

WHO/ASD/98.1
UNAIDS/98.7
Distr: General

Guidance Modules on Antiretroviral Treatments

Module 6

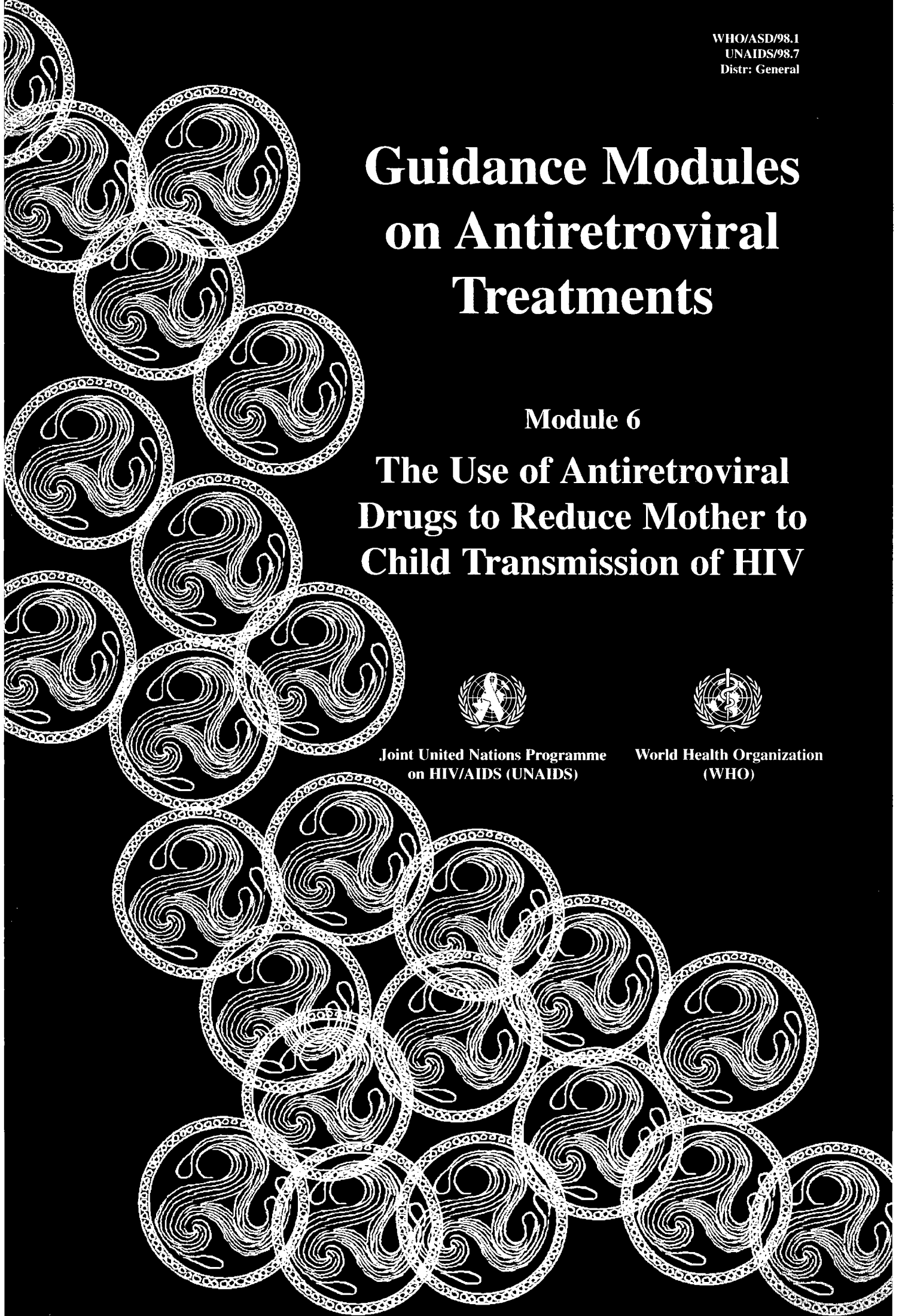
The Use of Antiretroviral Drugs to Reduce Mother to Child Transmission of HIV



Joint United Nations Programme
on HIV/AIDS (UNAIDS)



World Health Organization
(WHO)



Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Glenda Gray and Dr James McIntyre, Baragwanath Hospital, Johannesburg, South Africa, for preparing the text of this module;

Dr Isabelle De Vincenzi, Policy, Strategy and Research, UNAIDS, Dr Elizabeth Hoff, Division of Reproductive Health, WHO, Dr Kevin De Cock, Centers for Disease Control and Prevention, Atlanta, USA, and Dr Felicity Savage-King, Division of Child Health and Development, WHO, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriens, Policy, Strategy and Research, UNAIDS, for coordinating the project.

