WORLD HEALTH ORGANIZATION

Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting

WHO Headquarters, Geneva, Switzerland
10-11 April 2008

EXECUTIVE SUMMARY

In April 2008 the WHO Technical Reference Group for Paediatric HIV/Antiretroviral Therapy and Care met to consider the implications of recent research findings for existing WHO guidelines for treatment and care of infants infected with HIV. As a result of this consultation and review of data, the group revised recommendations for diagnostic testing, initiation of treatment, and treatment regimens for HIV-exposed and infected infants.

This report details the new recommendations, GRADE evidence profiles and the reference group's decision making behind these revisions to the WHO guidelines for antiretroviral therapy for HIV infection in infants and children.

INTRODUCTION

While progress has been made in preventing new HIV infections in children, the number of infants and children newly infected in 2007 was estimated at 420,000. Greater efforts are therefore needed to scale up the known effective preventive interventions if we are to meet ambitious goals of eliminating HIV in infants and children.

Data emerging since the publication of the 2006 WHO recommendations for antiretroviral treatment for infants and children suggest that in young infants earlier initiation of antiretroviral therapy (ART) is life saving.

The WHO Technical Reference Group on Paediatric HIV/ART Care (TRG), initially constituted in 2005 to develop WHO paediatric antiretroviral therapy recommendations, was convened to review this new evidence and consider if revisions to the existing recommendations were needed.

MEETING BACKGROUND

Existing WHO paediatric HIV treatment guidelines recommend the use of clinical or immunological criteria to guide initiation of antiretroviral therapy in infected infants and children, but recognize that CD4 -- either percent of T cells expressing CD4 (% CD4) or total CD4 -- is not a reliable predictor of likelihood of disease progression in infants.

Data emerging from recent studies in resource constrained settings confirm that for infants acquiring HIV at or around delivery, disease progression occurs very rapidly in the first few months of life, often leading to death. Over 80% of infected infants rapidly became eligible to start antiretroviral therapy before 6 months of age [1,2].

In a randomized clinical trial conducted in South Africa[2] asymptomatic infants with %CD4 >25 started antiretroviral therapy as soon as possible after diagnosis of HIV. A dramatic reduction in mortality (75%) was observed in these infants compared to infants who were started on treatment based on the immunological or clinical criteria as outlined in the current treatment guidelines. Other research and observational data also suggest that early antiretroviral therapy in infancy dramatically reduces the risk of death and disease progression.

Data from a recent meta-analysis and from observational studies [18, 20-28] confirm that HIV infected infants exposed to nevirapine through infant or maternal treatment or prophylaxis have demonstrable viral resistance. Another observational study [18] also suggests that response to nevirapine-containing first line treatment regimens may be compromised in infants who acquire HIV despite intra- or peripartum exposure to nevirapine.

In light of these recent findings the Technical Reference Group sought to examine current WHO recommendations and formulate revisions as required. The group followed recently revised WHO regulations for guideline development based on the GRADE approach [3].

Meeting objectives

1. Review existing WHO recommendations for antiretroviral therapy in infants.
2. Review evidence summaries prepared for when to start antiretroviral therapy in infants, what antiretroviral therapy regimens to use and whether diagnostic and monitoring protocols need to be modified.
3. Determine whether revisions to WHO recommendations are required.
4. Develop consensus on final WHO recommendations.
5. Identify simple implementation tools required.
6. Identify key recommendations for future research.

Meeting outputs

1. Consensus on whether revisions to WHO antiretroviral therapy recommendations are required.
2. Revised recommendations for initiation and follow up of antiretroviral therapy in infants (if required).
3. Revised recommendations for diagnostic testing and follow up of HIV exposed infants (if required).
4. Implementation steps and required simple implementation tools described.
5. Recommendations, research, and other issues requiring urgent attention.

Preparatory work

The questions to be addressed in this guideline review were agreed upon by a subgroup of the Technical Reference Group which met in February at the 2008 Conference on Retroviruses and Opportunistic Infections (CROI 2008).

GRADE evidence profiles and summary of findings tables were prepared to guide the development of the recommendations for the three key questions being examined:

1. When to start antiretroviral therapy in HIV infected infants?
2. What to use for first line antiretroviral therapy in HIV infected infants?
3. What is the most appropriate timing for HIV diagnostic testing in HIV exposed infants?

In addition, a survey of current treatment guidelines and practice was undertaken, scenarios were developed to examine timing of virological testing, and summaries of current costs and use of antiretrovirals (ARVs) in paediatric populations compiled.

Meeting participants
Members of the Technical Reference Group were selected from the original 2005 expert group and additional methodological and non-HIV experts were also invited, in accordance with WHO procedures for guideline development. Regional advisers nominated suitable experts from within countries to provide perspectives from all WHO regions.

Meeting process
Potential declarations of interests were identified and assessed prior to developing recommendations, and no Technical Reference Group members with conflict were identified.

For each subject area examined, a series of plenary presentations and discussion sessions were followed by group work on draft recommendations. Discussions focused on consideration of costs, values, preference, feasibility and the balance of evidence for desirable and undesirable effects (risk-benefit assessment). Consensus was achieved in plenary sessions on the wording and strength of the recommendations.

Meeting presentations are available at
http://www.who.int/hiv/pub/meetingreports/art_meeting_april2008/en/index.html

KEY FINDINGS AND RECOMMENDATIONS

***Table A: Explanation of age terminology used in these recommendations**

Infant	=	Under 12 months of age
Under 12 months	=	< 12 months
12 months or older	=	≥12 months = Equal to or older than 12 months
Age 1-4	=	12 through 59 months
Age 5 and over	=	60 months and over

WHEN TO TEST INFANTS

1. RECOMMENDATION:
Infants known to be exposed to HIV should have a virological test (HIV nucleic acid test) at 4-6 weeks of age or at the earliest opportunity for infants seen after 4-6 weeks.

STRONG RECOMMENDATION

Note: Testing at this time (4-6 weeks of age) will identify >95% of infants infected intra- and peripartum. However, some flexibility in implementation of this recommendation may be required based on current national or local postpartum and infant follow-up practices and service configuration. Delaying testing beyond this time will delay diagnosis and put HIV infected infants at risk of disease progression and death.

Note: If virological testing is not available, presumptive clinical diagnosis in accordance with nationally defined algorithms will be required.

2. RECOMMENDATION:
Urgent HIV testing is recommended for any infant presenting to health facilities with signs, symptoms or medical conditions that could indicate HIV.

STRONG RECOMMENDATION

Note: In this situation, infants should initially be tested using HIV antibody testing, and those with detectable HIV antibody should go on to have virological testing.

3. RECOMMENDATION:
All infants should have their HIV exposure status established at their first contact with the health system, ideally before 6 weeks of age.

STRONG RECOMMENDATION

Note (a): In most cases infant HIV status will be established by asking the mother, by checking the child's and/or mother's health card, or by requesting a history of maternal HIV testing in pregnancy, labour or the postpartum period.

Note (b): while the TRG felt this was strong recommendation they also recognised that countries may choose to identify circumstances or settings where this recommendation may need modification, based on HIV prevalence.

4. RECOMMENDATION:
Infants under 6 weeks of age, of unknown HIV exposure status and in settings where local or national antenatal HIV seroprevalence is greater than 1%[a,] should be offered maternal or infant HIV antibody testing[b] and counselling in order to establish exposure status.

CONDITIONAL RECOMMENDATION (Context Specific)

Note (a): Countries should determine prevalence thresholds and other circumstances where this recommendation should be followed.

Note (b): Nationally or internationally approved rapid HIV antibody tests may be used.

WHEN TO INITIATE ANTIRETROVIRAL THERAPY

5. RECOMMENDATION:
All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage.

STRONG RECOMMENDATION

6. RECOMMENDATION:
Where virological testing is not available, infants under 12 months of age *(see Table A)* with clinically diagnosed presumptive severe HIV should start antiretroviral therapy. Confirmation of HIV infection should be obtained as soon as possible.

