitivity allergic reaction can be confused

- Monitor cyclosporin levels with EFV and NVP
- They increase the toxicity of cocaine.
- NVP increases the level of ethinyl estradiol and EFV reduces them.

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

	Contraindications	Potential interaction	No relevant interactions	Comments
EFV	Amodiaquine Oral contraceptives Astemizole Bepridil Bupropion Cisapride Ergotamine derivatives. Etravirine Fluvastatin Midazolam Pimozide SQV7 Terfenadine Triazolam Voriconazole	<u>Rifampicin and rifabutin may lower levels</u> <u>Clarithromycin. this antibiotic concentration may be ↓ by 40%</u> <u>↓ Carbamazepine 47% of both.</u> <u>↓ levels of lipid-lowering</u> <u>Possible ↓ tacrolimus and cyclosporine.</u> <u>↓ 30% AUC of IDV.</u> <u>↓ 35% AUC of APV / FPV (Use FPV / r).</u> <u>↓ 20-50% levels of LPV.</u> <u>↓ levels of ATV. Use ATV / r.</u> <u>Not recommended SQV + APV</u> <u>Do not combine with NVP</u> <u>Monitor concentration of oral anticoagulants.</u> <u>Monitor toxicity and efficacy of antiarrhythmics.</u> <u>Erectile dysfunction drugs should be used with caution or at low doses</u>	Acetylsalicylic acid Amitriptyline, Amphotericin B Antacids Antivirals: Most Atovaquone Azithromycin B-blockers: Most Cetirizine, ciprofloxacin Clindamycin, chloroquine Chlorpromazine, Dapsone, Domperidone, Doxorubicin, Enfuvirtide, Erythromycin, Fluconazole, Flucytosine, Ethambutol Fluoxetine Gabapentin Ibuprofen, Haloperidol Isoniazid, Lamotrigine Lansoprazole, Lorazepam, Mefloquine Morphine, Metronidazole, NA Omeprazole Ondansetron, Oxazepam Acetaminophen, Paroxetine Pentamidine, Pyrazinamide Pyrimethamine, Piroxicam, Proguanil, Ranitidine, Streptomycin Sumatriptan sulfadoxine Theophylline Terbinafine, Tetracyclines TMP-SMX Rosuvastatin Valproate, Vigabatri	Clinical monitoring of CNS symptoms when combining with interferon <u>Caution when starting with ABC.</u> Severe ABC related hypersensitivity could be confused with EFV related rash Other accepted: Clofibrate. Gemfibrozil Budesonide Fluticasone Megestrol
NVP	Oral contraceptives Carbamazepine. Etravirine Phenytoin Phenobarbital Ketoconazole Rifampicin SQV8 Voriconazole	Clarithromycin. this antibiotic concentration may be ↓ by 35% Rifampicin could ↓ concentration. Improved lipid lowering concentration: pravastatin, rosuvastatin Possible ↓ Cyclosporine, tacrolimus, sirolimus and prednisone. Fluconazole may ↑ ↑ concentration and hepatotoxicity ↓ 30% AUC IDV. ↓ AUC of APV. 20-25% ↓ LPV levels ↓ concentration of ATV; use ATV / r. Do not combine with EFV Monitor toxicity and efficacy of antiarrhythmics. ↓ concentration of erectile dysfunction drugs (individualize) Monitor concentration of oral anticoagulants.	Similar to EFV with the following differences: <u>Possible interactions:</u> Erythromycin <u>No interaction:</u> Cimetidine DRV FPV Loratadine NFV RTV Pravastatin Rifabutin	<u>Not expected important interaction:</u> TPV. Sulfonamides. <u>Caution when starting with ABC.</u> Severe ABC related hypersensitivity could be confused with NVP related rash

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Fusion Inhibitors

Enfuvirtide (T20)	No clinically significant interactions
-------------------	--

Protease Inhibitors (PI)

Common interactions with IPs			
Contraindications	Potential interaction	No relevant interactions	Remarks
Contraindicated drugs Astemizole Cisapride Ergotamine derivatives Halofantrine Lumefantrine Midazolam Pimocide Terfenadine Triazolam	May ↑ levels of Cyclosporine and other IS: monitor Monitor levels with steroids There is a potential interaction with drugs metabolized through the CYP3A4 pathway (see footnote) and other P450 enzymes. Consider the interactions of RTV in the IP combinations Monitor anticoagulants Usually antiarrhythmics: monitor	Best lipid reducing agent: pravastatin Caution with antiepileptics: they could ↓ IP levels. Most adequate: gabapentin and vigabatrin Safe drugs to all PIs: 33TC, AAS ABC (possible with LPV and TPV) Adefovir (possible with TPV) Amphotericin B Antivirals: majority (possible adefovir with SQV) Azithromycin (possible with DRV, NFV and RTV) Cefidizine, Ciprofloxacin Clindamycin (possible with RTV) Clotifibrate Chloroquine (possible with RTV) d4T, Domperidone Doxorubicin Enfuvirtide (possible with TPV) Streptomycin Etambutol, Flucitosis FTC Fluconazole (possible with TPV) Fluvastatin, Gabapentin Gemfibrozil, Hydroxyurea	Some IPs might produce a disulpham effect when combined with certain drugs (containing alcohol) Ibuprofen (possible with RTV) Interferon, Interleukin 2 Isoniazid Lorazepam, Megestrol Metoclopramide (no data with SQV), Ofloxacin Ondansetron (possible with TPV) Oxazepam, Paracetamol Pentamidine (possible with RTV) Pyrimethamine (possible with RTV) Proguanil (possible with RTV) Raltegravir (possible with TPV) Risperidone (possible with RTV and DRV) Sulfadoxine (possible with RTV and TPV) Terbinafine Tetracycline Thioridazine (possible with DRV and RTV) TMP-SMX (possible with TPV) Vigabatrin

APV			
Contraindications	Potential interaction	No relevant interactions	Remarks
Amiodarone Oral contraceptives Bepridil Cisapride Flecainide Propafenone Quinidine Rifampin Terfenadine	Simvastatin Vitamin E Astemizole Diazepam Flurazepam Midazolam Pimocide Triazolam Ergotaminic derivatives	Antacids: 1 hour apart Phenitoin, carbamazepine and phenobarbital may ↓ APV Monitor IS Sildenafil ⁸ TPV ¹⁰ Not recommended: Lovastatin, Simvastatin, vitamin E, SQV + EFV	Atovaquone B blockers: atenolol, bisoprolol, propranolol Elvitegravir IDV, Lamotrigine Loperamide, NFV Pravastatin Rosuvastatin Theophylline Valproate

IDV			
Contraindications	Potential interaction	No relevant interactions	Remarks
Alprazolam Astemizole Cisapride Carbamazepine Ergotamine derivatives Midazolam Pimocide Amiodarone ATV ¹¹ Carbamazepine Clozapine Etravirine Flecainide Rifampin Rifapentin Simvastatin Terfenadine Trazodone ¹²	Leave at least 1 hour between the doses of dd ¹³ , omeprazole and antacids Phenitoin, carbamazepine and phenobarbital They may reduce ↓ IDV Anticoagulants ¹⁴ Sildenafil ⁸ SQV: in vitro antagonism and complicated dosaging. Possible ↑ Cyclosporin, prednisone, tacrolimus and sirolimus EFV and NVP: better IDV/r Broad variability with LPV/r Antiarrhythmics: monitor Avoid ↑ dose atorvastatin Dexamethasone: ↑ IDV	Oral contraceptives APV (scarce studies) Atovaquone B blockers: atenolol, bisoprolol, metoprolol, propranolol Cimetidine Caspofungine Dapsone Eritromycin NRTI (see dd) Lansoprazole Loperamide Metronidazole Paroxetin: antidepressant of choice Pravastatin Ranitidin Rosuvastatin Theophylline Valproate	No data are available with TPV Avoid grapefruit juice Not recommended: Lovastatin, simvastatin.