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Module 6

The Use of Antiretroviral Drugs to Reduce Mother-to-Child Transmission of HIV

Introduction

Mother-to-child transmission (MTCT) is responsible for 5-10% of the total of new HIV infections each year in many developing countries, with more than 500,000 children being infected each year. The introduction of antiretroviral (ARV) drugs for the prevention of MTCT has dramatically reduced rates of transmission among non-breastfeeding mothers in many developed countries, and continued improvements are being seen as more women enter pregnancy while on combination ARV therapy in developed countries. A recent study has shown that short course zidovudine (ZDV) is also effective and major reductions in the cost of ZDV for use in perinatal transmission interventions have been negotiated. These developments will make ARV therapy for MTCT more accessible than before.

The use of antiretroviral drugs for the prevention of perinatally acquired HIV infection should always be considered in the context of optimal health care for the mother. Emphasis on the provision of high quality antenatal and voluntary counselling and testing services must be seen as prerequisites for the introduction of any MTCT ARV initiative.

The use of zidovudine (ZDV) in either “long” or “short”¹ course regimens has been shown to reduce the risk of mother-to-child transmission of HIV in non-breastfeeding mothers. This represents an important preventive strategy. The use of ARVs in pregnancy for the purpose of preventing transmission should be viewed primarily as part of HIV prevention activities. Although routine treatment with ARVs may not be accessible in all settings for pregnant women, if they are available, the prevention of MTCT should be considered as part of a holistic care plan for the pregnant woman and the child, which extends beyond pregnancy.

1. Transmission of HIV from mother-to-child

At the beginning of 1998, more than thirty two million people were estimated to be living with HIV/AIDS, almost half of whom were women in their reproductive years. Mother-to-child transmission of HIV remains the main mode of acquisition of infection for children. Over one and a half million HIV infected women become pregnant each year, the majority in Africa and Asia, with more than half a million children infected. Between 5 and 10 million children are expected to be infected with HIV by the end of the 1990s. If they survive the first few years of childhood, they are likely to suffer the same fate as the 8.2 million children who have lost their mothers or both parents to AIDS in the epidemic to date. Estimates of MTCT vary from 14-42%² in different regions, before the use of antiretroviral therapy. With access

1 “Long course” as defined by ACTG076 and similar regimens (including pre-natal, intra-partum and post natal components). “Short course” refers to four weeks ZDV given to the mother at 36-40 weeks antenatally.

2 Mother-to-child transmission rates: Zambia 39% (Hira, 1989); South Africa 35-39% , (Lyons 1996); Europe 13%; USA, New York State, 25%, (Dabis et al 1995).

to zidovudine during pregnancy, MTCT in the developed world has been reduced to below 9% in mothers who do not breastfeed their babies, with further reductions to below 5% in many areas. In two small studies in developed world settings no transmission has been seen in children born to women receiving ARV monotherapy with elective caesarean section or combination ARV, and not breast-feeding.

Factors affecting transmission

Transmission of HIV³ can occur prenatally, at the time of labour and delivery or postnatally through breastfeeding. The contribution of each of these routes to overall transmission has not been quantified exactly but it appears that a substantial proportion of infection occurs at the time of delivery. A number of factors are associated with higher risks of transmission. These can be divided into viral, maternal, obstetrical, fetal and infant factors

Viral factors

Transmission is increased by high maternal viraemia, such as in advanced disease and at the time of seroconversion. With the development of new techniques for the measurement of the virus, such as quantitative PCR DNA and RNA, an association has been shown between the maternal viral load and the risk of transmission from mother to child. More than half of the women with viral loads of >50 000 RNA copies per ml at the time of delivery have been shown to transmit the virus, although there does not seem to be a lower limit below which transmission does not take place. The local viral load in cervico-vaginal secretions and in breastmilk may also be an important determinant of transmission risk intrapartum and through breastfeeding. Other characteristics of the virus, such as the genotype and phenotype may be associated with higher transmission risks.

Maternal factors

Maternal risk factors

- Advanced immunosuppression
- Advanced clinical disease
- High viral load
- Recent infection
- Vitamin A deficiency
- Placental barrier integrity: chorioamnionitis

The risk of MTCT of HIV is higher in women with clinical, immunological or virological markers of advanced HIV infection. A low CD4 count or low CD4 percentage correlates with an increased risk of MTCT. Immunological factors such as the presence of neutralising antibodies may play a role in minimising transmission. The involvement of specific T-cell immunity in the pathogenesis of MTCT has yet to be described.

