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Peer Review of Regional Paediatric Antiretroviral Treatment Guidelines

A Report
New Delhi, India, 4-5 May 2006

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Annexes

ACRONYMS

ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine
ART	Antiretroviral treatment
ARV	Antiretroviral
AZT	Azidothymidine (zidovudine)
CD4	CD4+ T Lymphocyte
CPR	Cotrimoxazole preventive therapy
CTX	Cotrimoxazole
d4T	Stavudine
EFV	Efavirenz
ENF	Enfuvirtide
FDC	Fixed dose combination
HIV	Human immunodeficiency virus
LDC	Least developed countries
NAP	National AIDS Programme
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside analog reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PCP	Pneumocystis jiroveci pneumonia (previoulsy pneumocystis carinii)
PCR	Polymerase chain reaction
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
SEA	South-East Asia
SEAR	South-East Asia Region
SEARO	South-East Asia Regional Office
STI	Sexually transmitted infection
TB	Tuberculosis
WHO	World Health Organization

1. Introduction

WHO Headquarters, Geneva, along with its global implementing partners, convened a technical consultation meeting in June 2005 to review the existing antiretroviral treatment (ART) guidelines for children. This consultation meeting reviewed the new data on and experiences with the scaling-up of paediatric ART and made recommendations for revision of current WHO guidelines. The consultation also considered the needs to harmonize the guidelines with adult ART guidelines and prevention of mother-to-child transmission (PMTCT) and to simplify them to facilitate implementation at the country level.

The aforesaid consultation agreed that stand-alone guidelines for children will help understand better the need to incorporate the treatment and care of infants and children to ongoing ART scaling-up activities. These guidelines are intended to provide technical guidance, primarily at the national level. In order to adapt global guidelines, regional consultations play an important role to identify regional priorities, resources available and sharing of experiences among countries in a similar situation.

The United Nations Children's Fund, Regional Office for South Asia (UNICEF/ROSA), and the World Health Organization, Regional Office for South-East Asia (WHO/SEARO) have undertaken a joint initiative to develop Regional Paediatric Antiretroviral (ART) Guidelines. A consultant assisted in producing the first draft of the guidelines. A meeting was organized in WHO's Regional Office in New Delhi, India, on 4-5 May 2006 to peer review the draft. The following is a brief account of the meeting.

The list of participants and the programme are at Annexes 1 and 2 respectively.

2. Inaugural session

2.1 Inaugural address by Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region

The inaugural address was delivered by Dr Myint Htwe, Director, Programme and Management, on behalf of Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia (SEA) Region.

The Regional Director welcomed the participants and highlighted some important aspects of the HIV/AIDS epidemic in the SEA Region. Although the overall HIV prevalence in the Region is still low, the absolute number of people living with HIV/AIDS is high due to the large population size. With an average 0.8% prevalence, the number of adults and children infected in 2005 was nearly 1 million.

The Regional Director informed that in 2005, an estimated 120 000 children were living with HIV/AIDS in the SEA Region. More than 30 000 need antiretroviral treatment (ART). Available information indicated that less than 1% infected children are receiving ART. He pointed out that ART has substantially changed the face of HIV infection in countries where it has been successfully introduced. HIV-infected infants and children survive to adolescence and childhood if managed and cared for appropriately. Dr Samlee stressed the need for adopting a public health approach to make ART for children a reality. One prerequisite for this is stand-alone paediatric ART guidelines. He hoped that the Regional Paediatric ART Guidelines would accelerate the scale-up of ART for children in national HIV/AIDS initiatives. In conclusion, he thanked UNICEF and the John A. Burns School of Medicine, University of Hawai at Manoa, and the Armed Forces Research Institute in Medical Sciences, Bangkok, for their collaboration with WHO SEA Region in producing the Regional Paediatric ART Guidelines.

2.2 Opening Remarks by Ms Cecilia Lotse, Regional Director, UNICEF South Asia Region

Ms. Cecilia Lotse, Regional Director, UNICEF Regional Office for South Asia (ROSA), expressed satisfaction at the collaborative effort between WHO/SEARO and UNICEF/ROSA which she hoped would make children the focus of the HIV/AIDS treatment agenda. She hoped that the outcome

of the meeting would ensure that evidence-based guidance does not remain confined only to tertiary-level hospitals and among specialists but also percolates to the health facilities and staff at the field level which children have access to. She also stressed the need for adopting a public health approach for paediatric HIV/AIDS to address issues related to care, treatment and support of children with HIV. At the global level, less than five per cent of the one million people in resource-poor settings who receive antiretrovirals are children. She pointed out that since children account for about 15% of the disease burden they should receive proportionate ART. UNICEF, UNAIDS and partners have launched the global "Unite for children, Unite against AIDS" campaign to highlight the issue of paediatrics HIV/AIDS. This campaign focuses on prevention of HIV infection among adolescents and young people; protection and support of children affected by HIV/AIDS; prevention of mother-to-child transmission (PMTCT), and provision of paediatric treatment and care. The outcome of the meeting would thus contribute towards fulfilling the objectives of the campaign, she said. She cited several examples of UNICEF-WHO collaboration in the area of paediatric HIV/AIDS and reiterated that WHO and UNICEF are committed to use their comparative expertise and capacities to support governments in this important area of child health.