STRONG RECOMMENDATION

Note: Improved clinical and laboratory based algorithms to support this recommendation are expected and are likely to refine the specificity of this recommendation; therefore it should be reviewed within the next two years.

7. RECOMMENDATION:
For children age 12 months or older *(see Table A)*, clinical and immunological thresholds should be used to identify those who need to start antiretroviral therapy.

STRONG RECOMMENDATION

Criteria to start ART				
Age	**Infants <12 months**	**12 months through 35 months**	**36 months through 59 months**	**5 years or over**
% CD4	All	<20	<20	<15
Absolute CD4 #		<750mm^3	<350mm^3	As in adults (<200)

Absolute CD4 count is naturally less constant and more age-dependent than %CD4; it is not therefore appropriate to define a single threshold.

WHAT TO START

8. RECOMMENDATION:
For HIV infected infants with no exposure to maternal or infant non-nucleoside reverse transcriptase inhibitors, or whose exposure to maternal or infant antiretrovirals is unknown, standard nevirapine-containing triple therapy should be started.

STRONG RECOMMENDATION

9. RECOMMENDATION:
For HIV infected infants with a history of exposure to single dose nevirapine or non-nucleoside reverse transcriptase inhibitor containing maternal antiretroviral therapy or preventive antiretroviral regimens, a protease inhibitor-based triple antiretroviral therapy regimen should be started. Where protease inhibitors are not available, affordable or feasible, nevirapine-based therapy should be used.

CONDITIONAL RECOMMENDATION (Context specific & time limited)

Note: While the Technical Reference Group felt the evidence and risk-benefit analysis warranted a strong recommendation, they also recognized that currently, in many resource limited settings, lopinavir/rotanivir is not available, affordable, or, due to cold chain requirements, not feasible for use. In addition, the use of lopinavir/rotanivir in a first line regimen compromises the potential to construct a potent second line regimen. On-going studies are likely to provide information that may result in modification of this recommendation.

NEXT STEPS AND OUTSTANDING ISSUES

Guideline Revision Process

The revised recommendations for antiretroviral therapy in infants will be compiled and made available in the following ways:

- A summary report of the revised recommendations will be reviewed by the Technical Reference Group meeting participants. A final draft will be circulated for peer review by experts and organizations prior to publication.
- A pamphlet summarizing the new recommendations will be prepared for the June 2008 Implementers Meeting
- Revision will be made to the existing full guidelines, to be published in a future edition of *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach.*
- The above will also be made available as on-line, downloadable publications on the WHO website.

Paediatric Antiretroviral Dosing

The meeting participants approved the work, tables, tools and recommendations reported from the WHO Paediatric ARV Working Group.
http://www.who.int/hiv/events/paediatricmeetingreport.pdf

The TRG requested the working group to review or develop the following:

- additional data on dosing of Efavirenz for young children and infants;
- dosing for lopinavir/ritonavir for the group under six months and five kilograms, based on a target dose of 300mg/m2

Dosing for infants needs to be provided to support these revised recommendations and the Technical Reference Group requested the Paediatric ARV Working Group to undertake this work urgently.

New formulations for infants and children recognized to be urgently required to be able to implement these recommendations were:

- Lopinavir/ritonavir sprinkles (50/12.5mg)
- Atazanavir/ritonavir (heat stable)
- Ritonavir (solid, heat stable forms)

Dissemination and Implementation

- The summary of revised recommendations will include figures for the key recommendations.
- IMAI, IMCI and operational manuals need to be updated to reflect the revised recommendations.
- The WHO HIV department (Headquarters) should inform WHO regional and country representatives of these revised recommendations.
- The WHO HIV department (Headquarters) should inform key implementing partners, stakeholders and professional groups affiliated to child health and paediatric HIV.
- Presentations at Implementers Meeting in Kampala and the upcoming IAS conference in Mexico should be organized.
- Technical support to help countries adopt and adapt the revised guidelines will be provided and/or facilitated by WHO in collaboration with various partners.

Additional WHO Recommendations requiring review/revision

- HIV treatment recommendations for infants and children co-infected with tuberculosis.
- Criteria for recognition of treatment failure and switching of antiretroviral therapy regimens
- Revision of existing recommendations for the use of BCG in HIV-exposed infants. (This area of work is coordinated by the WHO department of Immunization, Vaccines and Biologicals.)
- Specific recommendations on the management of HIV and viral hepatitis co-infection in children.

Outstanding Issues for further research:

- Studies evaluating treatment approaches for HIV infected infants who have been exposed to PMTCT antiretrovirals are needed, including whether treatment, once started, can be interrupted.
- Adherence in infants starting early antiretroviral therapy
- Incidence of IRIS with early therapy
- Pharmacokinetic studies in infants under 6 months for first line ARVs lopinavir/ritonavir.
- Cost effectiveness of testing and treatment approaches
- Strategies for retesting and evaluation of infant testing algorithms
- Algorithms and approaches to presumptive diagnosis of HIV in infants;
- Optimum timing and efficacy of initiation of cotrimoxazole prophylaxis in infancy
- Role and reliability of HIV RNA using dried blood spots (DBS) for infant diagnosis
- Disease progression and treatment responses in older infants infected through breastfeeding

New products or technologies required:

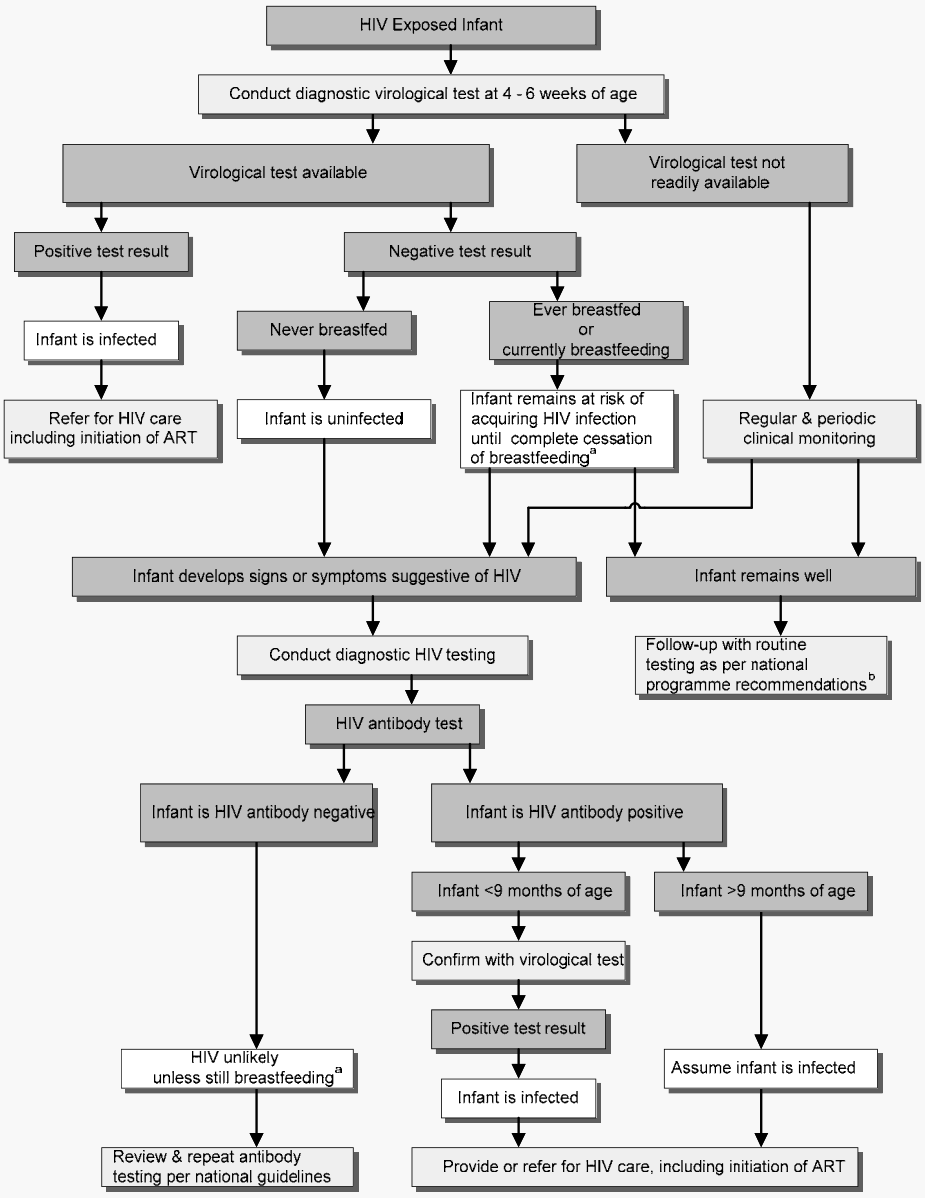
- Improved heat stable formulations of protease inhibitors
- Rifabutin and isoniazid formulations to improve co-treatment and co-management of tuberculosis in infants and young children with HIV
- Point of care viral diagnostics