Maternal nutritional factors, such as serum Vitamin A levels have been correlated with the risk of transmission in a Malawi study. The mean vitamin A level in mothers who transmitted

³ Throughout this document HIV refers to HIV-1 since cases of MTCT of HIV-2 are extremely rare

virus to their children was significantly lower than in those who did not transmit. The mechanism is uncertain, but it has been suggested that vitamin A may maintain the integrity of the vaginal mucosa or placenta and may have immune stimulatory properties. Alternatively, low vitamin A levels may be a marker for other deficiencies or behavioural factors, which influence transmission. Several behavioural factors have also been associated with an increased risk of transmission from mother-to-child. These include cigarette smoking, illicit drug use and high rates of unprotected sexual intercourse with a seropositive partner during pregnancy.

The cellular composition of the placenta changes with gestation, and the risk of placental infection may vary over pregnancy. Placental disruption, for example chorioamnionitis, and cigarette smoking have been associated with increased transmission rates.

Obstetric factors

Delivery factors

- Mode of delivery: vaginal vs caesarean section
- Prematurity
- Prolonged rupture of membranes
- Use of instruments

Obstetric factors are important determinants of transmission, as most transmission takes place around the time of labour and delivery. Several factors have been implicated, although results are not consistent across studies with regard to their relative importance. These include preterm delivery, intrapartum haemorrhage, obstetric procedures, the use of foetal scalp electrodes, episiotomy and vaginal tears. The duration of labour does not appear to be as important as the duration of rupture of membranes, and the transmission risk is doubled with ruptured membranes for longer than four hours. Delivery by caesarean section has been shown to be protective in some prospective follow up studies, but not in all. A randomised controlled trial is in progress in Europe to attempt to answer this question.

Foetal factors:

Preterm infants have higher reported rates of transmission of HIV. The increased risk of infection in premature infants is likely to be due to increased susceptibility to intrauterine acquisition of infection as a result of immaturity of the immune system and low levels of maternally derived HIV antibodies. First born twins have higher rates of infection than second born twins. However this difference is particularly striking in first born infants delivered vaginally (35% infected), when compared with second born twins born by caesarean section (8% infected), highlighting the importance of intra-partum factors in transmission. Other foetal factors may include co-infection with other pathogens, foetal nutrition and foetal immune status.

Breast feeding and infant factors:

Breastfeeding is responsible for a high proportion of mother-to-child transmission in developing countries, where 1 in 7 children born to HIV-positive mothers will be infected

through breastmilk. This is less common in the developed world, where most HIV-positive women will not breastfeed. A meta-analysis of studies of transmission through breastfeeding showed the additional risk of transmission through breastfeeding to be between 7 and 22%, equivalent to a doubling of transmission rates. **Late postnatal transmission**, after the age of three months, has been described and may contribute 4-20% to the overall rate of vertical transmission in breastfed infants according to several studies from Africa.

The risks of postnatal transmission may also be related to other factors in the new-born. HIV may enter through the gastro-intestinal tract following ingestion of virus in utero or at birth. There is decreased acidity, decreased mucus, lower IgA activity and thinned mucosa in the newborn gastro-intestinal tract, which may facilitate transmission. The newborn immune system may also be deficient in macrophage and T cell immune response, increasing the susceptibility to infection. At least part of the effect of antiretroviral drugs in pregnancy appears to be due to a post exposure prophylaxis effect after birth.

In summary, MTCT appears to be governed by an interaction between viral, immunological and other factors such as the mode of delivery, length of rupture of membranes and infant feeding practice. Interventions to reduce MTCT of HIV should target these factors.

2. Strategies to reduce mother-to-child transmission

The only interventions proven to reduce mother-to-child transmission significantly are the use of ARVs and the avoidance of breastfeeding.

ZDV therapy:

The first indication that ARV treatment can help to prevent MTCT of HIV came with the results of the ACTG076 study in 1994. In 1998, results from a short course ZDV study in Thailand showed that a lesser but significant reduction could be obtained with shorter courses of therapy.

Long course, ACTG076

The reduction of MTCT of HIV with zidovudine (ZDV) in the ACTG076 study constitutes a major breakthrough, opening new areas for research and interventions in MTCT. Antiretroviral therapy may decrease viral load and/or inhibit viral replication in the infant. Results from the ACTG076 study, which looked at the effect of zidovudine in pregnancy, during delivery and for six weeks to the infant, support these hypotheses. In this randomised placebo-controlled trial in a non-breastfeeding population, treatment with ZDV (100mg 5 times daily) or placebo was started between 14-34 weeks of pregnancy (median 26 weeks). Women also received intravenous ZDV or placebo during labour and the infants received oral ZDV (2mg/kg qid) or placebo for six weeks. All women had CD4 counts >200 per mm^3 , were symptom free and were ZDV naive.