3. Objectives

The objectives of the workshop were to:

(1) Peer review and finalize the draft Regional Paediatric Antiretroviral Treatment Guidelines.

(2) Reach a consensus on the next steps for roll-out of paediatric antiretroviral treatment in the Region.

4. Global situation of paediatric AIDS

Dr Chewe Luo, Senior Programme Adviser, HIV and Health, UNICEF Headquarters, New York, made a presentation on the global situation of paediatric AIDS.

The following major issues emerged:

(1) High resource settings have practically eliminated infections in children: there is an urgent need for a commitment to eliminating HIV infections among children towards an HIV-free and AIDS-free generation. (Abuja, Nigeria, PMTCT Meeting 2005).

(2) Only 7% of women in South-East Asia who need PMTCT interventions have access to services: only one country in South-East Asia (Thailand) has reached the 2005 UNGASS target to provide ARV prophylaxis to >40% of HIV-infected women.

(3) The major concerns were:

(a) Lack of attention to children;

(b) No treatment targets for children;

(c) Child focused national resources are limited, and

(d) Inadequate follow-up. Institutionalization of early diagnosis of paediatric HIV infection is a priority (clinical or laboratory) to get more mothers and their infants into the system.

(4) Estimates of the numbers of children in need of HIV treatment and care have been made based on the spectrum model of UNAIDS. 37 000 children (0-14 years) in South and South-East Asia are in need of ART, out of which 21 000 are below 18 months of age. 290 000 HIV-exposed children need cotrimoxazole (CTX) prophylaxis, a figure that could be reduced to 130 000 if early diagnosis was possible.

(5) HIV-exposed infants lost to follow-up from PMTCT and MCH centres: The experience from South Africa was alarming since 44% lost to follow-up at two weeks while 85% at 12 months. This has been reported from many other countries also**.**

(6) Optimizing identification of children and entry into chronic pediatric care and treatment, considering multiple entry points such as PMTCT, family voluntary screening, TB clinics, nutrition rehabilitation units, paediatric wards, other child programmes, schools and orphanages.

(7) A total of 43 ARV formulations are approved by WHO; 23 of those are products that can be used for children <13 years.

About 10% of 2005 global ARV procurement value has been spent on paediatric products.

(8) Children respond well to ART, even if severely immuno-compromized. A 75% survival rate among children on ART with CD4% less than 15 percent. CTX prophylaxis has shown to reduce mortality by 43%.

(9) Future direction:

(a) Galvanize accelerated responses, adapt and adopt.

(b) Continue to foster dialogue between key partners and with national governments to galvanise accelerated responses.

(c) Support establishment of population-based programme and national targets (cotrimoxazole and ART) to inform result-based programme design (need benchmarks and monitor progress).

(d) Support to country led evidence-based processes.

(e) Foster country-owned accountability systems.

5. Regional situation and issues

Dr Ying-Ru Lo, Regional Adviser in HIV/AIDS, WHO/SEARO, New Delhi, made a presentation on the regional situation and issues.

The following major issues emerged at the presentation:

(1) The South-East Asia Region has the second highest HIV prevalence in the world after sub-Saharan Africa.

(2) Though ART coverage has increased four-fold from December 2003 to December 2005, it is still very far from reaching 50% coverage. Thailand is the only nation close to complete coverage with 74% of people with advanced HIV infection receiving ART followed by Indonesia with 28%.

(3) 120 000 children are living with HIV in South-East Asia. Of them about 35 000 need treatment. However, less than five per cent are currently receiving treatment.

Barriers

The major hindrances to increasing ART coverage were:

- Lack of advocacy and attention to children (HIV contribution to under-five mortality is low).
- Lack of trained paediatric health-care professionals.
- Lack of affordable diagnostics.
- Lack of affordable ARV drugs for paediatric use.
- Lack of data for production and demand forecasting.

6. Establishing HIV infection in infants and children with confirmed HIV exposure

Dr Siobhan Crowley from the Department of HIV/AIDS, WHO headquarters, Geneva, made a presentation on the staging of HIV in children.

The following major issues emerged:

(1) Key recommendations that have been recently developed in relation to paediatric clinical care:

   (a) Recommendations on Cotrimoxazole (CTX) prophylaxis including when to start, correct dosage and when to discontinue.