Technical assistance, tools and advocacy required:

- Document and describe effective systems that ensure HIV virological test results are made available at the facility level in a timely manner.
- Develop plans to identify sources of technical assistance for the timely update and dissemination of national HIV policies, strategies and guidelines which incorporate these latest recommendations.
- Price reductions for second line medicines and AZT-based fixed dose combinations (FDCs).
- Defined care package for infants initiating early antiretroviral therapy (an initial draft will be included as an annex based on CHER study protocols and existing WHO guidelines)
- Updated ARV dosing guidance for infants under 6 months of age

Annex 1
Summary Figures for Key Recommendations

Figure 1: Testing Sequence for Inital and Subsequent Visits of HIV Exposed Infant



a The risk of HIV transmission remains as long as breastfeeding continues
b Usually HIV antibody testing from 9-18 months of age

Figure 2: Initiating ART for Infants and Children

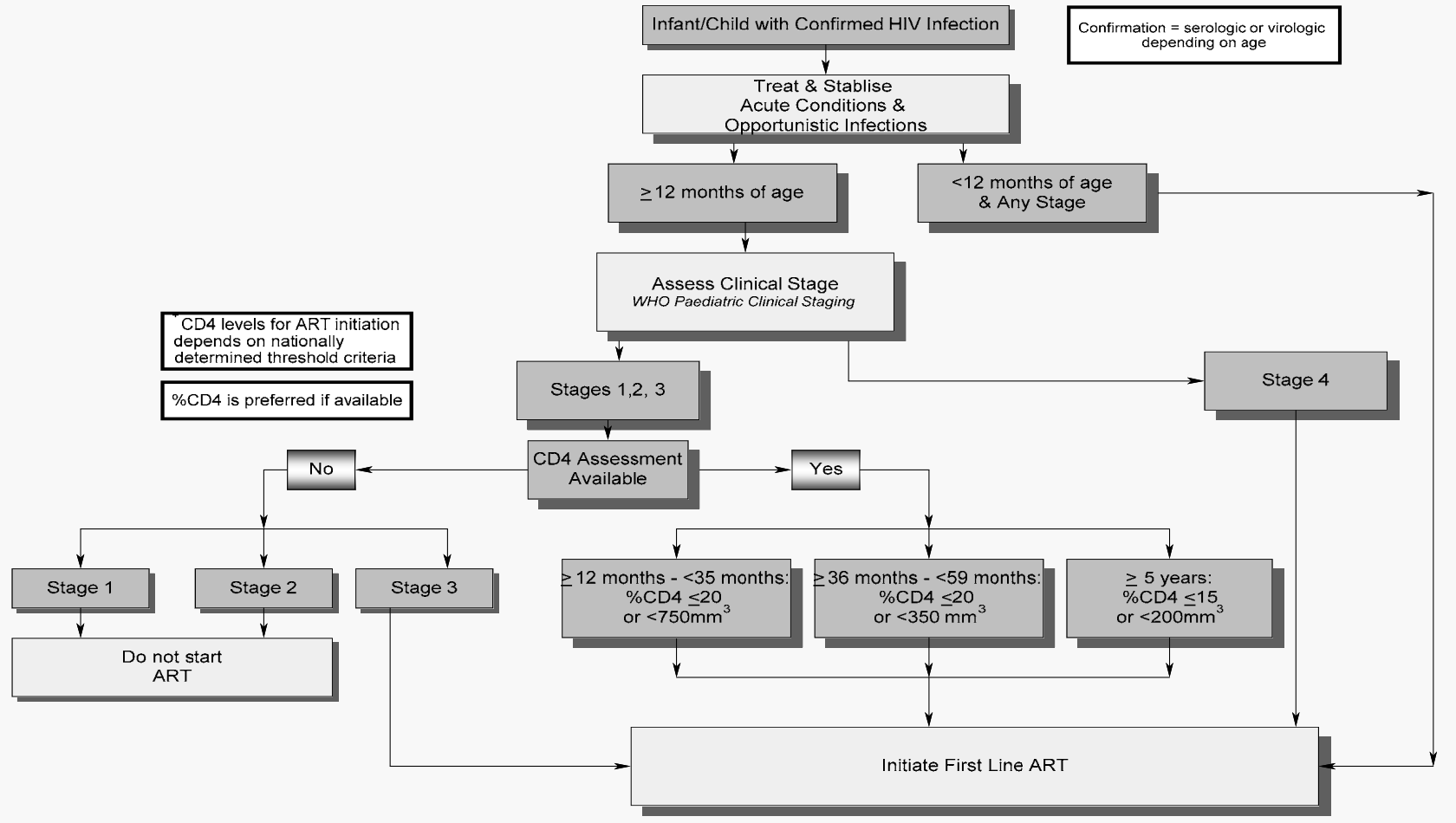
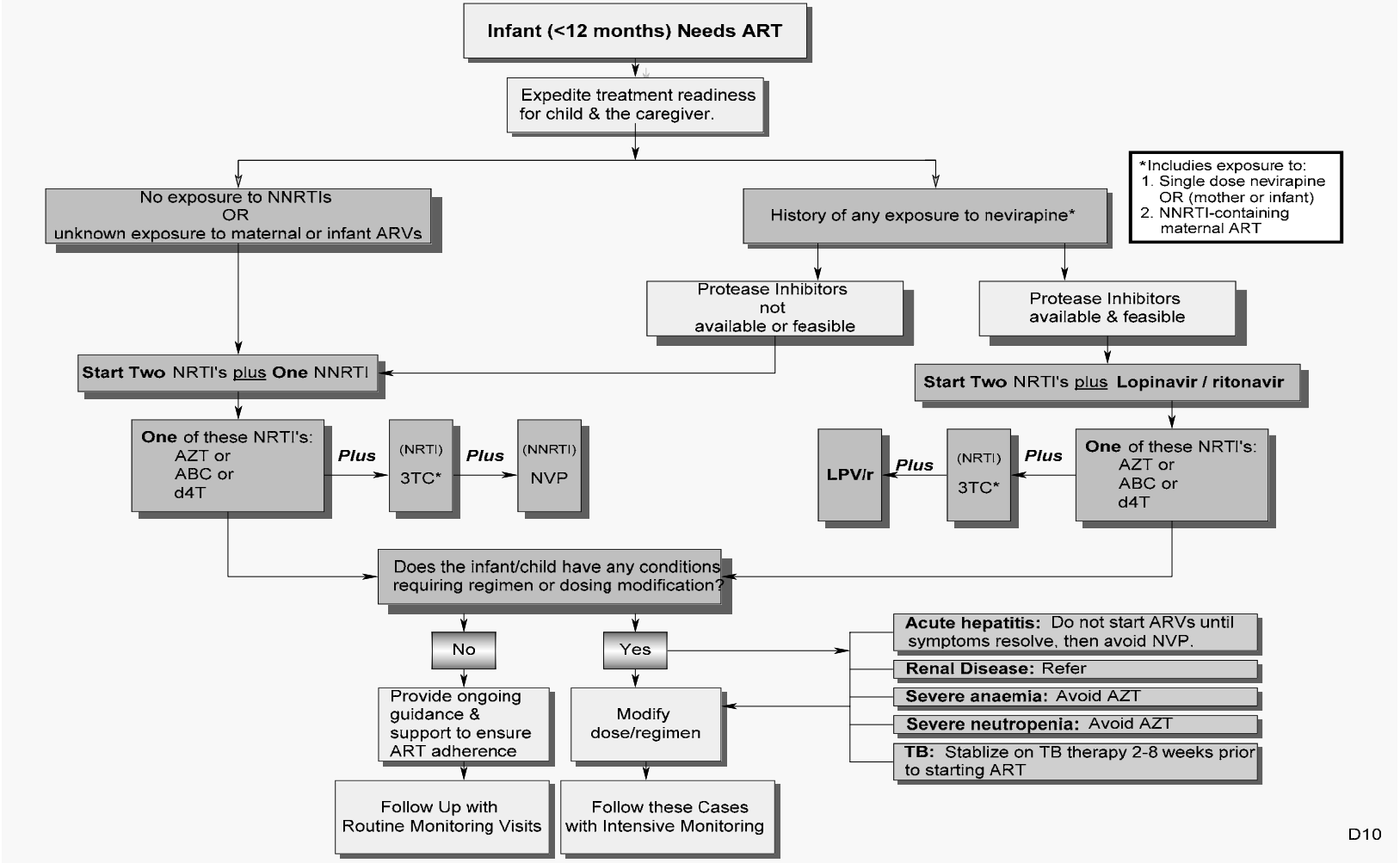