The results of this study show that perinatal transmission can be significantly reduced by the use of antiretrovirals. The first interim analysis on 356 mother-infant pairs demonstrated a reduction in the risk of MTCT transmission from 25.5% in the placebo group to 8.3% in the ZDV group. ZDV achieved a 67.5% reduction in transmission risk. The drug was well

tolerated in both the pregnant women and the neonates. The results from the ACTG076 trial and the ZDV in Pregnancy Register show as yet no evidence of teratogenicity or short term adverse effects in the foetus or new-born, but long term follow up is still required.

ZDV in this regimen (or with minor adaptations in the oral dosing regimen) has become the standard of care for prevention of perinatal transmission in HIV infected women in the USA and other developed countries. On the basis of the ACTG076 and the recent availability of new classes of antiretrovirals, further reductions in perinatal transmission may be possible in the developed world with combination therapy.

These results are not applicable to most women in the developing world where most MTCT transmission occurs. This is because of the high cost of the intervention, the logistics of carrying out a regimen requiring intravenous infusions during delivery and therapy to the new-born for six weeks and the need to start the intervention early on in pregnancy, in situations where most women book late. In addition, the ACTG076 trial was conducted in a non-breastfeeding population so the efficacy of the regimen in a breastfeeding population needs to be determined.

The effect of ZDV in this regimen may have been sub-optimal among those pregnant women who received more than 14 weeks of therapy. The initial reduction in HIV viral load induced by ZDV in ZDV-naive patients disappears after an average of 14 weeks of treatment to baseline levels. Therefore, with a shorter regimen (<14 weeks), the reduction in perinatal transmission may be greater.

Short course (CDC THAILAND STUDY)

The ACTG076 regimen has not been implementable in developing countries due to cost and logistical issues. In March 1998, the Bangkok Perinatal ZDV Study announced preliminary results. This study was a randomized placebo controlled trial to evaluate the safety and efficacy of a short course of oral zidovudine (ZDV) administered during late pregnancy and labour to reduce the risk for perinatal HIV transmission. The regimen was of 300 mg ZDV orally twice daily from 36 weeks gestation until the onset of labour and 300 mg every three hours from the onset of labour until delivery. All women were advised *not* to breastfeed and were provided with infant formula, and it is important to bear in mind that these results are directly applicable only to formula fed infants.

397 women were enrolled in the study (198 in ZDV arm, 199 in placebo arm); 4 women were lost to follow up before delivery and 393 women delivered. At enrollment, the median age was 24 years and the median CD4 count was 424 cells/uL. Baseline characteristics were balanced between the two arms. The median duration of antenatal treatment was 24 days and the median number of labour doses was three. Ninety-nine percent of women took at least 90% of pills in the antepartum period, and 99% took at least one dose during labour. 96% of antenatal and post natal study visits were kept by the women. There were 19 routine contacts between health worker and the mother during the antenatal and post natal period.

Fifty-two of the 391 children were infected: 17 in the ZDV arm and 35 in the placebo arm. The Kaplan-Meier estimates for transmission risk in the ZDV and placebo arms were 9.2% (95% confidence interval, 5.0%-13.5%) and 18.6% (95% confidence interval, 13.0%-24.0%), respectively, representing a 51% reduction in transmission risk (95% confidence interval, 15% - 71%).

The Thailand results demonstrate that a short course of twice-daily oral ZDV used from 36 weeks gestation until delivery was safe and reduced the risk for mother-infant HIV transmission by approximately one half. Following the release of the results, Glaxo-Wellcome has announced a major reduction in the price of ZDV for use in prevention of mother-to-child transmission in developing countries, increasing the likelihood of this intervention being implemented.

It must be noted that in both these studies the majority of women were not severely immunosuppressed, adherence to ARVs and clinic attendance was very good and no women were breastfeeding.

2.2 Avoidance of breastfeeding

Few HIV-positive women in industrialised countries choose to breastfeed, but this remains the norm for most infected women in developing countries. This is possibly the major reason for the higher rates of transmission seen in these settings. The additional risk of infection in breastfed infants is estimated to be between 7% and 22%. This must be considered in the introduction of any ARV strategy. The issue of infant feeding is complex, with the need to preserve the benefits of breastfeeding for uninfected women and children, while finding suitable and affordable (in adequate quantities - 20kg for 6 months) breast milk substitutes⁴. Mothers must be given guidance on how to prepare breast milk substitutes as safely as possible and enough clean water, fuel and time to do so.

2.3 Combination ARVs and other interventions

Many of the current interventions being studied are based on the premise that a substantial proportion of HIV transmission occurs in late pregnancy, during labour and delivery. A number of studies are in progress with results expected through 1998 and 1999. These are summarised in Table 1. Results are expected in mid-1998 from the UNAIDS PETRA study (ZDV and 3TC), from the Malawi Vitamin A study and by late 1998 from the randomised study on breastfeeding and the vaginal cleansing with 0.25% chlorhexidine study in Kenya. These results will help in the design of the most appropriate interventions for developing countries. The presence of sexually transmitted infections (STIs) increases viral shedding. Therefore, pregnant women who have concurrent STIs will have higher levels of HIV in vaginal secretions and this may increase MTCT.