   (b) Recommendations on diagnosing HIV in children including the use of virological tests, antibody tests and clinical diagnosis.

   (c) Recommendations on how to classify HIV infections in children including the use of clinical signs and symptoms, lab-based tests (%CD4) and how this translates into when to start and who needs ART.

   (d) Simplified recommendations for doses based on commonly available drugs.

(2) The need to have a health strategy for the "exposed child" along with the "treatment of confirmed diagnosis". The health strategy should reflect a

   (a) **Public health care approach:** Multiple entry and delivery points; integrated care and decentralized delivery; family friendly care; chronic disease approach involving clinical care teams; and simplified and standardized comprehensive package of care.

   (b) **Life course approach**: Public health approach for different age groups (infants <18 months; children 18 months - 10 years; adolescents >10 years) with different inputs and outputs.

Questions

The following questions emerged during the proceedings:

(1) **Establishing HIV disease:** When we give ZDV prophylaxis for MTCT for six weeks to the infant, but do virological testing at four weeks of age, is the test reliable?

   (a) Expert's groups at the global level have chosen six weeks as a recommendation on when to do the first virological test. RNA tests perform equally sensitively and specifically in both cases whether the child is on ARV or not. There is no data on if the RNA tests perform worse than the DNA test.

   (b) Most sensitivity for virus from six weeks; use WHO validated diagnostics.

(2) Is antibody-testing of HIV-exposed children at nine months appropriate? The age of nine months would be a good time since children in any case come to the clinic for measles vaccination at this age.

   (a) At the age of nine months, specificity of the antibody test is 76%, but positive results may be misleading and the family as well as the child may experience stigmatization. If the child is unwell, repeat test one or two months later.

   (b) At 12 months, infection can be ruled out for 96% of those who are not infected by using antibody testing. It is very

important that adequate tests are used. The national reference laboratory needs to ensure quality of testing and local products should be validated by WHO. Therefore, this would be a feasible option.

Cotrimoxazole

(1) If there is no CD4 available in the country, when should we give CTX prophylaxis?

   (a) Start at 4-6 weeks till one year to all HIV-exposed children. Give CTX to children over one year of age if there are any clinical symptoms.

(2) Why the CD4<350 in > 6-year-old children? Should we not stick to the CD4 200 threshold in > 6-year-olds?

   (a) A broader range of diseases such as pneumonia and malaria are prevented by CTX prophylaixis.

   (b) If ART is started at CD4<200, then in some settings it has been recommended to start CTX prophylaxis earlier, such as at CD4<350 to practice drug treatment adherence.

(3) What are the resistance issues created by CTX?

   (a) Research shows that CTX improved morbidity in uninfected children in the community.

   (b) Research and data including from the SEA Region have shown *in-vitro* antimicrobial resistance to CTX for many common bacterial infections.

   (c) ARI/Malaria: If the child has been on CTX once and then presents itself with pneumonia, CTX is not recommended.

   (d) The overall long-term effects are not known but a study by Boston University is currently on in Zambia to look into the systematic delivery of CTX starting at six weeks. Preliminary results are expected by the end of 2006.

Comments on access to PCR testing

(1) Dried blood spot technology can help scale up access to polymerase chain reaction (PCR) testing. In Botswana, the

government has used DHL courier service as the most efficient way to send specimens to the central laboratory which then faxed the result and sent the original copy back to the sending site. Central PCT testing facilities are being recommended. Collection of specimens, storage and transportation needs to be addressed. The timely reporting of the test results should be looked into.

7. Access to paediatric formulations

Ms Sonali Duggal from the Clinton Foundation, New Delhi, made a presentation on the access to paediatric formulations. The following major questions and issues emerged:

(1) What paediatric formulations are available?

(2) What paediatric formulations are in the pipeline?

  (a) Pedimune B and Pedimune Jr. (Cipla)

  (b) Emtri (Emcure). No field test; no bioequivalence; not submitted to WHO.

(3) What are the costs?

  (a) Rule: Solutions are double the cost of pills

  (b) Cost of first-line treatment is approximately US$150-250 per patient per year. Adult treatment is pegged at around US$110.

  (c) Second line treatment is at about 10 times the cost of first-line treatment and no generics are available.

(4) Difficulties

  (a) Registration of paediatric drugs.

  (b) Need for solid forecasting, modeling and working procedures.

  (c) A minimum of 3 months stock.

(5) The Clinton Foundation is trying to get WHO to prioritize paediatric formulations over other qualification of other drugs

Discussion

The following questions were raised during the discussions:

(1) Why is Pedimune not cleared yet?

  (a) Bioequivalence trials on Pedimune are not clear and guidelines for clearance are not clearly understood.

(2) Can we get FDC containing AZT as paediatric formulation?

  (a) AZT is based on body surface area while other ARVs are based on weight. It is, therefore, difficult to manufacture. A product will be available possibly by the end of the year.