Soft gel SQV – hard gel SQV					
Contraindications		Potential interaction	No relevant interactions	Remarks	
Amiodarone Bepridil Carbamazepine		Monitor IS Sildenafil ⁹	Antacids ATV: synergistic effect Atovaquone	NRTI Itraconazole Famotidine	Take with fatty meals
DRV Dexamethasone EFV ¹⁵ Phenitoin Phenobarbital Flecainide NVP ¹⁵ Propafenone		IDV: <i>in vitro</i> antagonism and complicated dosing.	B blockers: atenolol, bisoprolol, propranolol, metoprolol	Ketoconazole Lamotrigine Lansoprazole LPV/r: synergistic effect Metronidazole	No data available with oral contraceptives or voriconazol
Rifabutin ¹⁶ Rifampin	Quinidine Terfenadine	Grapefruit juiceo: ↑ levels of SQV	Caspofungin Clarithromycin Erythromycin FPV/r: better with 200 mg of RTV	NFV Ranitidin Rosuvastatin Teophyllin Valproate	IDV: not enough data available
Astemizole Cisapride Pimocide					Not recommended: Lovastatin, simvastatin

LPV/r			
Contraindications	Interacción potencial	No interacciones de interés	Remarks
Amiodarone Oral contraceptives Astemizole Bupropion DRV Encainide Flecainide FPV17 Quinidine Propafenone Rifampicin Terfenadine Voriconazole Ergotaminic derivatives Midazolam Pimocide Triazolam TPV	Phenytoin could ↓ LPV and viceversa. <u>Phenobarbital</u> : could ↓ LPV Monitor IS, especially Cyclosporine and tacrolimus ↑ digoxin AUC Caution with verapamil and doxorubicin. <u>Sildenafil</u> ⁹ EFV and NVP: ↓ LPV 25% TPV10: could ↓ levels of LPV <u>Avoid</u> combination with oral solution of metronidazole Monitor efficacy of atovaquone IDV	ATV Antacids Cimetidine Dapsone Etravirine Famotidine Fluvastatin NRTI Lansoprazole Omeprazole Paroxetine: best antidepressant Pravastatin Ranitidin SQV/r: synergic effect; favorable combination	Take with food (with the new formulation it is indifferent) No data with voriconazole Few studies with IDV and ↑ variability of levels Not recommended: Lovastatin, simvastatin

FPV			
Contraindications	Potential interaction	No relevant interactions	Remarks
Oral contraceptives Atorvastatin Clozapine LPV ¹⁷ Loratadin ¹⁸ Rifampin Rifapentin Terfenadine	TPV ¹⁰ Voriconazole Cisapride Pimocide Midazolam Triazolam Propafenone Flecainamide Phenytoin, carbamazepine and phenobarbital pueden ↓ FPV Monitor IS, Sildenafil ⁹ ↑ paroxetin levels EFV: ↓ FPV 36%; always use FPV/r (the same with NVP) Monitor toxicity of antiarhythmics and anticoagulants. Corticosteroids may ↓ APV	Azythromycin as an alternative to clarythromycin and erythromycin Alternative Antiepileptics: gabapentin, lamotrigine, valproate Cetrizine Fluconazole: best antifungal NRTI NVP Omeprazole Ranitidin	Administer 1h. before proton pump inhibitors There are no data IDV/r or with NFV,

NFV					
Contraindications		Potential interaction	No relevant interactions		Remarks
Amiodarone	Lumefantrine	Some cases of toxicity for <u>carbamazepin</u>	Atovaquone	NRTI	Take with fatty meal
Oral contraceptives	Midazolam	Monitor IS	APV	Itraconazole	There are no data with <u>voriconazole</u> or FPV.
Astemizole	Omeprazole	<u>Sildenafil</u> ⁹	Amitriptyline	Ketoconazole	
Bupropion	Pimocide	EFV: may ↓ levels NFV	β blockers: atenolol, bisoprolol, propranolol, metoprolol	Lamotrigine	
Cisapride	Quinidine	Phenobarbital: may ↓ levels NFV	Caspofungin	Lansoprazole	
Ergotamine derivatives	Rifampin	Atorvastatin: use at lower dose possible	Metronidazole	Loperamide	
Halofantrine	Simvastatin	Not recommended: lovastin, simvastatin	Cimetidine	Metronidazole	
Lansoprazole	Terfenadine		Dapsone	NVP	
Lovastatin	Triazolam		Erithromycin	Nortriptyline	
	TPV ¹⁰		Famotidine	Omeprazole	
			Ranitidine	Paroxetine	
			Fluoxetine	Ranitidin	
				SQV	
				Theophylline	

RTV				
Contraindications		Interacción potencial	No relevant interactions	Remarks
Alprazolam	Flecainide	<u>Rifampin</u> : ↓ 35% RTV. Monitor liver toxicity.	Antacids	Pravastatin: More hypolipidemic
Astemizole	Flurazepam	<u>Rifabutin</u> : ↑ 450%	Cimetidine	
Amiodarone	Fluvastatin	<u>Clarithromycin</u> : ↓ dose if there is renal or liver failure	Dapsone	
Oral contraceptives	Ketoconazole	RTV may ↓ levels of <u>phenytoin, lamotrigine and valproate</u> .	Escitalopram: best antidepressant	Normally used at reduced doses as an enhancer of other IPs (see dosaging).
Atorvastatin	Loratadine	Several cases of toxicity with <u>carbamazepine</u> .	Famotidine	
Bepidil	Meperidine	Anticoagulant ⁵	NRTI	
Bupropion	Midazolam	↑ Levels of <u>Cyclosporine and tacrolimus</u> and maybe sirolimus.	NVP	
Cisapride	Piroxicam	Monitor IS.	Omeprazole	Increases levels of albendazole (monitor toxicity)
Clorazepate	Propafenone	There are cases reported of adrenal suppression with inhaled <u>fluticasone</u> .	Pravastatin	
Clozapine	Quinidine	<u>Sildenafil</u> ⁹	Ranitidin	
Diazepam	Terfenadine	Space ddl 2 hours ¹³	Anticonvulsant alternative: gabapentin, lamotrigine, valproate	
Encainide	Voriconazole	Possibly ↑ <u>clindamycin</u>		
Estazolam	Zolpidem	Avoid lovastatin, simvastatin, metronidazole. With acyclovir: increased risk of crystaluria. Monitor efficacy of atovaquone.		
Etravirine ¹⁹	Ergot derivatives			
Phenobarbital				