4 "Breastmilk substitutes" refer to all alternatives to breast feeding and include commercial formula feeding, home prepared formulas, and modified animal milk feeds

"Artificial feeding" means feeding an infant on breastmilk substitutes.

3. Implementation

There are certain requirements within services that need to be fulfilled to ensure the successful introduction of an antiretroviral strategy for pregnant women.

Minimum requirements for ARV therapy in pregnancy

1. Access to and utilization of appropriate antenatal, intrapartum and post-partum care with adequately trained health workers.
2. Adequate voluntary pre- and post- test counselling services (VCT).
3. Affordable and reliable HIV testing.
4. Acceptance and uptake of VCT by HIV infected women
5. Providing an enabling environment; preventing discrimination and abuse of women who test positive.
6. Continuing medical and social support for HIV infected women.
7. Laboratory services to monitor blood parameters (for the short course regimens haemoglobin estimation at enrollment is sufficient).
8. Delivery units with access to safe standard precautions: disinfectants, gloves and needles.
9. Affordable ARV drugs.
10. A sustainable pharmaceutical distribution and storage system for ARV drugs, to include quality control.
11. The availability of an adequate supply of affordable breastmilk substitutes, counselling about infant feeding options including guidance on how to prepare feeds as safely as possible, access to safe water and fuel for those who choose not to breast feed their infants, for the maximum benefit of an ARV intervention.

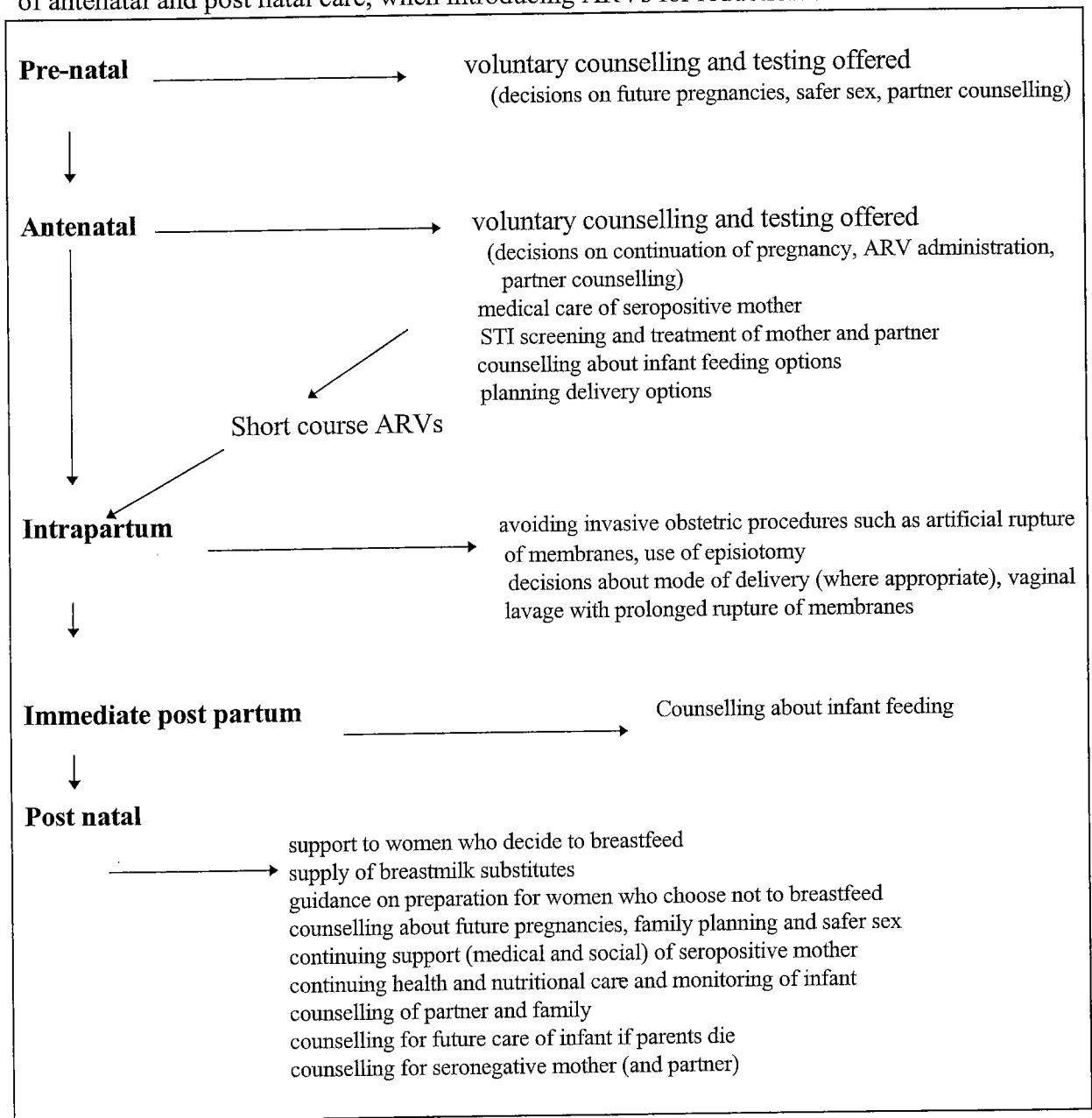
Setting up ARV services in maternal health services