Comments by Clinton Foundation

(1) The Clinton Foundation is offering procurement services for anyone who wants to buy drugs through them.

(2) Lessons learnt by the Clinton Foundation regarding supply chain management: Start with solid forecasting. Procurement can potentially take much longer than expected due to custom clearance processes etc.

(3) Companies have guidelines on how to dose drugs with appropriate weight bands, which is different for every type of drug. Simplify and standardize weight bands for paediatric ARV. Different dosing guidelines make it difficult to switch drugs.

8. Regional paediatric ART guidelines

Dr Jintanat Ananworanich, South-East Asia Research Collaboration with Hawaii (SEARCH), Thailand, was contracted to develop the first draft regional paediatric ART guidelines. She introduced them to the peer review group, and the following major issues emerged:

(1) Regional paediatric ART guidelines are based on the new WHO global paediatric ART guidelines.

(2) The ideal end product is a user-friendly clinical manual for clinicians, providing concise and practical information. Information should be presented in figures and tables by using a

step-by-step of a virtual patient approach. The guide would also support the development of a care and treatment roll-out plan.

(3) Five types of information are provided: (1) assessment and monitoring visits; (2) when and how to treat – require selecting the best choice for an individual child; (3) algorithms; (4) reference materials; and (5) examples of cases.

(4) There is need to have OI section as well, which is not yet included in the current draft guide.

(5) Timeline: Finalize a clinical manual two weeks after this peer-review meeting.

Discussion

(1) What is the scope of the guide, what is the target group?

(a) The goal is to have a pocket-sized manual with focus on ART

(b) The guide is targeted at medical doctors, not at nurses or primary care providers.

(c) The clinical manual aims at the HIV-exposed and/or symptomatic child.

(d) It was not felt necessary to include a session on infant feeding in this guide. This will be covered by the global PMTCT guidelines, which is the more appropriate document to include infant feeding with the link to vertical transmission.

(e) Issues like childhood immunization, disclosure, malnourishment and general health information should be excluded. The reader might be referred to existing text books and studies.

(f) Adherence as a social and clinical issue needs to be considered in this guide since the problem of adherence is the main cause of treatment failure.

(g) What needs to happen at each contact point for follow-up care cannot be included in this guide, but will be discussed

as part of the respective training for care providers. An operational manual needs to be developed.

(2) Where is the "first visit"?

(a) First entry visit, such as PMTCT program, adult ART sites, etc.

(b) Clarifications required if the provider is already a special care provider or if he/she should identify the child and refer to specialist.

(c) There was a need to include an initial session on the setting and potential conditions where the child would be looked at. Different scenarios should include seeing an exposed well child and seeing a sick child.

(d) Information is required on when to follow-up an HIV-exposed child.

(3) Adherence

(a) A team approach is required to promote adherence. Very practical information should be given on who can give what advice at what point of time. It needs to be ensured that the entire team is sending out the same overall message.

(4) NVP exposure through PMTCT intervention

(a) We do not have sufficient information as a basis for recommending not to use NVP.

(b) We can still use NVP even with previous exposure to NVP. Patients in the first year still benefit; when they show treatment failure, the child will already be 1-2 years of age and PIs can be used. This is a better approach than immediately starting PIs for all children with previous exposure. Only 10-20% of children are expected to show treatment failure with NVP.

Issues discussed by working groups

The following section describes the issues contained in the draft regional pediatric ART guidelines that were deliberated by the working groups.

What is the first-line regimen to use for infants and children?

Results and recommendations

The following recommendations were made:

- Include the following: "Based on availability and national ART guidelines, these are the three NRTI combinations to be considered."
- Simplify lay-out
  - Recommend the use of 3TC.
  - Chose one more out of 3 recommended NRTIs: AZT is the preferred choice if the Hb-level is above 8g/dl. When d4T is used, consider switching to AZT because of the risk of lipodystrophy. Don't give time indication (e.g. "after 12 months of use") since there are no data supporting any specific range of time.
  - Regarding the risk of hepatotoxicity and rash related to NVP, the following statement is sufficient: "For adolescent girls, the risk of NVP associated hepatotoxicity or serious rash increases with CD4 > 250 cells/mm3."
  - ABC is not available in most of the countries, but is kept in the guidelines in order to reflect what pediatricians recommend.
- Do not include 3NRTI regimens as an alternative first-line regimen.

What is the first-line regimen to use if the child is on rifampicin as part of TB treatment?

Results and recommendations

The following recommendations were made:

- Switch preferred regimens: recommend 2 NRTI + EFV as preferred regimen in children >= 3 years old; alternatively, ZDV or d4T + 3TC + ABC.