Figure 3: First Line ARV Treatment Regimens for Infants



Annex 2

Summary of Evidence & Risk Benefit Analyses

A. WHEN TO TEST

1. RECOMMENDATION:
Infants known to be exposed to HIV should have a virological test (HIV nucleic acid test) at 4-6 weeks of age or at the earliest opportunity for infants seen after 4-6 weeks.

STRONG RECOMMENDATION

Note: Testing at this time (4-6 weeks of age) will identify >95% of infants infected intra- and peripartum. However, some flexibility in implementation of this recommendation may be required based on current national or local postpartum and infant follow-up practices and service configuration. Delaying testing beyond this time will put HIV infected infants at risk of disease progression and death.

Note: If virological testing is not available, presumptive clinical diagnosis in accordance with nationally defined algorithms will be required.

2. RECOMMENDATION:
Urgent HIV testing is recommended for any infant presenting to health facilities with signs, symptoms or medical conditions that could indicate HIV.

STRONG RECOMMENDATION

Note: In this situation, infants should initially be tested using HIV antibody testing, and positive HIV antibody results confirmed by virological testing wherever possible.

3. RECOMMENDATION:
All infants should have their HIV exposure status established at their first contact with the health system, ideally before 6 weeks of age.

STRONG RECOMMENDATION

Note (a): In most cases infant HIV status will be established by asking the mother, by checking the child's and/or mother's health card, or by requesting a history of maternal HIV testing in pregnancy, labour or the postpartum period.

Note (b): while the TRG felt this was strong recommendation they also recognised that countries may choose to identify circumstances or settings where this recommendation may need modification, based on HIV prevalence.

4. RECOMMENDATION:
Infants under 6 weeks of age, of unknown HIV exposure status and in settings where local or national antenatal HIV seroprevalence is greater than 1%[a], should be offered maternal or infant HIV antibody testing[b] and counselling in order to establish exposure status.

CONDITIONAL RECOMMENDATION (Context Specific)

Note (a): Countries should determine prevalence thresholds and other circumstances where this recommendation should be followed.

Note (b): Nationally or internationally approved rapid HIV antibody tests may be used.

Table 1: Summary and strength of recommendations for provider initiated diagnostic HIV testing in infants

Population	HIV exposure unknown -well infant	Well infant Unknown Exposure Specified high HIV settings	HIV-exposed infants	Any signs/ symptoms suggestive of HIV
Recommendation	Ask all about HIV Exposure	Ensure /maternal/ infant testing within first 6 weeks at first contact with health system	Virological testing at 4-6 weeks of age	Urgent age appropriate test for all
Strength	STRONG	CONDITIONAL (ANC prevalence >1% and other selected settings)	STRONG	STRONG

Table 2. Summary of testing methods for early infant diagnosis

Test	HIV DNA nucleic acid testing at 6 weeks of age		HIV RNA NAT at 6 weeks of age		Ultra sensitive p24 antigen	
Specimen	Plasma, serum	DBS (whole blood)	Plasma, serum	DBS (whole blood)	Plasma, serum	DBS (whole blood)
Strength of recommendation	Strong	Strong	Strong	Need Research	Conditional (for review)	Need Research

Table 3: GRADE profile for the use of HIV DNA PCR for diagnosis of HIV infection in infants.

Question: Should HIV infection in infants be diagnosed performing an HIV DNA PCR test at 4-6 weeks?							
Population group: infants exposed to HIV (i.e.<18 months infants born to an HIV positive mother)							
Intervention: HIV DNA PCR at 4-6 weeks							
Comparator: HIV diagnosed by HIV culture or HIV antibody testing after 18 months of age							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
Outcome: **SENSITIVITY** (282/306) 92,15 [89,13-95,16] CI 95%							
5 studies*[*] (306 infected among infants 1611)	VALID ACCURACY Cohort studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious Indirectness[3] **-1**	No serious imprecision	No Publicati on bias	**MODERATE QUALITY**
Outcome: **SPECIFICITY** (1298/1305) 99,46 [99,85-99,06] 95% CI							
5 studies* (306 infected among infants 1611)	VALID ACCURACY Cohort studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious Indirectness[4] **-1**	No serious imprecision		**MODERATE QUALITY**
Outcome: **POSITIVE PREDICTIVE VALUE** (282/289) 97,57 [95,79-99,34] 95% CI							
5 studies* (306 infected among infants 1611)	VALID ACCURACY Cohort studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious Indirectness[3] **-1**	No serious imprecision		**MODERATE QUALITY**
Outcome: **NEGATIVE PREDICTIVE VALUE** (1298/1322) 98,18 [97,45-98,90] 95% CI							
5 studies* (306 infected among infants 1611)	VALID ACCURACY Cohort studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious Indirectness[4] **-1**	No serious imprecision		**MODERATE QUALITY**

1. According to this hecklist: is the population of interest represented? Are patients with an uncertain diagnosis included? Are patients consecutively enrolled? is there an appropriate comparison with a gold standard test?
2. According to QUADAS assessment [29]
3. Indirect population: HIC vs MIC/LIC and Indirect comparison: Operational characteristics or operator are not always standardized or specified
4. Indirect population: patients considered were all not breastfed and Indirect comparison: Operational characteristics or operator not always standardized or specified
* [30-34]

Table 4: GRADE profile for the use of HIV RNA NAT for diagnosis of HIV infection in infants.