MTCT interventions must be part of a comprehensive approach to HIV prevention and care and to antenatal care. A number of guiding principles should underlie these interventions:

- Primary prevention of HIV infection in women
- Non-stigmatisation of women
- Support services for HIV positive women and children
- The health and well-being of mothers and other children should not be altered by MTCT interventions
- Resources should not be diverted from antenatal care and related programmes

Any ARV intervention will require the identification of HIV positive women at an early enough stage of pregnancy for them to access the intervention. Voluntary counselling and testing (VCT) is thus the cornerstone of an HIV care service for pregnant women, and should be established concurrently if interventions to reduce MTCT are proposed.

The following table highlights the essential activities that need to be addressed at each phase of antenatal and post natal care, when introducing ARVs for reduction of MTCT :



The following steps need to be considered by MCH programme managers before setting up ARV MTCT services:

1. STRENGTHENING ANC AND WOMEN'S HEALTH SERVICES

Currently many women in developing countries are either not receiving antenatal care or are receiving inadequate care. Furthermore, less than 50% of women deliver with the aid of a skilled attendant. It is therefore important to improve access to and quality of ANC services when considering the introduction of ARV interventions.

Problems associated with artificial feeding

- Cost, supply, distribution and control
- Risk of morbidity and mortality
 - lack of clean water, fuel, time, bottles/feeding cups
 - lack of immunological benefits of breast milk
- Cultural acceptability, stigmatisation
- Common knowledge of mother's serostatus
- Undermining breastfeeding in HIV-uninfected (or untested) population

The risk of infant feeding with alternatives to breastmilk should be less than the potential risk of HIV transmission.

Infections may be more common in the postpartum period and women should be told about the signs and symptoms of these in order to seek care early. Where ARVs are available for treatment of adults, mothers should be evaluated to determine the need for appropriate ARV therapy for their own HIV related disease. Where ARVs are not available for general use other treatments for HIV disease and prevention of opportunistic infections (OIs) can be of great benefit to seropositive women.

7. CARE OF INFANTS

Anaemia has been the most common complication seen in the neonate with the long course treatment of six weeks ZDV. Haemoglobin should be measured at baseline and after six weeks and twelve weeks if this regimen is used. The risk of anaemia is much less with the short course therapies. Infants receiving ARVs may experience a transient elevation of hepatic transaminases. There is less experience with the use of combination therapy in the pregnant mother and the risk of toxicity to these infants, and more intensive haematological monitoring is advisable.

Mothers should decide on infant feeding practice before delivery and be supported in their choice. Those who choose to breastfeed should be warned about the possible increased risk of HIV transmission from breastmilk if the infant has oral thrush, or in the presence of cracked nipples or breast abscess and need to be counselled on good breastfeeding techniques in order to avoid these problems. Women who choose artificial feeding for their infants must be given guidance on their accurate and safe preparation in order to avoid morbidity and mortality due to inadequate amounts and contamination.

Children should be referred for long term follow up, health and nutrition care, and for repeat testing for diagnosis of HIV infection, either by early polymerase chain reaction (PCR) or viral culture if available, or by HIV antibody testing at 15 to 18 months, when maternal antibodies will have disappeared.

Although with ARV treatment the number of infants who contract HIV will be greatly reduced, a proportion will still unfortunately develop HIV disease. They will need continuing medical care and the mother and family will need social and emotional support. Although some infected babies will become sick and die quickly many appear healthy and HIV-related symptoms may not be apparent for many months or years after birth. In industrialised countries the oldest children who were infected perinatally are now 17 years old.

In developing countries where ARVs are not generally available to treat HIV infection in mothers, children who are not HIV-infected are very likely to become orphans. Although this may be a difficult area to explore with mothers, studies have shown that women value guidance from counsellors about making plans for their children's future care and help with making wills so that their children benefit from any material resources.