- Suggest including the statement: "In children with HIV and TB co-infection, ART should be started 2-8 weeks after anti-TB treatment". However, it must be included in the statement that criteria for eligibility to initiate ART must always be reflected, and that if ART is indicated, it should be started after anti-TB treatment as soon as TB treatment is stabilized if advanced. If the case is not of advanced HIV or AIDS wait until deduction phase or till treatment is finished.
- Data indicates that weight restriction on EFV does not apply but that age is the better cut-off point compared to weight.
- Triple NRTI listed as an option – an explanation is required as to why this has not been mentioned earlier as an alternative regimen (e.g. place an asterix under 9.2 indicating that triple NRTI should only be used if there is a co-infection, otherwise triple NRTI is less potent than 2NRTI and 1NNRTI). Concern has been raised that we might have to revise the guide within a few years when new data will be available on triple NRTI regimen.

Monitoring after ART initiation

Results and recommendations

The following recommendations were made:

- Monitor monthly until six months and then once every three months, since concern has been expressed that a six-month interval might be too long to support adherence. Paediatricians felt that they wanted to hold the mothers into the system. At this stage of the response they would like to provide optimum care.
- Provide family planning counselling for teenage girls with risk of pregnancy,
- CD4 every six months or earlier, if signs of clinical progression of disease is seen.
- Include the table "monitoring after initiation of ART", evaluating the response to ART, and leading up to the OI section.

Managing ART drug toxicity

Results and recommendations

The following recommendations were made:

- To prevent anaemia due to ZDV: Include "If there is drop in Hb by 2g below the baseline, we can change from ZDV to d4T."
- Rash and liver toxicity particularly due to NVP: Include "Severe rash and liver toxicity (ALT > 5 ULN) can be life-threatening and NVP should be substituted (see Annex G)."

Evaluate response to ART

Results and recommendations

The following recommendations were made:

- The table will be split in two parts: one on clinical and laboratory improvement and another on treatment failure.
- Rearrange boxes in the first chart in order to reflect that clinical and laboratory improvement do not always go hand in hand.

When to start ART in children with and without confirmed HIV diagnosis?

- The group discussed modifying the introduction chapter with "provision for multiple entry points" in order to detect children with HIV infection as early as possible.
- Highlighting the assessment of preparedness of family/child before starting and helping for preparedness was emphasized. (A separate page on these issues, before the one on starting ART, was recommended).
- The group also discussed algorithms on: (1) When to start ART in children with confirmed HIV diagnosis, (2) When to start ART in children without confirmed HIV diagnosis, and (3) HIV staging in children using clinical and immunological criteria. Changes were made as per group discussion and later endorsed by the larger group for including in the guidelines.

Team effort to ensure adherence and successful response to ART

The group recommended addition of a page on "Prepare for ART"

- Prepare child,
- Prepare caregiver parent,
- Prepare and agree on treatment plan,
- Assess treatment preparedness,
- Assess disclosure.

Additional issues to be covered

- Review treatment plan at next visit.
- Go through anticipated regimen.
- Assess understanding.
- Anticipate adherence pitfalls, both early and late.

Adherence to ART

The group suggested an additional section on "Adherence" with focus on:

- Respond to adherence issues.
- Anticipating problems (early, late).
- Practical tips: reminders, organizations.
- Practical strategy/plan.
- Referral for team approach if beyond the scope of clinic visit.

This section should also include guidance on key factors:

(1) Care provider - patient relation.

(2) Disclosure.

(3) Drugs - regimen, toxicity other conditions, formulations.

(4) Disease factors – OIs, concomitant infections.

(5) Programme factors - cost, availability of ART, other drugs.

(6) Assess adherence:

  (a) Before starting ART,

  (b) At around initiation,

  (c) Long-term,

  (d) Assess at each visit.

(7) Describe care team (clinical; family-care giver; child; community). List major roles and responsibilities of each member of the care team.

Recommended second-line regimens and monitoring after switching to second-line regimen

The following points emerged during a plenary discussion led by Dr Jintanat Ananworanich.

Major issues and recommendations

The following issues were discussed and recommendations made:

(1) Treatment failure should be presented separately from evaluation of treatment response. The child has to be on at least six months of ART, medium time to treatment failure four years.

(2) Monitoring after switching to second-line regimen should be scheduled quite frequently in order to avoid early failure. In the interest of keeping the document brief, refer to monitoring box earlier (first-line regimen) and insert a footnote on differences on monitoring in second-line.

(3) Choose second-line regimen depending on first-line regimen (see presentation or guide for details).

(4) Many children will have partial viral load response due to cross-resistance. Recovery is expected.

(5) Caution needs to be exercised about when to start second-line regimen, since it may require local experts to guide when to switch over to second-line treatment.

Questions

(1) When there is first-line treatment failure, it is very likely because of lack of adherence, what do we need to do? We continue the same drugs. The response needs to be evaluated for some time.