ATV				
Contraindications		Potential interaction	No relevant interactions	Remarks
Astemizole	Omeprazole	<u>Omeprazole</u> ²⁰	Dapsone	With meals
Oral anticonceptives	Propafenone	Monitor IS.	DRV	No data with <u>voriconazole</u> .
Bepidil	Pimocide	Use ATV/r with TDF	Erithromycin	NVP: no data.
Cisapride	Quinidine	<u>Sildenafil</u> ⁹	FPV/r	Consider as with EFV.
Flecainide	Rifampicin	Administer 12 hours apart with anti H2 and 1-2 h with <u>antacids</u> .	NRTI (possible interaction with TDF and ddl)	Synergic effects with <u>SQV/r</u> .
FVP	SQV	With NVP and EFV: ↓ 74% levels of ATV/administer always with RTV	LPV/r Pravastatin	If it is administered with ddl, separate the dose.
IDV ¹¹	Terfenadine	↑ 94% levels of <u>clarithromycin</u> : avoid.	SQV/r	
Lansoprazole	TPV ¹⁰	Avoid carbamazepine, phenytoin, phenobarbital: ↓ ATV.		
Midazolam	Triazolam	Not recommended: IDV, lovastatin, simvastatin		
NVF	Ergot derivatives	↑ levels of <u>oral anticonceptives</u>		

Darunavir			
Contraindications	Interacción potencial	No interacciones de interés	Remarks
Amiodarone Bepiridil Carbamazepin Phentoin Phenobarbital Flecainide Lidocaine LPV Propafenone Quinidine Rifampin SQV Terfenadine	Adjust doses of: Atorvastatin Pravastatin Rifabutin Erectile dysfunction drugs	Antacids ATV Cimetidine Elvitegravir Etravirin Famotidine Lansoprazole	No data available for: Antiarrhythmics Anticoagulants Anticonvulsants Calcium antagonists

TPV			
Contraindications	Potential interaction	No relevant interactions	Remarks
Alprazolam Amiodarone Oral contraceptives ABC ²¹ Bepiridil Bupropion Clozapine Encainide Etravirine Phenobarbital Flecainide	Loratadine LPV Propafenone Quinidine Rifampin SQV Terfenadine AZT TPV/r ↓ ↓ levels of <u>atorvastatin</u> . Separate 1-2 hours from <u>antacids</u> . TPV could ↓ levels of <u>LPV, ATV, SQV and FPV</u> ¹² ABC: Avoid TPV/r could ↓ 44% ABC levels ddl, Administer 2 hours apart. IP: avoid combination (except for RTV as enhancer) by ↓ levels. <u>Clarithromycin</u> ↓ ↓ dose in renal failure Antidepressants: monitor adverse effects <u>Rifabutin</u> : ↑ 90%	3TC d4T EFV: monitor hepatotoxicity. Administer with TPV/r Elvitegravir FTC Fluvastatin Loperamide Maraviroc NVP: administer with TPV/r Omeprazole Pravastatin Rosuvastatin TDF	With meals. No data available with oral anticonceptives with voriconazole or with IS. <u>ATV, IDV, NFV</u> : no data <u>Antiepileptics</u> <u>antifungal</u> <u>antiulcer agents</u> <u>erectile dysfunction</u> : Few data.

- 1 Except for potential interaction with TPV.
- 2 Potential inhibition of intracellular phosphorylation with d4T, not seen in patients co-infected with HIV-VHC. With d4T or ddl there could be risk of the mitochondrial toxicity.
- 3 Risk of therapeutic failure with low CD4s and high viremias. Risk if lactic acidosis and pancreatitis: levels of ddl.
- 4 Increased risk of lipodystrophy, especially at the start of therapies and in pregnant women. There is also an risk of lactic acidosis, pancreatitis and neuropathy.
- 5 Monitor renal toxicity when it is administered with RTV.
- 6 Potential interaction with LPV and TPV.
- 7 It can be combined with the usual doses if it is associated with RTV.
- 8 In hard capsules it can be used if it is combined with RTV the levels of SQV.
- 9 It may the levels of this drug (especially IDV, RTV, FPV and SQV), as well as vardenafil and tadalafil, especially if it is associated to RTV.
- 10 It induces the reduction of the levels of several IPs. Probably less marked with TPV/r. It is generally not recommended to associate with other IPs except for RTV.
- 11 Both produced indirect hyperbilirubinemia
- 12 Reduce the dose of trazodone or use alternative drugs.
- 13 This refers to a buffered ddl. There is no interaction with enteric capsules of ddl.
- 14 It may the plasma levels of warfarin and acenocoumarol: monitor levels.
- 15 Not recommended with Invirase® as single IP. ↓ levels of SQV. Use SQV/r.
- 16 Contraindicated when SQV is used as a single IP (SQV/r).
- 17 Great variability of plasma levels.
- 18 Could increase the risk of long QT.
- 19 The interaction ~ 46% of etravirine) it was described with RTV at full doses, not as an enhancer of other IPs.
- 20 Administer 2 hours apart if it is administered without RTV. It needs no adjustment with ATV/r (study performed with famotidine).
- 21 Avoid, unless there is no other alternative. TPV ~ 44% ABC.

- All PI increase concentration of atorvastatin, starting at low dose and monitor toxicity (cramps).
- All PI may decrease the metabolism of cyclophosphamide and increase the toxicity of cyclosporine.
- All PI increase concentration of cocaine
- When using midazolam with any PI, consider using single dose with close monitoring. If possible, use lorazepam, oxazepam instead.
- All PI interact with voriconazole.
- ATV increases concentration of estradiol and the rest of the PI decrease it.
- Major drugs metabolized by CYP3A4: alprazolam, amiodarone, amlodipine, bupropion, cyclophosphamide, cyclosporine, clonazepam, clorazepate, dextropropoxyphene, diazepam, diltiazem, disopyramide, estazolam, ethionamide, ethosuximide, felodipine, fentanyl, finasteride, flunarizine, flurazepam, lacidipine, lidocaine, loratadine, meperidine, nicardipine, nifedipine, nimodipine, nitrendipine, prednisone, quinidine, quinine, sertraline, sildenafil, vardenafil, tadalafil, tacrolimus, verapamil, vincristine, and zolpidem.