Question: Should HIV infection in infants be diagnosed performing an HIV RNA NAT test at 4-6 weeks?							
Population group: infants exposed to HIV (i.e.<18 months infants born to an HIV positive mother)							
Intervention: HIV RNA NAT at 4-6 weeks							
Comparator: HIV diagnosed by HIV culture or DNA PCR or HIV antibody testing after 18 months of age							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factor**	**QUALITY RANK**
Outcome: Sensitivity (197/201) 96.5% (93,86-99,04) 95% CI							
4 studies** (201 infected over 837 infants tested)	VALID ACCURACY Cohort studies[1] **4**	No serious limitations[2]	No serious inconsistency	Serious Indirectness[3] **-1**	No serious imprecision		**MODERATE QUALITY**
Outcome: Specificity (628/636) 98.7% (97,81-99,58) 95% CI							
4 studies** (201 infected over 837 infants tested)	VALID ACCURACY Cohort studies[1] **4**	No serious limitations[2]	No serious inconsistency	Serious Indirectness[3] **-1**	No serious imprecision		**MODERATE QUALITY**
Outcome: Positive Predictive Value 96,03 (93,37-98,72) CI 95%							
4 studies** (201 infected over 837 infants tested)	VALID ACCURACY Cohort studies[1] **4**	No serious limitations[2]	No serious inconsistency	Serious Indirectness[4] **-1**	No serious imprecision		**MODERATE QUALITY**
Outcome: Negative Predictive Value 99,21 (98,52-99,89) CI 95%							
4 studies** (201 infected over 837 infants tested)	VALID ACCURACY Cohort studies[1] **4**	No serious limitations[2]	No serious inconsistency	Serious Indirectness[4] **-1**	No serious imprecision		**MODERATE QUALITY**

1. According to this checklist: is the population of interest represented? Are patients with an uncertain diagnosis included? Are patients consecutively enrolled? is there an appropriate comparison with a gold standard test?
2. According to QUADAS assessment [29]
3. Indirect population because different PMTCT regimen used, the majority was not breastfed, HIC vs LIC/MIC and Indirect comparison: different HIV subtypes and different kit used (different thresholds and specimen handling)
4. Indirect population because different PMTCT regimen used, the majority was not breastfed, HIC vs LIC/MIC (different disease prevalence) and indirect comparison: different HIV subtypes and different kit used (different thresholds and specimen handling)

**[34,37-39]

Note: Other studies were reviewed to evaluate evidence concerning testing [35,36,40-42], but twere not characterized as "accurate" and are therefore not included in this table.

Table 5: GRADE profile for the use of HIV DNA PCR on DBS samples for diagnosis of HIV infection in infants

Comparison: Is HIV DNA PCR using DBS reliable for HIV diagnosis in infants?							
Population group: infants exposed to HIV (i.e.<18 months infants born to an HIV positive mother) in Low/Middle Income countries							
Intervention: HIV DNA PCR testing on DBS support at 4-6 weeks							
Comparator: HIV diagnosed by DNA PCR in plasma samples							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
Outcome: **SENSITIVITY** 94.35% CI 95% (92.64-96.05							
6[3] (637 infected among 2097 tested)	Valid accuracy studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious indirectness[3] **-1**	No serious imprecision	Publication bias?	**LOW MODERATE QUALITY**
Outcome: **SPECIFICITY** 98.00% CI 95% (97.42-98.57)							
6[3] (637 infected among 2097 tested)	Valid accuracy studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious indirectness[3] **-1**	No serious imprecision	Publication bias?	**LOW MODERATE QUALITY**
Outcome: **POSITIVE PREDICTIVE VALUE** 93.68% CI 95% (91.89-95.46)							
6[3] (637 infected among 2097 tested)	Valid accuracy studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious indirectness[3] **-1**	No serious imprecision	Publication bias?	**LOW MODERATE QUALITY**
Outcome: **NEGATIVE PREDICTIVE VALUE** 98.22% CI 95% (97.67-98.76)							
6[3] (637 infected among 2097 tested)	Valid accuracy studies[1] **4**	No Serious limitations[2]	No serious inconsistency	Serious indirectness[3] **-1**	No serious imprecision	Publication bias?	**LOW MODERATE QUALITY**
Outcome: **CORRELATION**							
No studies available	nv	nv	nv	nv	nv		**nv**

1. According to this checklist: is the population of interest represented? Are patients with an uncertain diagnosis included? Are patients consecutively enrolled? is there an appropriate comparison with a gold standard test?
2. Assessed with QUADAS [29]
3. Indirect population: Different PMTCT regimen used, the majority not BF, MIC/LIC vs HIC. Indirect comparison: HIV subtype, different kit used, half had in house DNA PCR, not reproducible.

* See references [43-48]

Table 6: GRADE profile for the use of HIV RNA NAT on DBS samples for diagnosis of HIV infection in infants

Comparison: Is RNA NAT using DBS samples reliable to diagnose HIV (infants)?							
Population group: infants exposed to HIV in Low/Middle Income countries							
Intervention: HIV RNA NAT ON DBS							
Comparator: HIV diagnosed by RNA NAT in plasma samples							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
Outcome: **SENSITIVITY** 81.91% CI 95% (78.01-85.80)							
4* (376 positive specimens among 992 specimens)	No Valid accuracy studies[1] **2**	No serious limitations[1]	No serious inconsistency	Serious indirectness[3] **-1**	Serious imprecision[4] **-1**		**VERY LOW QUALITY**
Outcome: **SPECIFICITY** 89.44% CI 95% (87.01-91.86)							
4* (376 positive specimens among 992 specimens)	No Valid accuracy studies[1] **2**	No serious limitations[1]	No serious inconsistency	Serious indirectness[3] **-1**	Serious imprecision[4] **-1**		**VERY LOW QUALITY**
Outcome: **POSITIVE PREDICTIVE VALUE** 82.57% CI 95% (78.73-86.40)							
4* (376 positive specimens among 992 specimens)	No Valid accuracy studies[1] **2**	No serious limitations[1]	No serious inconsistency	Serious indirectness[3] **-1**	Serious imprecision[4] **-1**		**VERY LOW QUALITY**
Outcome: **NEGATIVE PREDICTIVE VALUE** 89,01 CI 95% (86.54-91.47)							
4* (376 positive specimens among 992 specimens)	No Valid accuracy studies[1] **2**	No serious limitations[1]	No serious inconsistency	Serious indirectness[3] **-1**	Serious imprecision[4] **-1**		**VERY LOW QUALITY**
Outcome: **CORRELATION** (0.85-0.98)							
3** (205 positive specimens among 992 specimens)	No Valid accuracy studies[1] **2**	No serious limitations	No serious inconsistency	Serious indirectness[3] **-1**	Serious imprecision[5] **-1**		**VERY LOW QUALITY**

1. According to this checklist: is the population of interest represented? Are patients with an uncertain diagnosis included? Are patients consecutively enrolled? is there an appropriate comparison with a gold standard test?
2. Not a common standardized comparator across the studies (assessed according QUADAS)
3. Indirect comparison: different kit used, and different thresholds of detectability
4. Good sample size, but events <300 and wide CI.

* [51-54]

** [49,50,52]

Table 7: Summary of risk and benefits assessment discussed by the TRG working groups

Recommendation: Infants known to be exposed to HIV should have a virological test at 4-6 weeks of age, or at the earliest opportunity if older than 4-6 weeks.		
Population: Infants (≤12 months) born to HIV positive mothers		
Intervention: Early viral diagnostic testing		
Factor	**Decision**	Explanation
Quality of evidence	Strong	Supported by: Natural history and mortality data (GRADE Low) CHER study 75% reported reduction in mortality with early diagnosis and immediate treatment.(GRADE Moderate) Viral testing performance at 4-6 weeks >95% of sensitivity and specificity (GRADE Low)
Benefits or desired effects	Strong (Benefits outweigh risks)	Early diagnosis Early treatment with resultant reduction in morbidity and mortality Clarify choice of feeding
Risks or undesired effects		Issue of false positive and false negative test results Child might not be retested even if breastfed Lack of access to Virological testing Infants may be tested but unable to access ART Other aspects of child health programme may suffer
Values and preferences	Strong	Denial and stigma enhanced by identification of HIV in infant Neglect of child based on test result. Ethical obligation to identify and treat early if failed to prevent transmission
Costs	Strong (despite overall increase in cost)	Increased by: Required laboratory equipment, supplies, reagents, logistic support Training, personnel, counsellors, transport Longer time on treatment Emotional costs for families and staff Reduced by: Reduced morbidity costs i.e reduction of hospitalizations, OI diagnosis and treatment (when treated) costs. Increased productivity of parents Unit cost for per test decreases with increased numbers of specimens processed
Feasibility		Limited capacity to systematically perform viral testing turnaround time of results Need for repeat testing in BF populations (required strategy appropriate to setting) If included in EPI package may enhance 6 week visit as current point of contact. Data from country programme show feasibility and expansion of DBS testing. ANC and maternal HIV testing often at very low levels of health systems, integration of PMTCT/MCH and ART services challenging High volume testing needed as ANC HIV testing is expanded
Overall ranking of recommendation	For HIV exposed infants virological testing at 4-6 weeks of age **STRONG** When HIV exposure is unknown, antibody testing followed by virological testing if appropriate **CONDITIONAL**	

B. WHEN TO START ANTIRETROVIRAL THERAPY

5. RECOMMENDATION:
All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage.

STRONG RECOMMENDATION

Note: Initiation of antiretroviral therapy may be delayed for an asymptomatic infant where HIV is diagnosed at or over 11 months of age, if the infants' percent CD4 is above 25.