   (a) A plan of action is required for the group of children with problems of adherence, which is not yet included in the document. Make sure there is good adherence and only then give the second-line treatment, since if you cannot manage first-line, second-line is much harder to take.

   (b) Add a "pre-switching plan" to plan for adherence. Furthermore, make sure there is PCP prophylaxis.

   (c) Countries have very specific criteria: If you don't come for two months, you have to work through your first-line again. You have to work through three months of intensified treatment support, and if you still do not improve, then consider switching to second-line.

   (d) A box should be included in the document with the following statement: "Switching to second-line treatment should only be done by specialist."

   (e) Highlight the fact that first-line regimen adherence is most important.

(2) If you miss a dose on one day, is a double dose on the second day recommended?

   (a) Since we do not know if one or more days have been missed, do not give additional doses.

   (b) Include checklist of actions we need to take in such a situation.

9. WHO recommendations on dosage and tools for ARV in children

Dr Siobhan Crowley informed the peer review group on WHO's dosage recommendations and the following major issues evolved:

(1) Weight-based simplified dosage tables for most paediatric ARVs have been developed.

(2) A simplified **dosage tool** master sheet will be available on CD-Rom and on the Internet to enable countries develop and adapt their own tables based on locally available drugs.

(3) The underlying principle of dosage tool is:

  (a) To ensure any weight receives at least 100% dose;

  (b) Identify dosage form most accurate for weight band (given % age difference from 100%) and then most practical dose;

  (c) Use WHO dose – from 2003 guidance with agreed amendments;

  (d) "Intended dose" is that agreed by technical expert group = 2003 dose with amendments (Sept 2005); and 5) try to harmonize weights at which formulation switches occur.

(4) Additional rules:

  (a) Solid form preferred over liquid form;

  (b) Wherever possible avoid using two different strengths;

  (c) Never split below halves;

  (d) Prescribe tablet cutters.

(5) Use of dosage tool will require some training of specialists or have a group to work on the dosage tool.

Questions

(1) What extent of under or overdosing is acceptable?

  (a) The purpose of the tool is to allow seeing how much the child is over or under-dosed. The tool also shows the assumptions forming the basis of what has been proposed.

(2) Can a calendar marking the doses be hung on the walls of clinics?

  (a) It would help to have a visual aid in the form of a calendar to produce along with the guide.

10. Immune reconstitution syndrome

Dr Thanyawee Puthanakit of the Research Institute of Health Sciences, Chiang Mai University, Thailand, presented a broad overview of the immune reconstitution syndrome. The following issues came up for discussion:

(1) Whereas drug toxicities are included in the tool, Immune Reconstitution Inflammatory Syndrome (IRIS) is still missing, as well as the way how to differentiate between an adverse event from ARVs or IRIS. The consequences on treatment would be different: in the case of IRIS, continue ARV; if an adverse event occurs, consider stopping ARV.

(2) Include one page on IRIS in the guide and refer to it in the first algorithm.

11. Opportunistic infections (OI)

Dr Tripti Pensi, Associate Professor, Department of Paediatrics & Neonatology, Dr RML Hospital, New Delhi, introduced the subject of opportunistic infections. The following issues emerged:

(1) An overview of the most common opportunistic infections was given.

(2) A decision is required what kind of opportunistic infections should be included in the guide.

(3) Consider including the impact of Highly Active Antiretroviral Therapy (HAART) on OI in guide and provide examples and data.

(4) Pros and cons: Adopting a syndromic approach to public health is useful to suspect and refer cases to a higher-level clinic. A diagnosis-based approach, on the other hand, is suitable since the intervention is hospital-based and requires a case-by-case decision.

(5) Prophylaxis for common OIs should be included in the guide using a very simple flow chart.

Discussion

(1) It has been agreed to include IRS algorithm and four key syndromic algorithms.

(2) Opportunistic infections (OIs) that are most easily confused with toxicities on ART should be included; other OIs are adequately addressed in OI treatment guidelines.

(3) Include at what point of time we should be suspecting OI/toxicities and when to hospitalize the child.

(4) Take the syndromic approach for major conditions. Develop easy and concise flowcharts, which should not aim at replacing textbooks.

(5) Delete the session on "children with signs and symptoms consistent with pulmonary tuberculosis" (page 33); instead, use an algorithm which focuses on respiratory symptoms

12. Integrated Management of Childhood Illnesses (IMCI)

Dr Lulu Muhe, Medical Officer, Child and Adolescent Health, WHO headquarters, Geneva, explained how inclusion of HIV/AIDS in IMCI will help address this burden. The following issues were identified:

(1) Different countries, such as South Africa, Uganda and Ethipopia, have developed country-specific HIV/IMCI algorithms.

(2) Global guidelines are available on HIV-integration in IMCI as well as in the form of a chart booklet for HIV settings and training material.