9. BIBLIOGRAPHY

1. ONUSIDA. 09 Situación de la epidemia de Sida. URL available at: http://data.unaids.org/pub/Report/2009/2009_epidemic_update_es.pdf.
2. Calleja JM, Walker N, Cuchi P, Lazzari S, Ghys PD, Zacarias F. Status of the HIV/AIDS epidemic and methods to monitor it in the Latin America and Caribbean region. *Aids* 2002; 16 Suppl 3:S3-12.
3. UNICEF Statistics, 2006. URL available at: <http://www.unicef.org/infobycountry/cubastatistics.html#55>
4. EMMUS IV. Encuesta de mortalidad, morbilidad y utilización de servicios. Port au Prince: Haiti. Ministerio de Salud; 2006.
5. Avert. Caribbean HIV/AIDS statistics. URL available at: <http://www.avert.org/caribbean.htm>
6. PARO, WHO, UNAIDS. HIV and AIDS in the Americas 2007: report. the evolving epidemic, response and challenges ahead. Washington: PARO; Sept 2007.
7. WHO,UNAIDS,UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: report 2009. Geneva: WHO; 2009. URL available at: http://www.who.int/hiv/pub/tuapr_2009_en.pdf
8. UNICEF. The State of the World Children 2008: child survival. URL available at: <http://www.unicef.org/sowc08/docs/sowc08.pdf>
9. ONUSIDA. Informe sobre la epidemia mundial de SIDA 2006: anexo 2: Estimaciones y datos sobre el VIH y el SIDA, 2005 y 2003. URL available at: http://data.unaids.org/pub/GlobalReport/2006/2006_GR_ANN2
10. De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *Jama* 2000; 283(9):1175-82.
11. Schmid GP, Stoner BP, Hawkes S, Broutet N. The need and plan for global elimination of congenital syphilis. *Sex Transm Dis* 2007; 34(7 Suppl):S5-10.
12. Hira SK, Bhat GJ, Chikamata DM, Nkowane B, Tembo G, Perine PL, et al. Syphilis intervention in pregnancy: Zambian demonstration project. *Genitourin Med* 1990; 66(3):159-64.
13. Schulz KF, Cates W, Jr., O'Mara PR. Pregnancy loss, infant death, and suffering: legacy of syphilis and gonorrhoea in Africa. *Genitourin Med* 1987; 63(5):320-5.
14. WHO. The Global elimination of congenital syphilis: rationale and strategy for action. 2007. Geneva: WHO; 2007. [Consultado el 1 de Noviembre de 2007]. URL available at http://whqlibdoc.who.int/publications/2007/9789241595858_eng.pdf.
15. Tinajeros F, Grossman D, Richmond K, Steele M, Garcia SG, Zegarra L, et al. Diagnostic accuracy of a point-of-care syphilis test when used among pregnant women in Bolivia. *Sex Transm Infect* 2006; 82 Suppl 5:v17-21.
16. PARO. Plan of action for the elimination of congenital syphilis. Washington: PARO; 1995. (PAHO/WHO/CE116/14).

17. Valderrama J. Eliminación de sfilis congénita en América Latina y el Caribe: marco de referencia para su implementación. Washington: OPS; 2005. URL available at: <http://www.paho.org/Spanish/AD/FCH/A1/EliminaSifilisLAC.pdf>.
18. OMS. 59ª ASAMBLEA MUNDIAL DE LA SALUD, A59/11, Punto 11.6 del orden del día provisional 18 de mayo de 2006. Ginebra: OMS; 2006. URL available at: http://www.who.int/gb/ebwhalpdf/files/WHA59/A59_11-sp.pdf.
19. OMS. Estrategia mundial de prevención y control de las infecciones de transmisión sexual 2006-2015. Ginebra: OMS; 2006. URL available at: http://www.who.int/reproductive-health/publications/es/stisstrategv/stisstrategv_es.pdf.
20. OMS. Eliminación mundial de la sfilis congénita: fundamentos y estrategia para la acción. Ginebra: OMS; 2008. URL available at: <http://whqlibdoc.who.int/publications/2008/9789243595856spa.pdf>
21. Hossain M, Broutet N, Hawkes S. The elimination of congenital syphilis: a comparison of the proposed World Health Organization action plan for the elimination of congenital syphilis with existing national maternal and congenital syphilis policies. *Sex Transm Dis* 2007; 34(7 Suppl):S22-30.
22. WHO. Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges Switzerland, 20-22 March 2002. Geneva: WHO; 2003. URL available at: <http://www.who.int/hiv/pub/mtct/en/StrategicApproachesE.pdf>
23. Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, Wabwire-Mangen F, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a pmspective study. *Lancet* 2005; 366(9492):1182-8.
24. Mbizvo MT, Kasule J, Mahomed K, Nathoo K. HIV-I seroconversion incidence followingpregnancy and delivery among women semnegative at recruitment in Harare, Zimbabwe. *Cent Afr J Med* 2001;47(5):115-8.
25. Villar J, Ba'aqeel II, Piaggio G, Lumbiganon P, Miguel Belizan J, Farnot U, et al. WHO antenatal care randomised trial for the evaluation of a new model of routine antenatal care. *Lancet* 2001; 357(9268):1551-64.
26. Villar J, Carroli G, Khan-Neelofur D, Piaggio G, Gulmezoglu M. Pattenms of routine antenatal care for low-risk pregnancy. *Cochrane Database Syst Rev* 2001(4):CD000934.
27. WHO. Malaria and HIV interactions and their implications for public health policy: report of a Technical Consultation on Malaria and HIV Interactions and Public Health Policy Implications. Geneva: WHO; 2005. URL available at: http://www.who.int/malaria/malaria_111V/MalariaIIVinteractions_report.pdf
28. Newell ML, Coovadia II, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 2004; 364(9441):1236-43.
29. Zaba B, Whitworth J, Marston M, Nakiyingi J, Ruberantwari A, Urassa M, et al. HIV and mortality of mothers and children: evidence from cohort studies in Uganda, Tanzania, and Malawi. *Epidemiology* 2005; 16(3):275-80.
30. OPS. Salud en las Américas. Washington: OPS; 2007. (Publicación Científica y Técnica; 622)
31. UNFPA, UNAIDS, UNICEF, WHO EUROPE. Strategic Framework for the Prevention of HIV Infection in Infant in Europe. Copenhagen: WHO; 2004.
32. De Vincenzi I. The European Study Group on Heterosexual Transmission of HIV. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. *N Engl J Med* 1994; 331: 341-346.
33. Castilla J, del Romero J, Herrando V, Marincovich M, Garcia S, Rodríguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr* 2005; 40: 96-101.
34. British HIV Association, Children's IIV Association. Guidelines for the management of HIV infection in pregnant women 2008. London: BREVA; 2008. URL available at: <http://www.bhiva.org/files/file1031055.pdf>
35. Paraskevas GP, Kapaki E, Kararizou E, Mitsonis C, Sfagos C, Vassilopoulos D. Cerebrospinal fluid tau protein is increased in neurosyphilis: a discrimination from syphilis without nervous system involvement? *Sex Transm Dis* 2007; 34(4):220-3.
36. Centers for Disease Control and Prevention. 2006. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 55:11:1-96. URL available at: <http://www.cdc.gov/std/treatment/2006/rr5511.pdf>.