8. CONTINUING COUNSELLING AND CARE OF SEROPOSITIVE MOTHERS

As stated earlier one of the benefits of VCT for women attending antenatal care is allowing women who test seropositive earlier access to treatment and care. Symptomatic treatment, prevention of OIs and palliative care should be available across a continuum from hospital to home, and appropriate referrals made accordingly. Access to family planning services and condom supplies should also be considered an integral part of this comprehensive care. Seropositive women can be referred by their health care worker to social services and support groups in the community where available.

It is important that seropositive mothers are not "blamed" for their HIV infection. Where possible their partners should also be counselled and offered VCT. Up to 25% of couples in some developing country settings have been found to have discordant HIV results. For discordant couples advice about preventing HIV transmission by using safer sex has been shown to significantly reduce the rate of transmission to the uninfected partner. However, it is important that HIV counselling of partners be voluntary and that women who are ready to disclose their positive status not be subjected to abandonment and abuse.

9. CONTINUING COUNSELLING AND SUPPORT FOR SERONEGATIVE WOMEN

Even in high prevalence areas the majority of women attending antenatal clinics will test seronegative, but without continuing support, counselling and provision of condoms, many will acquire HIV. If they are pregnant or lactating, they should be encouraged to practice safer sex as the risk of MTCT is especially high with new infection.

Resistance and the use of antiretrovirals in pregnancy

Women who have received extensive prior ZDV therapy may be infected with viral strains that have reduced susceptibility to ZDV. These resistant strains may be transmitted from mother to foetus but the frequency with which such transmission occurs is uncertain, although there are reports that resistant strains are more likely to be transmitted to infants. The effectiveness of ZDV in reducing HIV transmission may be decreased for mothers in whom ZDV resistant strains predominate but this assumption is not yet supported by data. In

the developing world few women will have had prior access to antiretroviral therapy before becoming pregnant, therefore resistance may be less of a problem than that seen in the USA or Europe.

Concerns about the potential long-term adverse effects among women include the development of ZDV-resistant virus when ZDV therapy is used intermittently to reduce perinatal transmission, especially if used for more than one pregnancy, and the potential effect such resistance could have on disease progression. Even brief exposure to ZDV may decrease the effectiveness of the drug if used again. Similarly prior long term treatment with ZDV has been shown to decrease the potency of d4T plus 3TC more than ten fold. Although the results of some studies have demonstrated an association between emergence of ZDV resistance and total duration of ZDV exposure, none of the study designs have specifically addressed the effect of intermittent therapy on the development of resistance, or of the shorter antenatal regimens in the development of resistance. It is known that when a drug whose use has led to selection of a resistant viral population is withdrawn from the patient, selection forces favour the return of the wild type virus. How quickly the drug resistant mutant virus disappear from the peripheral circulation is predicted by the replication rate of the mutant form versus the wild type. However it appears that “memory” of this prior resistance is retained and the effect of this background resistance is often a very rapid reappearance of the drug-resistant form if the drug is re-instituted

As the clinical implications of resistance to ARV therapy become more obvious, new assays make it possible to measure these events in patients. How these tests should be employed and how considerations of drug resistance may affect the choice of drug remain unclear. Serial CD4 counts and estimates of viral load help elucidate the phenomenon of drug resistance. Resistance testing of any type will have to be interpreted against a background of previous drug therapy, duration of current therapy and the adherence of the patient.

ACCEPTANCE AND ADHERENCE

Acceptance of testing and treatment in the developing world needs to be studied further. In some reports (e.g. in a study from Kigali), the willingness of clinic attendees to know their HIV status was considerable, where two thirds of women tested in 1992/93 returned for post-test counselling. This is in contrast to findings in Cote d'Ivoire, where although antenatal attendees consented to testing, a substantial proportion of women did not return for their results or for post-test counselling. The implementation of an ARV regimen in poorly-resourced, overburdened midwifery/obstetrical units will depend on the number of women consenting to testing and returning for their results, on the simplicity of the regimen (oral dosing, absence of an intrapartum arm and minimal management in labour) and the ease with which they can return for follow-up. Adherence will depend on how easy the regimen is, for example, the use of a single agent vs. multiple agents, oral dosing, daily or twice daily doses vs. multiple doses during the day, if there is a need to take it with/out food and if there are minimal side-effects. Adherence is enhanced if the healthworker and the client understand the regimen and its benefits. Seropositive women receiving ARVs to reduce MTCT may decide to share them with a sick partner or friend, so counselling must include information on the dangers of sub-optimal or intermittent dosing.