(3) The WHO generic IMCI/HIV algorithm recommends screening for pneumonia, persistent diarrhoea, discharging ear (acute or chronic) and a very low weight for age. Infants with unknown HIV status who show these symptoms should be tested for HIV.

(4) Infants with known HIV-exposure should be tested for HIV.

(5) For children with confirmed HIV-infection, provide the following:

(a) treat, counsel and follow up on current illness

(b) give cotrimoxazole prophylaxis;

(c) check immunization status;

(d) give vitamin A supplements every six months beginning at the age of six months;

(e) assess the child's feeding and provide appropriate counselling to the mother;

(f) refer for further assessment including ART; and 7) advise the mother on home care.

Questions

Since this strategy is for high-prevalence areas, would a similar model work in low-prevalence areas? Are the clinical signs valid?

(1) Encourage proper validation in every setting.

Is HIV the only addition to the previously existing IMCI tool or has the algorithm been modified?

(1) Infant feeding, with addition of HIV: Other algorithms have been changed and adapted to include HIV.

Comments

(1) Concern was raised that the importance of early diagnosis is not reflected in IMCI algorithm. Every pregnant woman should know her HIV status. Information of HIV exposure must also be transferred to health card. When a child comes to the clinic it must be ensured that the child is tested.

(2) With the majority of mothers not knowing their status, the provider needs to be alert on signs and symptoms in children.

(3) It is useful for all health workers to understand the package for care of a child born to an infected mother, which is embedded in the IMCI approach (e.g. CTX prophylaxis).

(4) We should use IMCI to sensitize counsellors at VCT centres to adopt a family-centric approach.

13. Proposed roll-out plan for paediatric ART guidelines

Dr Rakesh Lodha, Assistant Professor, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, will develop a roll-out plan for introduction and adaptation of paediatric ART guidelines at the national and community levels. The following issues came up for the consideration of the peer review group:

(1) The need to treat indefinitely is a unique challenge.

(2) Offering treatment to those who need it is currently at 5%, except for Thailand which has reached close to 75% of treatment coverage.

(3) Key elements necessary for scale-up are a national strategy; exact numbers required; MTCT strengthening; plan for early diagnosis; training plan and a supply plan.

(4) Simplified, standardized tools for delivering ART: multiple entry points, simple testing procedures; technical guidelines, monitoring and evaluation systems.

(5) Multiple entry points: MTCT, IMCI, adult ART centres with a family approach. (Lessons learnt from adult TB programmes show that a family approach does not come naturally). Routine offer of testing in high-yield paediatric sites.

(6) Determinants of roll out strategy: need/demand (number of infected children; awareness and demand for ART); existing infrastructure (adult ART centres, laboratory infrastructure, CD4% facilities/many laboratories only offering absolute CD4; existing child health care services; infrastructure for outreach/level of training/workload); human resources trained; quality assurance; operational research; and ability to ensure adherence.

Questions

Are we looking at the central or district level to roll out services?

(1) Countries expressed plans to build up capacity for specialized care, if possible in combination or in addition to ongoing ART

and PMTCT interventions. Family focussed care delivery and mapping where we need to concentrates resources and services.

(2) In low-prevalence countries, services will have to be centralized at the beginning.

(3) On the other hand, use also existing potential at the country in the form of institutions that are already doing very good work and support them in their specific needs rather than contemplate centralized training.

VCT in region still very weakly developed – how do we access these children?

(1) Optimize entry into care: Set targets and hold sites accountable to reach targets based on the population base for ART sites. Conduct a mapping exercise as a base for decision on where to provide services. Use algorithms for optimizing entry into care (IMCI). Adopt a family approach. Link district hospital to community facilities, and build a team for management of HIV in children.

(2) Define who is responsible for paediatric ART and build ownership. Put validation of HIV/IMCI in roadmap.

(3) Look at the Cambodia experience for lessons learnt.

14. Recommendations

To develop the roll-out plan a two-step approach was recommended.

(1) General principles: Provide recommendations in the form of a checklist for countries – national policy, target setting, quantification and mapping, 3x5-initiative, Universal Access. Through these initiatives governments could come up with a strategic plan. Harmonization of roll-out with PMTCT and adult ART. Synchronize supply chain management, stress importance of knowledge management. Provide recommendations on what kind of facility we are discussing: tertiary and district level. In addition, IMCI would play a very important role as we consider the community level.

(2) Individualized approach: Support countries with regard to adopting the guide and developing a training plan.

15. Next steps for regional paediatric ART guidelines

The peer review group arrived at the following consensus for finalization of the Regional Paediatric ART Guidelines:

(1) Dr Jintanat Ananworanich will amend the draft by incorporating the recommendations of the peer-review meeting with the support of Dr Thanyawee over the section on 'Opportunistic Infections'.