37. Lewis DA, Young H. Syphilis. *Sex Transm Infect* 2006; 82 Suppl 4:iv13-5.
38. Hyman EL. Syphilis. *Pediatr Rev* 2006; 27(1):37-9.
39. Muller I, Brade V, Hagedorn HJ, Straube E, Schorner C, Frosch M, et al. Is serological testing a reliable tool in laboratory diagnosis of syphilis?: meta-analysis of eight external quality control surveys performed by the german infection serology proficiency testing program. *J Clin Microbiol* 2006; 44(4):1335-41.
40. Manavi K, Young H, McMillan A. The sensitivity of syphilis assays in detecting different stages of early syphilis *Int J STD AIDS* 2006; 17(11):768-71.
41. Pai NP, Tulskey JP, Cohan D, Colford JM, Jr., Reingold AL. Rapid point-of-care HIV testing in pregnant women: a systematic review and meta-analysis. *Trop Med Int Health* 2007;12(2):162-73
42. WHO. Clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. Geneva: WHO; 2005. URL available at: <http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf>
43. PARO. Guidelines for the implementation of Reliable and Efficient diagnostic HIV Testing. Region of the Americas. Washington: PARO; 2008. URL available at: <http://motherchildnutrition.org/nutrition-hiv-aids/pdf/mcn-guidelines-for-the-implementation-of-reliable-efficient-diagnostic-hiv-testing.pdf>
44. OPS. Tratamiento Antirretroviral de la infección por VIH en niños en América Latina y el Caribe: en la ruta hacia el acceso universal: recomendaciones para un enfoque de salud pública. Washington: OPS; 2008. URL available at: <http://www.paho.org/Spanish/AD/FCH/AI/GuiaARVninos.pdf>
45. Luján-Zilbermann J, Bitar W, Knapp K, Flynn P. Human immunodeficiency virus type 1 RNA polymerase chain reaction reasonably excludes infection in exposed infants. *Pediatr Infect Dis J* 2003; 22:97-99.
46. SADI. Primer Consenso Argentino de Terapia Antirretroviral. [fecha de consulta 1 de setiembre de 2007] URL available em:<http://www.sadi.org.ar/images/CONSENSOTAARV2006.pdf>.
47. Brasil. Ministerio de Saúde. Recomendações para Profilaxia da transmissão vertical do HIV e terapia anti-Retroviral em gestantes. Brasília: Ministério de Saúde; 2006. [fecha de consulta 1 de octubre de 2007]. URL available at: <http://www.aids.gov.br/data/documents/storedDocuments/%7BB8EF5DAF-23AE-4891-AD36-1903553A3174%7D/%7B672FA510-A296-41BC-9D63-D413775714BA%7D/Consenso%20gestantes%202007%20-%20final.pdf>
48. Shibuyama S, Gevorkyan A, Yoo U, Tim S, Dzhangiryan K, Scott JD. Understanding and avoiding antiretroviral adverse events. *Curr Pharm Des* 2006; 12(9):1075-90.
49. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 — 31 Januar), 2007. Wilmington: Registry Coordinating Center; 2007. [fecha de consulta junio de 2007]. URL available at: <http://www.apregistry.com/>
50. SaitohA, Hull AD, Franklin P, Spector SA. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol* 2005; 25(8): 555-6.
51. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *Aids* 2002;16(2): 299-300.
52. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med* 2002; 162(3): 355.
53. Winston A, Pozniak A, Smith N, Fletcher C, Mandalia S, Patinar D, et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? *Aids* 2004;18(3): 572-4.
54. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. *N Engl J Med* 1999; 341(20):1509-19.
55. Chersich MF, Urban MF, Venter FW, Wessels T, Krause A, Gray GE, et al. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Res Ther* 2006; 3:11.
56. Bucceri AM, Somigliana E, Matrone R, Uberti-Foppa C, Vigano P, Vignali M. Discontinuing combination antiretroviral therapy during the first trimester of pregnancy: insights from plasma human immunodeficiency virus-1 RNA viral load and CD4 cell count. *Am J Obstet Gynecol* 2003;189(2): 545-51.
57. Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised

- trial. *Lancet* 2006; 367(9527): 1981-9.
58. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; 355(22): 2283-96.
 59. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *Pediatric AIDS Clinical Trials anup Protocol 076 Study anup*. *N Engl J Med* 1994; 331(18): 1173-80.
 60. Lalléman M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *Perinatal my Prevention Trial (Thailand) Investigators*. *N Engl J Med* 2000; 343(14): 982-91.
 61. Chaisilwattana P, Chokephaibulkit K, Chalermchokchatnenkit A, Vanprapar N, Sirimai K, Chearskul S, et al. Short-course therapy with zidovudine plus lamivudine for prevention of mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. *Clin Infect Dis* 2002; 35(11):1405-13.
 62. Bardsley-Elliot A, Peny CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000; 2(5): 373-407.
 63. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; 354(9181): 795-802.
 64. Moodley D, Moodley J, Coovadia H, Gray G, McIntyre J, Hofmyer J, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; 187(5): 725-35.
 65. Huttner HB, Kolhner R, Hug A, Meisel F, Kress B, Schwab S. Fatal tuberculous meningitis caused by immune restoration disease. *J Neurol* 2004; 251(12):1522-3.
 66. Lalléman M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; 351(3): 217-28.
 67. Shapiro RL, Thior I, Gilbert PB, Lockman S, Wester C, Smeaton LM, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *Aids* 2006; 20(9): 1281-8.
 68. Dabis F, Bequet L, Ekouevi DK, Viho I, Rouet F, Horo A, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *Aids* 2005; 19(3): 309-18.
 69. Tonwe-Gold B, Ekouevi DK, Viho I, Amani-Bosse C, Toure S, Coffie PA, et al. Antiretroviral treatment and prevention of peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered approach. *PLoS Med* 2007; 4(8): e257.
 70. Monis AB, Dobles AR, Cu-Uvin S, Zorrilla C, Anderson J, Harwell JI, et al. Protease inhibitor use in 233 pregnancies. *J Acquir Immune Defic Syndr* 2005; 40(1): 30-3.
 71. Marazzi MC, Germano P, Liotta G, Guidotti G, Loureiro S, da Cruz Gomes A, et al. Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1- infected pregnant women. *HIV Med* 2006; 7(5): 338-44.
 72. Read JS, Cahn P, Losso M, Pinto J, Joao E, Duarte G, et al. Management of human immunodeficiency virus-infected pregnant women at Latin American and Caribbean sites. *Obstet Gynecol* 2007; 109(6):1358-67.
 73. Chama C, Gashau W, Oguiche S. The value of highly active antiretroviral therapy in the prevention of mother-to-child transmission of HIV. *J Obstet Gynaecol* 2007; 27(2): 134-7.
 74. Chile. Ministerio de Salud. Guías clínicas síndrome de inmunodeficiencia adquirida: VITT/Sida Santiago, Chile: Ministerio de Salud; 2005. [fecha de consulta 1 de setiembre de 2007] URL available at: <http://www.minsal.cl/ici/guiasclnicas/vihsidaRMayoLO.pdf>
 75. Uruguay. Ministerio de Salud Pública. Programa Prioritario ITS-Sida, OPS, Centro Internacional en Cooperación Técnica en VIH-Sida. Infección por el Virus de la Inmunodeficiencia Humana. Guías para