6. RECOMMENDATION:
Where virological testing is not available, infants under 12 months of age with clinically diagnosed presumptive severe HIV should start antiretroviral therapy. Confirmation of HIV infection should be obtained as soon as possible.

STRONG RECOMMENDATION

Improved clinical and laboratory based algorithms to support this recommendation are expected and are likely to refine the specificity of this recommendation; therefore it should be reviewed within the next two years.

7. RECOMMENDATION:
For children age 12 months or older, clinical and immunological thresholds should be used to identify those who need to start antiretroviral therapy.

STRONG RECOMMENDATION

Table 8: Summary and strength of recommendation for when to start ART

POPULATION	**< 12 mo Confirmed HIV**	**≤ 12 mo Presumptive * severe HIV**	**1- 4 yrs**	**≥ 5yrs**
START ART	All with confirmed HIV regardless of clinicial/CD4	All	Clinical or immunological criteria	Clinical or immunological criteria
Strength of Recommendation	Strong	Strong review within 2 years	Strong	Strong

*****Presumptive diagnosis of severe HIV may need to be made for infants and children under 18 months of age who have positive antibody testing and symptoms suggestive of HIV, where virological testing is not available.

Table 9: GRADE profile for early versus deferred ART in infants with HIV

Comparison:	**EARLY vs DEFERRED ANTIRETROVIRAL TREATMENT IN INFANTS (≤ 1 YEAR)**						
Outcome: EARLY MORTALITY (<1ST) YEAR							
Population group: HIV INFECTED INFANTS (≤1 YEAR)							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
2[*] (440 infants)	RCT	Minor Limitations[1]	No Serious inconsistency	Serious undirectness[2]	No Serious imprecision[3]		**3 MODERATE QUALITY**
Outcome: **LATE MORTALITY (<5th) YEAR**							
5[**] (616 infants)	Observational	Serious Limitations[4]	No serious inconsistency	Serious undirectness[5]	Good sample sizes		**1 VERY LOW QUALITY**
Outcome: **DISEASE PROGRESSION**							
2 (440 infants)	RCT	Minor Limitations[1]	No Serious inconsistency	Serious undirectness[2]	No Serious imprecision[3]		**3 MODERATE QUALITY**
Outcome: **SEVERE/LIFE THREATENING EVENTS**							
2[*] (440 infants)	RCT	Minor Limitations[1]	No serious inconsistency[6]	No serious indirectness[7]	Serious imprecision[8]		**3 MODERATE QUALITY**

1. Prendergast study was not blinded (minor limitation, not downgraded).
2. Indirect population: 80% in CHER and 60% in Prendergast study were not breastfed. Indirect comparison: symptomatic children have been included in the early treatment group.
3. The number of events is small (<300), however considering the specific outcome we don't downgrade for that.
4. All but one was not designed to assess the main question: the majority of the observational studies available were not designed to compare "early initiation" vs. "clinical-immunological guided initiation".
5. Indirect population because there is very different background mortality and feeding approach in low/middle income countries LIC/MIC compare with high income countries HIC.
6. No life-threatening adverse events are reported in early or deferred arms.
7. Prendergast study: 4 class regimen. CHER study: PI-based regimen.
8. CHER study reports very few major adverse events, no detail available.

* References: 1, 2,

**References: 7-9, 12-13

Table 10: Summary of risk and benefits assessment discussed by the TRG working groups

Recommendation: All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage.		
Population: Infants (≤1year) with confirmed HIV infection **HIV infection**: Confirmed by viral testing (HIV DNA, or HIV RNA or Up24 Ag)		
Intervention: Immediate ART		
Factor	**Decision**	Explanation
Quality of evidence	Strong	Quality of evidence is moderate for a highly significant critical outcome: early mortality Highly supported by comparative and non-comparative observational studies as well as field experience Further trials unlikely to gain ethical approval CHER is context specific, reports mortality on short term follow up in largely non-breastfed infants. Benefits may therefore not be generalizable to breastfeeding infants or infants infected through breastfeeding
Benefits or desired effects	Strong (Benefits outweigh risks)	Decrease in early mortality Decrease morbidity and disease progression (especially reduction in CNS impairment and hospitalizations) and possibly IRIS Improvement in growth and development Reduction in lost to follow up/better retention Less intense pre-ART follow up required Drives better PMTCT at national policy level
Risks or undesired effects		Development of resistance early May result in early switch to 2nd line (previous ART exposure in PMTCT, Pk issues, difficult long term adherence) Greater time on ART Longer term toxicity Unnecessary exposure to treatment in long term non progressors. Need to establish viral diagnosis may lead to less emphasis being placed on clinical algorithms
Values and preferences	Strong	Families concern about treating infants Health care worker fears about managing infants Implications for disclosure of maternal status **But….** Strong ethical obligation Care givers will like immediate ART Allows a new focus on reaching and managing infants
Costs	Strong (likely to increase cost but may be offset by other cost savings)	Reduced by: Mortality reduced Morbidity related costs (hospitalizations, OIs diagnosis, treatment and prevention etc..)Lab monitoring pre-ART no longer necessary to start ART Linkage with PMTCT sites and activities Families cost (less hospitalization, less sick, parents can work and earn money) Life long savings if child survives to adulthood Increased by: Greater need for Virological tests ART life long costs (related to choice of starting regimen) Strengthening of infrastructure to deliver care Additional man power (HCW specifically trained within labs and clinics) Increased drugs delivery costs (delivery and storage of infants formulations)
Feasibility	Conditional to country setting	Easier to start all if no requirement for CD4 Access to infant diagnosis still limited in many countries, scale up is challenging EID programs need more capacity on the ground Delays in getting results of virological tests Need for increased human resources (esp. lab staff) Need for strong linkages between PMTC and ART clinics May become feasible if less MTCT transmission Availability of infant formulations Need infrastructure to do quick counselling for mothers Need for integration of services…family based care
Overall ranking of recommendation	STRENGTH OF RECOMMENDATION **STRONG**	

C. WHAT TO START

8. RECOMMENDATION:
For HIV infected infants with no exposure to maternal or infant non-nucleoside reverse transcriptase inhibitors, or whose exposure to maternal or infant antiretrovirals is unknown, standard nevirapine-containing triple therapy should be started.

STRONG RECOMMENDATION

9. RECOMMENDATION:
For HIV infected infants with a history of exposure to single dose nevirapine or non-nucleoside reverse transcriptase inhibitor containing maternal antiretroviral therapy or preventive antiretroviral regimens, a protease inhibitor-based triple antiretroviral therapy regimen should be started. Where protease inhibitors are not available, affordable or feasible, nevirapine-based therapy should be used.

CONDITIONAL RECOMMENDATION (Context specific & time limited)

Note: While the Technical Reference Group felt the evidence and risk-benefit analysis warranted a strong recommendation, they also recognized that currently, in many resource limited settings, lopinavir/rotanivir is not available, affordable, or, due to the requirements for refrigeration, not feasible for use. In addition, the use of lopinavir/rotanivir in a first line regimen compromises the potential to construct a potent second line regimen. On-going studies are likely to provide information that may result in modification of this recommendation.