(2) WHO/UNICEF to reach agreement on pre-final draft submitted by Dr Jintanat.

(3) Circulate the pre-final draft to the members of the peer review group for inputs.

(4) Incorporate inputs received and finalize guidelines.

(5) Send guidelines for designing and printing.

(6) Disseminate in August 2006.

(7) WHO/UNICEF to work on potential launch of guidelines and to make provision to provide additional help to countries with regard to usage of the guidelines.

16. Next steps for roll-out plan

The peer group agreed to the following schedule for the development of the Roll-Out Plan:

(1) Develop ToR for consultant by 31 May 2006.

(2) Award contract by 15 June 2006.

(3) First draft ready by 31 July 2006.

(4) Circulate first draft of roll-out plan by 15 August 2006.

(5) Feedback by peers by 15 September 2006.

(6) Finalize by 15 October 2006.

(7) WHO to plan organization and conduct of a consultation on scaling up tentatively in the first week of November 2006 held in

New Delhi and use this opportunity to assemble group of pediatricians for a one-day exclusive session on reviewing the roll-out plan. Alternatively, the session could follow the PMTCT Task Force Meeting scheduled to be held in the first week of November 2006 in Kuala Lumpur, Malaysia.

Annex 1

Programme

Thursday, 4 May 2006

0830–0900 hours	Registration	
0900–0940 hours	Inaugural Session • Introduction – Dr Sudhansh Malhotra, RA-CHD, WHO/SEARO introduces himself, RD, UNICEF/ROSA, Ag.RD, WHO/SEARO, UNICEF staff, WHO Departmental Directors, and WHO Secretariat – Dr Sudhansh Malhotra invites Dr Myo Zin Nyunt, Regional HIV/AIDS Officer, UNICEF/ROSA to introduce participants and facilitators • Address by Dr Myint Htwe, Director, Programme Management, Acting Regional Director, WHO/SEARO • Opening remarks by Ms Cecilia Lotse, Regional Director, UNICEF/ROSA • Objectives and Announcements by Dr S. Malhotra, Regional Adviser, Child Health and Development	
0940–1000 hours	Group photograph and tea/coffee	
1000–1015 hours	Global situation of pediatric HIV infection and responses	Dr Chewe Luo, UNICEF/HQ
1015–1030 hours	Regional situation and issues	Dr Ying-Ru Lo, WHO/SEARO
1030–1100 hours	• Staging of HIV disease in children • Establishing HIV infection in infants and children with confirmed HIV exposure • Cotrimoxazole guidelines	Dr Siobhan Crowley WHO/HQ

1100–1130 hours	Access to pediatric formulations	Ms Sonali Duggal Clinton Foundation
1130–1200 hours	Introduction to regional paediatric ART guidelines	Dr Jintanat Ananworanich
1200–1300 hours	Lunch	
1300–1430 hours	**Working Group 1** When to start ART in children with confirmed HIV diagnosis and without confirmed diagnosis	Dr Siobhan Crowley WHO/HQ
	Working Group 2 What first-line regimen to use for infants and children	Dr Thanyawee Puthanakit
	What first-line regimen to use if the child is on rifampicin as part of TB treatment	
1430–1500 hours	Tea/coffee	
1500–1630 hours	**Working Group 1** A team effort to ensure adherence and successful response to ART	Dr Lulu Muhe
	Working Group 2 Monitoring after ART initiation	Dr Thanyawee Puthanakit
	Managing ART drug toxicity	
	Evaluate response to ART	
1630–1800 hours	Report back from Working Groups	

Friday, 5 May 2006

0830–0900 hours	Treatment failure and recommended second-line regimens in infants and children in the event of treatment failure of first line regimens	Dr Jintanat Ananworanich
	Monitoring after switching to second line regimen	
0900–0930 hours	Introduction to the draft WHO dosing tool for pediatric formulations	Dr Siobhan Crowley
0930–1000 hours	Tea/Coffee	
1000–1200 hours	**Working Group 1**	
	Diagnosis and management of opportunistic infections in infants and children	Dr Thanyawee Puthanakit

	Working Group 2	
	Diagnosis and management of opportunistic infections in infants and children	Dr Tripti Pensi
1200–1300 hours	Lunch	
1300–1415 hours	Report back from group work	
1415–1430 hours	The integrated management of child hood infections (IMCI)	Dr Lulu Muhe WHO/HQ
1430–1500 hours	Tea/Coffee	
1500–1700 hours	Proposed roll out plan for pediatric ART guidelines	Dr Rakesh Lodha
	Discussions on action plan on paediatric care and treatment roll out	
1700–1715 hours	Next steps and closing	Dr Myo Zyn Nyunt UNICEF-ROSA Dr Sudhansh Malhothra WHO/SEARO

Annex 2

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