- diagnóstico, tratamiento antirretroviral y monitorización de adultos y embarazadas. Capítulo III: VIH-Sida y embarazo Montevideo: MSP; 2006. [fecha de consulta 1 de setiembre de 2007]. URL available at: <http://www.msp.gub.uy/imgnoticias/8535.pdf>
76. Colombia. Ministerio de Salud. Consejo Nacional de Seguridad Social en Salud. Guía para el manejo del VIH/sida. Basada en la evidencia. Bogotá: Ministerio de Salud; 2006. [fecha de consulta el 1 de setiembre de 2007]. URL available at: <http://www.minproteccionsocial.gov.co/VBeContent/library/documents/DocNewsNo15675DocumentNo3251.PDF>
 77. Nicaragua. Ministerio de Salud de Nicaragua. Norma y protocolo para la prevención de la transmisión vertical del VIH. Managua: Ministerio de Salud; 2008. URL available at: <http://www.minsa.gob.ni/bns/regulacion/2009/N-014-PrevencionTransmisionVerticalVIH.pdf>
 78. Mrus JM, Tsevat J. Cost-effectiveness of interventions to reduce vertical HIV transmission from pregnant women who have not received prenatal care. *Med Decis Making* 2004; 24(1): 30-9.
 79. The International Perinatal my Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999; 340(13): 977-87.
 80. The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; 353(9158):1035-9.
 81. Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV 1. *Cochrane Database Syst Rev* 2005(4): CD005479.
 82. Jamieson DI, Read A, Kourtis A, Durant T, Lampe M, Dominguez K. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol* 2007; 197(3 Supp11):S96-100.
 83. Boer K, Nellen JF, Patel D, Tinunermans S, Tempelman C, Wibaut M, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *Bjog* 2007; 114(2):148-55.
 84. Ioarmidis JP, Abrams FJ, Ammann A, Bulterys M, Goedert JJ, Gray L, Korber BT, Mayaux MJ, Mofeson LM, Newell ML, Shapiro DE, Teglas JP, Wilfert CM. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis* 2001; 183(Supp14): 539-45.
 85. Palombi L, Marazzi MC, Voetberg A, Magid A, and the DREAM Program Prevention of Mother-To-Child Transmission Team. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of 1111V, 2007.
 86. Arendt V y col. AMATA study: effectiveness of antiretroviral therapy in breastfeeding mothers to prevent post-natal vertical transmission in Rwanda. Fourth International AIDS Society Conference, Sydney, Australia, 22-25 July 2007. [ha3://www.52&ALE5043](http://www.52&ALE5043)
 87. Kilewo C y col. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania - the MITRE PLUS study. Fourth International AIDS Society Conference, Sydney, Australia, 22-25 July 2007. [ha://www.wlas2007.org/pag/Abstracts.aspx?S152&ALE2982](http://www.wlas2007.org/pag/Abstracts.aspx?S152&ALE2982)
 88. Coovadia HM, Rollins NC, Bland RM, Little K, Coutoudis A, Bennish ML, et al. Mother-to-child transmission of infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* 2007; 369(9567):1107-16.
 89. Coutoudis A. Breastfeeding and the HIV positive mother: the debate continues. *Early Hum Dev* 2005; 81(1):87-93.
 90. Timmermans S, Tempelman C, Godfried MH, Nellen J, Dieleman J, Sprenger H, et al. Nelfinavir and nevirapine side effects during pregnancy. *Aids* 2005; 19(8):795-9.
 91. Best BM, Mirochnick M, Capparelli EV, Stek A, Burchett SK, Holland DT, et al. Impact of pregnancy on abacavir pharmacokinetics. *Aids* 2006; 20(4):553-60
 92. Moodley J, Moodley D, Pillay K, Coovadia H, Saba J, van Leeuwen R, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency

- virus type 1- infected pregnant women and their offspring. *J Infect Dis* 1998;178(5):1327-33.
93. Wade NA, Unadkat JD, Huang S, Shapiro DE, Mathias A, Yasin S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis* 2004; 190(12):2167-74.
 94. Wang Y, Livingston E, Patil S, McKinney RE, Bardeguez AD, Gandia J, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus--infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis* 1999; 180(5):1536-41.
 95. Gaillard P, Fowler MG, Dabis F, Coovadia II, Van Der Horst C, Van Rompay K, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr* 2004; 35(2):178-87.
 96. Shapiro RL, Holland DT, Capparelli E, Lockman S, Thior I, Wester C, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *J Infect Dis* 2005; 192(5):720-7.
 97. Mandelbrot L, Kennarrec N, Marcollet A, Lafanechere A, Longuet P, Chosidow D, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *Aids* 2003; 17(2):272-3.
 98. Samer L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect* 2002; 78(1):58-9.
 99. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, Berrebi A, Benifla JL, Burgard M, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *Jama* 2001 ;285(16):2083-93.
 100. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003; 362(9387):859-68.
 101. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr* 2004; 35(5):538-9.
 102. Leith J, Piliero P, Storfer S, Mayers D, Hinzmann R. Appropriate use of nevirapine for long-term therapy. *J Infect Dis* 2005; 192(3):545-6; author reply 546.
 103. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr* 2003; 34 Suppl 1:S21-33.
 104. Hitti J, Frenkel LM, Stek AM, Nachman SA, Baker D, Gonzalez-Garcia A, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr* 2004; 36(3):772-6.
 105. Lyons F, Hopkins S, Kelleher B, McGeary A, Sheehan G, Geoghegan J, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *my Med* 2006; 7(4):255-60.
 106. Phanuphak N, Apompong T, Teeratakulpisarn S, Chaithongwongwatthana S, Taweepolcharoen C, Mangclaviraj S, et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. *HIV Med* 2007; 8(6):357-66.
 107. Thomas T et al. Preliminary findings: incidence of serious adverse events attributed to nevirapine among women enrolled in an ongoing trial using HAART to prevent mother-to-child HIV transmission. 12th Conference on Retroviruses and Opportunistic Infections Boston, MA, USA, 22-25 February 2005 (Abstract 809).
 108. Joao EC, Calvet GA, Menezes JA, D'Ippolito MM, Cruz ML, Salgado LA, et al. Nevirapine toxicity in a cohort of HIV-1-infected pregnant women. *Am J Obstet Gynecol* 2006;194(1):199-202.
 109. Sanase I, Mommeja-Marin H, Hinde J, Barde JA, Lederman MM, Maartens G, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005; 191(6):825-9.
 110. Nightingale SL. From the Food and Drug Administration. *Jama* 1998; 280(17):1472.
 111. Dear Health Care Provider. Re: Important change in SUSTIVA® (efavirenz) package insert — change from pregnancy category C to D. Bristol-Myers Squibb; March 2005.
 112. Watts DH, Covington DL, Beckerman K, Garcia P, Scheuerle A, Dominguez K, et al Assessing the risk of birth