Table 11: Summary and strength of recommendation for what ART regimens to start

POPULATION	**Up to 12 months**	**Up to 12 months**	**1- 4 years**	**≥ 5 years**
START ART	PMTCT/NVP exposure : PI-regimen	No PMTCT exposure: NVP-regimen	NVP/EFV + 2NRTI	NVP/EFV + 2NRTI
Strength of recommendation	Conditional	Strong	Strong	Strong

Table 12: GRADE profile of evidence for nevirapine versus protease inhibitor-based first line regimens in infants with HIV

Comparison:	**NVP-BASED vs PI-BASED ANTIRETROVIRAL REGIMENS IN INFANTS (< 1 YEAR)**						
Outcome: EARLY MORTALITY (<1ST) YEAR							
Population group: HIV INFECTED INFANTS (<1 YEAR)							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
10[a] (1190 infants)	Observational	Serious Limitations[1]	No serious inconsistency	Serious Uncertainty[2]	No serious imprecision		**1 VERY LOW QUALITY**
Outcome: **LATE MORTALITY (<5th YEAR)**							
4[b] (372 infants)	Observational	Serious Limitations[1]	No serious inconsistency	Serious Uncertainty[2]	No serious imprecision		**1 VERY LOW QUALITY**
Outcome: **ADVERSE EVENTS**							
6[c] (770 infants)	Observational	Serious Limitations[1]	No serious inconsistency	Serious Uncertainty[3]	Serious Imprecision[4]		**1 VERY LOW QUALITY**
Outcome: **DETECTABLE VIRAL LOAD**							
8[d] (828 infants)	Observational	Serious Limitations[1]	No serious inconsistency[5]	Serious Uncertainty[6]	Serious Imprecision[4]		**1 VERY LOW QUALITY**

1. None of the studies available designed to compare NVP-based vs PI-based regimens in infants.
2. Indirect population: the majority of the studies have been performed in high income settings-HIC (in low and middle income countries (LIC/MIC) very different mortality background as well as different breastfeeding patterns).
3. Different ART components have been considered within the studies.
4. Small number of events.
5. No serious inconsistency, only PENTA 7 reports incomplete viral suppression.
6. Indirect comparison: different ART components have been considered within the studies and different thresholds were defined for viral suppression and viral failure.

a. See references: 1, 2, 4-6, 12, 14, 15, 17, and 18.
b. See references: 11-12, 15, and 16.
c. See references: 1, 2, 4-6, and 16.
d. See references: 1, 2, 4-6, 12, 16, 18 and 19

Table 13: Summary of risk and benefits assessment discussed by the TRG working groups.

Recommendation: For HIV infected infants with no exposure to maternal or infant non-nucleoside reverse transcriptase inhibitors, or whose exposure to maternal or infant antiretrovirals is unknown, standard nevirapine-containing triple therapy should be started.		
Population: HIV infected infants (< 12 months) **HIV infection:** Confirmed by viral testing, or clinical diagnosis of presumptive severe disease		
Intervention: Combination ART using 2NRTI + NVP		
Factor	**Decision**	**Explanation**
Quality of evidence	Weak	Sufficient evidence of efficacy of NVP based regimen and PI based regimens mostly from studies in older infants Insufficient evidence of superiority of PI regimen over NVP based regimen (GRADE: very low)
Benefits or desired effects	Strong (Benefits outweigh risks)	Reduce complexity of treatment algorithm Better adherence compared with PI Reduced long term toxicity Dosing for infants is well established FDC available More cost effective approach to use NVP containing regimen in infants that are likely not to have NVP resistance
Risks or undesired effects		Low genetic barrier to resistance Poor viral suppression in those exposed to NNRTI Issue of TB co-treatment
Values and preferences	Strong	Using a regimen already known makes it easier for staff and care takers.
Costs	Strong	Avoid unnecessary use of more expensive regimen in HIV exposed infants not exposed to ARVs. PI regimen 95% more expensive than a NVP based regimen as an FDC, and 50% more expensive than a NVP regimen in liquid formulations. Reduced cold chain/delivery costs for NVP regimens
Feasibility	Strong	Easily available simplifying procurement and distribution. No need for cold chain Existing recommendations already implemented Majority of infants currently diagnosed do not have exposure to MTCT ARV
Overall ranking of recommendation	STRENGTH OF RECOMMENDATION **STRONG**	

Table 14: GRADE profile of evidence of ART efficacy post exposure to nevirapine

Comparison: ANTIRETROVIRAL TREATMENT EFFICACY IN NVP-EXPOSED vs NVP-UNEXPOSED INFANTS (< 12 months)							
Intervention: ART							
Outcome: RESPONSE TO ART REGIMEN determined by proportion on ART with no evidence of virological failure at 6 months or more into first line ART regimen							
Population group: HIV INFECTED INFANTS (<12 months) PREVIOUSLY EXPOSED to ARVs							
No of studies	**Design**	**Limitations**	**Consistency**	**Directness or generalisability**	**Imprecise or sparse data**	**Other factors**	**QUALITY RANK**
Outcome: DETECTABLE RESISTANCE							
16[a] (553 infants)	Observational[1]	Serious Limitations[2]	No serious inconsistency	No Serious Uncertainty	No Serious imprecision		**1 VERY LOW QUALITY**
Outcome: TREATMENT RESPONSE							
1[b] (30 infants)	Observational	No Serious Limitations	No Serious inconsistency	No Serious Uncertainty	Serious imprecision[3]		**0 VERY LOW QUALITY**

1. Recent meta analysis looked at 10 studies of which 3 are conference abstracts - none were designed as RCTs according the question defined.
2. Only one study reports a comparison between NVP exposure vs placebo
3. Small numbers

b. See reference: 18
a. See references: 18, 20, 22, 24, 25, 28

Table 15: Summary of risk and benefits assessment discussed by the TRG working groups.

Recommendation: For HIV infected infants with a history of exposure to single dose nevirapine or non-nucleoside reverse transcriptase inhibitor containing maternal antiretroviral therapy or preventive antiretroviral regimens, a protease inhibitor-based triple antiretroviral therapy regimen should be started. Where protease inhibitors are not available, affordable or feasible, nevirapine-based therapy should be used.		
Population: HIV infected infants (<12 months) with NNRTI exposure (mother or infant) **HIV infection:** Confirmed by viral testing, or clinical diagnosis of presumptive severe disease		
Intervention: Combination ART using 2NRTI+LPV/r		
Factor	**Decision**	**Explanation**
Quality of evidence	Weak	Acquisition of NVP resistance after NNRTI exposure (GRADE very low). Data show that nevirapine crosses into and is concentrated in breast milk. Direct and indirect data showing compromised response to NVP based regimens after NVP exposure.
Benefits or desired effects	Strong (Benefits outweigh risks)	Better efficacy and durability of first line therapy if all 3 drugs active Avoids potential for using therapy with only two active NRTI agents.
Risks or undesired effects		Long term toxicity not well known Intolerance more likely with PI: GI symptoms Limits options for second line therapy Difficult adherence Poor palatability of LPV/r PI therapy complicates treatment of TB. Dosing needs clarifications for infants under 6 month Increased complexity of treatment algorithms
Values and preferences	Strong	Many practitioners feel more confident using PI in face of possible resistance
Costs	Conditional (setting related)	LPV/r much more expensive than NNRTI Needs a liquid formulation more expensive Unlikely to be co-formulated with other drugs into an FDC
Feasibility	Weak	Conditional on LPV/r availability Logistic supply and storage more complex Cold chain requirements Palatability an issue with LPV/r LPV/r sprinkles may be an option in the future
Overall ranking of recommendation	STRENGTH OF RECOMMENDATION **CONDITIONAL** (context specific and time limited)	

Annex 3

THE GRADE APPROACH TO ASSESSMENT OF EVIDENCE

Table 1: Ranking the Quality of Evidence

Quality of evidence (summary score)	Study design	Lower if *	Higher if *
High (4)	Randomized trial or valid accuracy study for diagnostic tests	**Study quality:** -1 Serious limitations -2 Very serious limitations -1 Important inconsistency **Directness:** -1 Some uncertainty -2 Major uncertainty -1 Sparse or imprecise data -1 High probability of reporting bias	**Strong association:** +1 Strong, no plausible confounders, consistent and direct evidence +2 Very strong, no major threats to validity and direct evidence +1 Evidence of a dose response gradient
Moderate (3)			
Low (2)	Observational study or indirect accuracy studies for diagnostic tests		
Very low (1)			

* 1 = move up or down one grade (for example from high to intermediate)
2 = move up or down two grades (for example from high to low)

⊕⊕⊕⊕ High = Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕○ Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕ ○○ Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕○○○ . Very low = Any estimate of effect is very uncertain.