- defects associated with antiretroviral exposure during pregnancy. *Am J Obstet Gynecol* 2004; 191(3):985-92.
113. Covington DL, Tilson H, Elder J, Doi P. Assessing teratogenicity of antiretroviral drugs: monitoring and analysis plan of the Antiretroviral Pregnancy Registry. *Pharmacoepidemiol Drug Saf* 2004; 13(8):537-45.
 114. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. *Curr HIV/AIDS Rep* 2007; 4(3):135-40.
 115. Danel C, Moh R, Anzian A, Abo Y, Chenal H, Guehi C, et al. Tolerance and acceptability of an efavirenz-based regimen in 740 adults (predominantly women) in West Africa. *J Acquir Immune Defic Syndr* 2006; 42(1):29-35.
 116. Vithayasai V, Moyle GJ, Supajatura V, Wattanachariya N, Kanshana S, Sirichthapom P, et al. Safety and efficacy of saquinavir soft-gelatin capsules + zidovudine + optional lamivudine in pregnancy and prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr* 2002; 30(4):410-2.
 117. Covington DL, Conner SD, Doi PA, Swinson J, Daniels EM. Risk of birth defects associated with nelfinavir exposure during pregnancy. *Obstet Gynecol* 2004; 103(6):1181-9.
 118. Acosta EP, Bardeguet A, Zorrilla CD, Van Dyke R, Hughes MD, Huang S, et al. Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; 48(2):430-6.
 119. Kosel BW, Beckerman KP, Hayashi S, Homma M, Aweeka FT. Pharmacokinetics of nelfinavir and indinavir in HIV-1-infected pregnant women. *Aids* 2003; 17(8):1195-9.
 120. Van Heeswijk RP, Khaliq Y, Gallicano KD, Bourbeau M, Seguin I, Phillips ET, et al. The pharmacokinetics of nelfinavir and M8 during pregnancy and post partum. *Clin Pharmacol Ther* 2004; 76(6):588-97.
 121. Lyons F, Lechelt M, De Ruiter A. Steady-state lopinavir levels in third trimester of pregnancy. *Aids* 2007; 21 (8): 1053-4 .
 122. Hayashi S, Beckennan K, Homma M, Kosel BW, Aweeka FT. Pharmacokinetics of indinavir in HIV-positive pregnant women. *Aids* 2000; 14(8):1061-2.
 123. Warning about indinavir and pregnancy. *AIDS Patient Care STDS* 2005; 19(2):127.
 124. Cotter AM, Garcia AG, Duthely ML, Luke B, O' Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis* 2006; 193(9):1195-201.
 125. Thome C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *Aids* 2004; 18(17):2337-9.
 126. Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill II, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr* 2005; 38(4):449-73.
 127. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med* 2002; 346(24):1863-70.
 128. Tuomala RE, Yawetz S. Protease inhibitor use during pregnancy: is there an obstetrical risk? *J Infect Dis* 2006; 193(9):1191-4.
 129. Phanuphak N et al. Pregnancy outcomes alter combined ART or short-course AZT with single-dose nevirapine in Thai women with high and low CD4 cell counts. 13th Conference on Retroviruses and Opportunistic Infections. Denver, USA, 2006 (Abstract 712).
 130. Tonwe-Gold B et al. Highly active antiretroviral therapy for the prevention of perinatal HIV transmission in Africa: mother-to-child HIV transmission plus, Abidjan, Cote d'Ivoire, 2003-2004. 12th Conference on Retroviruses and Opportunistic Infections. Boston, USA, 22-25 February 2005 (Abstract 785).
 131. Watts DH, Balasubramanian R, Maupin RT, Jr., Delke I, Dorenbaum A, Fiore S, et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol* 2004; 190(2):506-16.
 132. Suy A, Martinez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *Aids* 2006; 20(1):59-66.
 133. Barret B, Tardieu M, Rustin P, Lacroix C, Chabrol B, Desguerre I, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *Aids* 2003; 17(12):1769-

134. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr* 2000; 25(3):261-8.
135. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr* 2003; 32(4):380-7.
136. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *Aids* 2003; 17(14):2053-61.
137. Mofenson LM, Munderi P. Safety of antiretroviral prophylaxis for perinatal transmission for HIV-infected pregnant women and their infants. *J Acquir Immune Defic Syndr* 2002; 30(2):200-15.
138. Bardeguez AD, Shapiro DE, Mofenson LM, Coombs R, Frenkel LM, Fowler MG, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *J Acquir Immune Defic Syndr* 2003; 32(2):170-81.
139. PETRA Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; 359(9313):1178-86.
140. Dorenbaum A, Cunningham CK, Gelber RD, Culnane M, Mofenson L, Britto P, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *Jama* 2002; 288(2):189-98.
141. Taha TE, Kumwenda N, Gibbons A, Hoover D, Lema V, Fiscus S, et al. Effect of HIV-1 antiretroviral prophylaxis on hepatic and hematological parameters of African infants. *Aids* 2002; 16(6):851-8.
142. Taha TE, Kumwenda N, Kafulafula G, Kumwenda J, Chitale R, Nkhoma C, et al. Haematological changes in African children who received short-term prophylaxis with nevirapine and zidovudine at birth. *Ann Trop Paediatr* 2004; 24(4):301-9.
143. Arrive E, Newell ML, Ekouevi DK, Chaix ML, Thiebaut R, Masquelier B, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int J Epidemiol* 2007; doi:10.1093/ije/dym104. URL available at: <http://ije.oxfordjournals.org/cgi/reprint/dym104v1>
144. Giuliano M, Palmisano L, Galluzzo CM, Amici R, Genniniano E, Okong P, et al. Selection of resistance mutations in pregnant women receiving zidovudine and lamivudine to prevent HIV perinatal transmission. *Aids* 2003; 17(10):1570-2.
145. Fowler MG, Mofenson L, McConnell M. The interface of perinatal HIV prevention, antiretroviral drug resistance, and antiretroviral treatment: what do we really know? *J Acquir Immune Defic Syndr* 2003; 34(3):308-11.
146. Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J Acquir Immune Defic Syndr* 2002; 30(2):216-29.
147. Larbalestier N, Mullen J, O'Shea S, Cottam F, Sabin CA, Chrystie IL, et al. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *Aids* 2003; 17(18):2665-7.
148. Cressey TR, Jourdain G, Lallemand MJ, Kunkew S, Jackson JB, Musoke P, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr* 2005; 38(3):283-8.
149. Loubser S, Balfe P, Sherman G, Hammer S, Kuhn L, Morris L. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission. *Aids* 2006; 20(7):995-1002.
150. Flys T, Nissley DV, Claassen CW, Jones D, Shi C, Guay LA, et al. Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women

- and infants alter the administration of single-dose NVP: HIVNET 012. *J Infect Dis* 2005; 192(1):24-9.
151. Johnson JA, Li JF, Morris L, Martinson N, Gray G, McIntyre J, et al. Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *J Infect Dis* 2005; 192(1):16-23.
 152. Palmer S, Boltz V, Martinson N, Maldarelli F, Gray G, McIntyre J, et al. Persistence of nevirapine-resistant HIV-1 in women after single-dose nevirapine therapy for prevention of maternal-to-fetal HIV-1 transmission. *Proc Natl Acad Sci U S A* 2006; 103(18):7094-9.
 153. Eshleman SH, Mracna M, Guay LA, Deseyve M, Cunningham S, Mirochnick M, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *Aids* 2001; 15(15): 1951-7.
 154. McIntyre JA. Controversies in the use of nevirapine for prevention of mother-to-child transmission of HIV. *Expert Opin Pharmacother* 2006; 7(6): 677-85.
 155. Martinson NA, Morris L, Gray G, Moodley D, Pillay V, Cohen S, et al. Selection and persistence of viral resistance in HIV-infected children after exposure to single-dose nevirapine. *J Acquir Immune Defic Syndr* 2007; 44(2):148-53.
 156. Clarke JR, Braganza R, Mirza A, Stainsby C, Ait-Khaled M, Wright A, et al. Rapid development of genotypic resistance to lamivudine when combined with zidovudine in pregnancy. *J Med Virol* 1999; 59(3):364-8.
 157. Duran AS, Losso MH, Salomon II, Harris DR, Pampuro S, Soto-Ramirez LE, et al. Drug resistance among infected pregnant women receiving antiretrovirals for prophylaxis. *Aids* 2007; 21(2):199-205.
 158. Kakehasi FM, Tupinambas U, Cleto S, Aleixo A, Lin E, Melo VII, et al. Persistence of genotypic resistance to nelfinavir among women exposed to prophylactic antiretroviral therapy during pregnancy. *AIDS Res Hum Retroviruses* 2007; 23(12):1515-20.
 159. Chaix ML, Ekouevi DK, Rouet F, Tonwe-Gold B, Viho I, Bequet L, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrane Plus, Abidjan, Cote d'Ivoire. *J Infect Dis* 2006; 193(4):482-7.
 160. Lyons FE, Coughlan S, Byrne CM, Hopkins SM, Hall WVJ, Mulcahy FM. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *Aids* 2005; 19(1):63-7.
 161. McIntyre J et al. Addition of short course combivir (CBV) to single dose viramune (sdNVP) for the prevention of mother to child transmission (PMTCT) of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI resistant virus. The 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil, 24-27 July 2005 (Abstract TuFo0204).
 162. Eshleman SH, Hoover DR, Hudelson SE, Chen S, Fiscus SA, Piwowar-Manning E, et al. Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Infect Dis* 2006; 193(4):479-81.
 163. Perez II, Vignoles M, Laufer N, Gomez A, Coll P, Lottner J, et al. Low rate of emergence of nevirapine and lamivudine resistance after post-partum interruption of a triple-drug regimen. *Antivir Ther* 2008; 13(1):135-9.
 164. Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. *Aids* 2005; 19(1):1-14.
 165. Viani RM, Hsia K, Ruiz-Calderon J, et al. Prevalence of primary HIV-1 drug resistance in pregnant women and in newly diagnosed adults at Tijuana General Hospital, Baja California, Mexico. *Int J STD AIDS* 2007; 18(4):235-8.
 166. Shekelle P, Maglione M, Geotz MB, Wagner G, Wang Z, Hilton L, et al. Antiretroviral (ARV) drug resistance in the developing world. *Evid Rep Technol Assess (Full Rep)* 2007(156):1-74.
 167. Paredes R, Cheng I, Kuritzkes DR, Tuomala RE. High prevalence of primary lamivudine and nelfinavir resistance in HIV-1-infected pregnant women in the United States, 1998-2004. *Aids* 2007; 21(15):2103-6.
 168. McConnell MS, Bakaki P, Eure C, Mubiru M, Bagenda D, Downing R, et al. Effectiveness of Repeat Single-

- Dose Nevirapine for Prevention of Mother-to-Child Transmission of HIV-1 in Repeat Pregnancies, Uganda. *J Acquir Immune Defic Syndr* 2007; Publish Ahead of Print.
169. Martinson N et al. Effectiveness of single-dose nevirapine in consecutive pregnancies in Soweto and Abidjan. 13th Conference on Retroviruses and Opportunistic Infections. Denver, CO, USA, 22-25 February 2006 (Abstract 722).
 170. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Bowonwatanuwong C, Kantipong P, Leechanachai P, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med* 2004; 351(3):229-40.
 171. Blanche S, Tardieu M, Rustin P, Slama A, Barret B, Firtion G, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; 354:1084-89.
 172. Noguera A, Fortuny C, Sanchez E, Artuch R, Vilaseca MA, Munoz-Almagro C, et al. Hyperlactatemia in human immunodeficiency virus-infected children receiving antiretroviral treatment. *Pediatr Infect Dis J* 2003; 22:778-82.
 173. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. *N Engl J Med* 1999; 340:977-87.
 174. Barret B, Tardieu M, Rustin P, Lacroix C, Chabrol B, Desguerre I, et al. persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS* 2003; 32:380-7.
 175. Dabis F, Msellati P, Meda N, Welfens-Ekra C, You B, Manigart O, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. *Diminution de la Transmission Mere-Enfant. Lancet* 1999;353 (9155):786-92.
 176. Dear Health Care Provider Letter. Roche Pharmaceuticals, 7 February 2005 [fecha de consulta agosto de 2007] URL available at: <http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Invirase>
 177. M Landes, M-L Newell, P Barlow, and others. Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe. *my Medicine* Aug 2008; 9(7): 526-534.
 178. Sulkowski MS, Benhamou Y. Therapeutic issues in HIV/HCV-coinfected patients. *J Viral Hepatitis* Jun 2007; 14(6): 371-386.
 179. WHO Europe. Prevention of Hepatitis A, B, and C and other Hepatotoxic Factors in People Living with HIV. Clinical Protocol for the WHO European Region. Copenhagen: WHO; 2006.
 180. España. Ministerio de Sanidad y Consumo. Recomendaciones para el seguimiento de la infección por el VIH con relación a la reproducción, el embarazo y la prevención de la transmisión vertical. Madrid: Ministerio de Sanidad y Consumo; 2007.
 181. Greene CM, Goodman MH. Neonatal abstinence syndrome: strategies for care of the drug-exposed infant. *Neonatal Netw* 2003; 22(4):15-25.
 182. WHO Europe. Prevention of HIV Transmission from HIV-infected Women to their Infants. Clinical Protocol for the WHO European Region. Copenhagen: WHO; 2006?.
 183. G.Birkhead, et al. The contribution of infection acquired during pregnancy to residual mother-to-child HIV transmission rates in New York State. : AIDS 2006 - XVI International AIDS Conference: Abstract no. WEPE0271
 184. Organización Panamericana de la Salud, Centro Latinoamericano de Perinatología, Salud de la Mujer y Reproductiva, UNICEF. Iniciativa regional para la eliminación de la transmisión materno infantil de VIH y de la sífilis congénita en América Latina y el Caribe: documento conceptual. Montevideo: CLAP/SMR; set 2009. URL available at: http://www.clap.ops-oms.org/web_2005/BOLETINES_Y_NOVEDADES/EDICIONES_DEL_CLAP/CLAP1569.pdf
 185. Centro Latinoamericano de Perinatología, Salud de la Mujer y Reproductiva, Fundación March of Dimes. Infecciones perinatales transmitidas por la madre a su hijo: material didáctico para el personal de salud. Montevideo: CLAP/SMR; 2008. (CLAP/SMR. Publicación Científica; 1567). URL available at: http://www.clap.ops-oms.org/web_2005/BOLETINES_Y_NOVEDADES/EDICIONES_DEL_CLAP/CLAP1567.pdf

186. Kesho Bora Study Group. Triple-antiretroviral prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Cape Town, South Africa. July 2009
187. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. Weekly Epidemiol Record, 25 May 2007(21): 193-196. URL available: <http://www.who.int/lwer/2007/wer8221.pdf>
188. Fescina RH, Butrón B, De Mucio B, Martínez G, Díaz Rossello JL, Camacho V, Simini F, Mainero L. Sistema Informático Perinatal: historia clínica perinatal: instrucciones de llenado y definición de términos. Montevideo: CLAP/SMR; 2007. (CLAP/SMR. Publicación Científica; 1563). URL available at: <http://www.clap.ops-oms.org/web 2005/BOLETINES Y NOVEDADES/EDICIONES DEL CLAP/CLAP1563pdf>.