Limitations = include problems in study design, such as for RCTs, lack of blinding or allocation concealment, incomplete reporting, selective outcome reporting, or use of unvalidated outcomes measures.
Inconsistency = Differences exist in the direction and size of the effect across the studies.
Uncertainty = Indirect comparisons or indirect populations have been considered across the studies, and there may be compelling reasons to expect important differences in the size of the effect.
Validity = Patients participating in RCTs are assessed to have same risk and/or mortality as non enrolled patients in whom the intervention is expected to be required.

Table 2: QUADAS Checklist for Diagnostic Accuracy Studies

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

Table 3: Explanation of Risk and Benefits Assessment

Factor	**Comments**
Quality of the evidence	Higher the quality of the evidence the more likely a strong recommendation can be made
Balance between desired and undesirable effects	Larger the gap or gradient between these then more likely a strong recommendation will be made
Values, preferences	If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted by the patient, health care worker or health systems then it is more likely a weak recommendation will be made.
Cost	Higher the cost both financial and in terms of infrastructure, equipment or requirements, and more resource intensive requirements, then less likely to make a strong recommendation
Feasibility	Is the intervention possible and practical in the settings where greatest impact is likely to be attained or is being sought, the more feasible the intervention is the more likely a strong recommendation should be made.

Table 4: Explanation of WHO Strength of Recommendations

Strong	Conditional	Research
Implications: The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.	**Implications:** The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, however, it is only applicable to a specific group, population or setting, or new evidence may result in changing the balance of risk to benefit, or the benefits may not warrant the cost or resource requirements.	**Implications:** Further research is required before any recommendations can be made.
Policy makers: Policy makers can be confident that the recommendation can be adopted as policy in most situations.	**Policy makers**: Policy makers need to consider that in specific situations this recommendation should be followed and identify and develop directives that outline those specific situations, or policy makers need to determine if the potential benefits warrant the health system costs, or policy makers need to recognize that there is currently insufficient evidence to make a strong recommendation and that further research is likely to have a potential for reducing uncertainty about the effects of the intervention.	**Policy makers**: Research is needed before any recommendations or policy directive can be developed.
Clinicians: Most patients should receive the recommended course of action.	**Clinicians**: Clinicians need to recognize that the recommended course of actions is applicable to specific patient subsets, or for patients in specific situations where the recommended course of action is feasible, acceptable or appropriate or new evidence may become available that will modify or change this recommendation.	**Clinicians**: Research on the safety, efficacy or accuracy related to the intervention is required before it can be recommended for use in patients.
Patients: Most people in your situation would want the recommended course of action and only a small proportion would not	**Patients**: Patients need to recognize that this recommendation is not applicable to everybody, and that they need to consider whether they are likely to benefit from the intervention. or further evidence may become available which will better inform their personal decision making.	**Patients:** Research is needed before patients should consider this intervention, and participation in clinical trials should be considered.

Annex 4
SEARCH STRATEGY

Independent searches were conducted to address the key questions for review by the TRG. The search strategy aimed to find systematic reviews, clinical trials and multicenter studies from 1994-2008 addressing HIV diagnosis, initiation of ART in infants and treatment regimens used in infants.

Sites and search engines consulted, and the terms used for *When to Start Treatment* and *What to Start*:

Data Bases Searched:
Medline
Embase
BMJ Clinical Evidence
The Cochrane Library
Trip Database
SUM search
Bandolier
Institute for Clinical Systems Improvement
CROI 2005-2008 Abstracts
IAS conferences 2005-2007 Abstracts

Search Terms:
Paediatric or Children or Infants
HIV infection
Antiretroviral treatment
Highly active antiretroviral therapy
Individual Drug names

Selection Criteria:
WHEN TO START TREATMENT?
Infant subjects included
Infants well represented
Outcomes stratified according to age
Early antiretroviral treatment
Early vs deferred treatment initiation

WHAT TO START?
Infant subjects
Infants well represented
Outcomes stratified according to age
Early antiretroviral treatment
Specified ART regimen (single regimen studies, cohort studies including NVP and PI based regimens)

Results:
Studies Retrieved: 435 clinical trials, 9 meta-analyses, 152 RTC, 328 reviews, 257 multi-center studies.
Studies of Interest: 70

Research for evidence concerning *HIV Diagnosis and Testing* was conducted by the guideline working group for the *Recommendations on the Diagnosis of HIV Infection in Infants and Children, 2007* (publication pending). Sites and search engines consulted included:

Data Bases Searched:
American Family Physician
Bandolier
The Journal of Family Practice
BMJ Clinical Evidence
The Cochrane Library
SUMsearch
National Guideline Clearinghouse
Institute for Clinical Systems Improvement
TRIP Database
PubMed
CROI 2005-2008 Abstracts
IAS conferences 2005-2008 Abstracts

Search Terms:
HIV Infant diagnosis - Reviews and trials
HIV antibody seroreversion infants
HIV Viral load assays infants - Trials
HIV p24 antigen infants - Trials
DBS Infants - Trials

Annex 5

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Annex 6
MEETING AGENDA AND PRESENTATIONS
Chairperson: Agnes Mahomva

Day 1

09.00–09.20	Opening	**Dr Teguest Guerma**
	Background, purpose and expected outcome	**Charlie Gilks**
09.20-10.15	Update on WHO guidelines on guidelines Overview of existing WHO recommendations Overview of areas requiring review & revision	**Siobhan Crowley** presentation
	Status of National Guidelines	**Martina Penazzato** presentation
10.30–12.30	**Early infant treatment: When to start ART in infants?**	
	The CHER Study	**Mark Cotton** presentation
	Early virological suppression in HIV-infected African infants	**Andy Prendergast** presentation
	Perspectives from Botswana national programme	**Gabriel Anabwani** presentation
	Presentation and review of evidence tables	**Martina Penazzato** presentation
12.30–15.30	**Group Work**	
	Developing recommendations on when to start ART in infants & simplification of criteria to start ART Analysis of risk/benefit/feasibility/cost assessment Reports back from each of 4 break-out groups & discussion	**4 Group reports**
16.00 - 17.15	**When is optimum time to perform diagnostic virological testing for early treatment?**	
	Current WHO recommendations	**Siobhan Crowley** **Sally Girvin** presentation
	Mortality data from South Africa	**Mark Cotton** (confidential data)
	Review of modelling outputs	**Martina Penazzato** presentation

	Feasibility of national coverage for HIV early viral testing	
	1. Malawi	**Peter Kazembe** presentation
	2. Clinton Foundation work on EID	**Shaffiq Essajee** presentation

Day 2

08.30–08.35	Review of day 1	**Siobhan Crowley**
08.35–09.30	**What to start for infants needing ART?**	**Martina Penazzato**
	Review of evidence tables	presentation
09.30-10.15	**ARV Dosing for infants**	
	Review of ARV working group dosing recommendations	**Edmund Capparelli** presentation
	Costs and Availability of children's ARV's	**Francoise Renaud-Thery** presentation
10.30-12.30	**Group Work**	
	Group A: When to Test	**Group reports**
	Groups B & C: What to Start?	
	Risk/benefit/feasibility/cost assessment and develop recommendations for each	
13.15-14.45	Feedback from break-out groups	
14.45-16:30	Additional tools required to accompany guidelines	**Plenary discussion**
	Development of an implementation plan for introduction of revised guidelines	**Summary report**
	Adoption of revised recommendations	
	Identification of key research issues arising	
	Identification of other recommendations requiring review	
	Next steps	
16.30	Closing	

Annex 7

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