CONCURRENT TREATMENT OF WOMEN WITH COMBINED ARV THERAPY

The use of antiretroviral drugs for the prevention of perinatally acquired HIV infection should always be considered in the context of optimal health care for the mother. In industrialised countries (and under some circumstances in developing countries) some women who become pregnant will already be taking ARVs for treatment of their own HIV infection. Where available and when indicated, appropriate ARV therapy should not be withheld because of pregnancy. Many pregnant women who are taking combinations of ARV drugs have reduced their viral load beyond detection. This may be of benefit to both foetus and mother. The management of combination ARV therapy during pregnancy is complex: only scanty data are available, safety in the first trimester of pregnancy has not been established and there are no controlled efficacy data yet for combination therapy. However data is currently being collected from women using ARVs during pregnancy and adverse effects quantified. The PACTG 219 study is also following children born to mothers who have taken ZDV and other ARVs during pregnancy.

ETHICAL ISSUES

Questions have been raised regarding the ethics of stopping antiretrovirals after delivery. The primary reason for using antiretrovirals in pregnancy is to reduce MTCT and the effects they may have on the mother's health are secondary. ARV use for this indication should be provided for all women regardless of their clinical status, and some of these women would not require ongoing ARV treatment at this stage.

In settings where access to antiretrovirals is not the norm, the cost of continuing these drugs for the duration of the mother's life is likely to be prohibitive. None the less governments, health ministries, pharmaceutical companies and international agencies should endeavour to make these drugs available to people in areas where the majority of HIV infection occurs. Strategies to reduce perinatal transmission will identify large numbers of HIV positive women who should be able to receive ongoing care of the standard available in their communities.

COST-EFFECTIVENESS OF ARV TREATMENT FOR PREVENTION OF MTCT

ARV Treatment	Cost/DALY (US\$)	Place, Date of Data, and Source
Prophylaxis for HIV+ pregnant women (076 protocol)	approx. \$40-60 (depending on life expectancy)	Model for "a developing country" (Mansergh et al 1996)

An economic assessment of the cost effectiveness of "long" course ARV regimen is shown above. These figures are based on the full price of ZDV and 3TC and will decrease somewhat with price reductions announced by Glaxo Wellcome. No allowance is made for the cost of infant feeding counselling and guidance, or for nutrition support after 6 months of age.

MONITORING AND QUALITY CONTROL OF ARV INTERVENTION

As noted above data on the prevention of MTCT by ARV interventions is either from industrialised countries or from trial settings. It is important that when ARV interventions are adopted in routine health settings that systems are in place for their monitoring. Both operational and efficacy factors must be considered.

Conclusion

Antiretroviral therapy in pregnancy, both in long course and short course regimens, has been shown to significantly reduce the rate of mother-to-child transmission for non-breast feeding mothers. The combined effects of ARV treatment, elective caesarean section, and formula feeding (or other combinations of alternative obstetric and infant feeding practices) are still to be determined. Short course ARV treatment, with ZDV alone has been shown to be effective in a non-breastfeeding population. Additional work on short course monotherapy and combination therapy will provide further information during 1998.

The significant reduction in the price of antiretrovirals for use in the prevention of mother-to-child transmission negotiated by UNAIDS for developing countries will make access to this preventive strategy available to many more women across the world. Drug supply alone is not enough to provide the service, and antenatal care services, voluntary counselling and testing services will be required as a starting point to identify infected mothers. Costs of administering the treatment and of alternative infant feeding options must also be taken into account.

The potential benefits in the reduction of infected infants are of great importance to countries with high HIV seroprevalence, and the early identification of infected women, allowing for appropriate treatment and the adoption of protective measure will provide secondary benefits.

Table 1:
CURRENT RESEARCH ON PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

STRATEGY	RESEARCH PROJECTS
A: ANTIRETROVIRAL THERAPY	Phase III: 1. PETRA: ZDV & 3TC 2. ZDV alone in short course in breastfeeding women 3. Nevirapine (HIVNET 012 & PACTG 316) 4. ZDV short course with early weaning Phase I/II: Drugs under investigation include: ddI, d4T, nevirapine, nelfinavir, ritonavir, indinavir, saquinavir, PMPA, MKC-442
B: ACTIVE IMMUNIZATION	1. Recombinant Gp120 vaccine to pregnant women (PACTG 235). 2. Recombinant Gp120 to new-borns ; phase I/II (PACTG 230) 3. Canary pox vaccine to new-borns (PACTG 327)
C: PASSIVE IMMUNIZATION	1. HIVIG (Uganda) 2. Phase I Katinger antibody
D: MICRONUTRIENTS	1. Vitamin A (Malawi: 10 000IU) 2. Vitamin A South Africa (5000 IU + B Carotene 30mg) 3. 13 Micronutrients (Zimbabwe) 4. Factorial design Vitamin A & B Carotene (Tanzania)
E: VAGINAL CLEANSING	Chlorhexidine (Kenya)
F: INFANT FEEDING	Randomised trial of breast vs formula feeding (Kenya)

Table 2:
FDA classifications of antiretroviral drugs for use in pregnancy

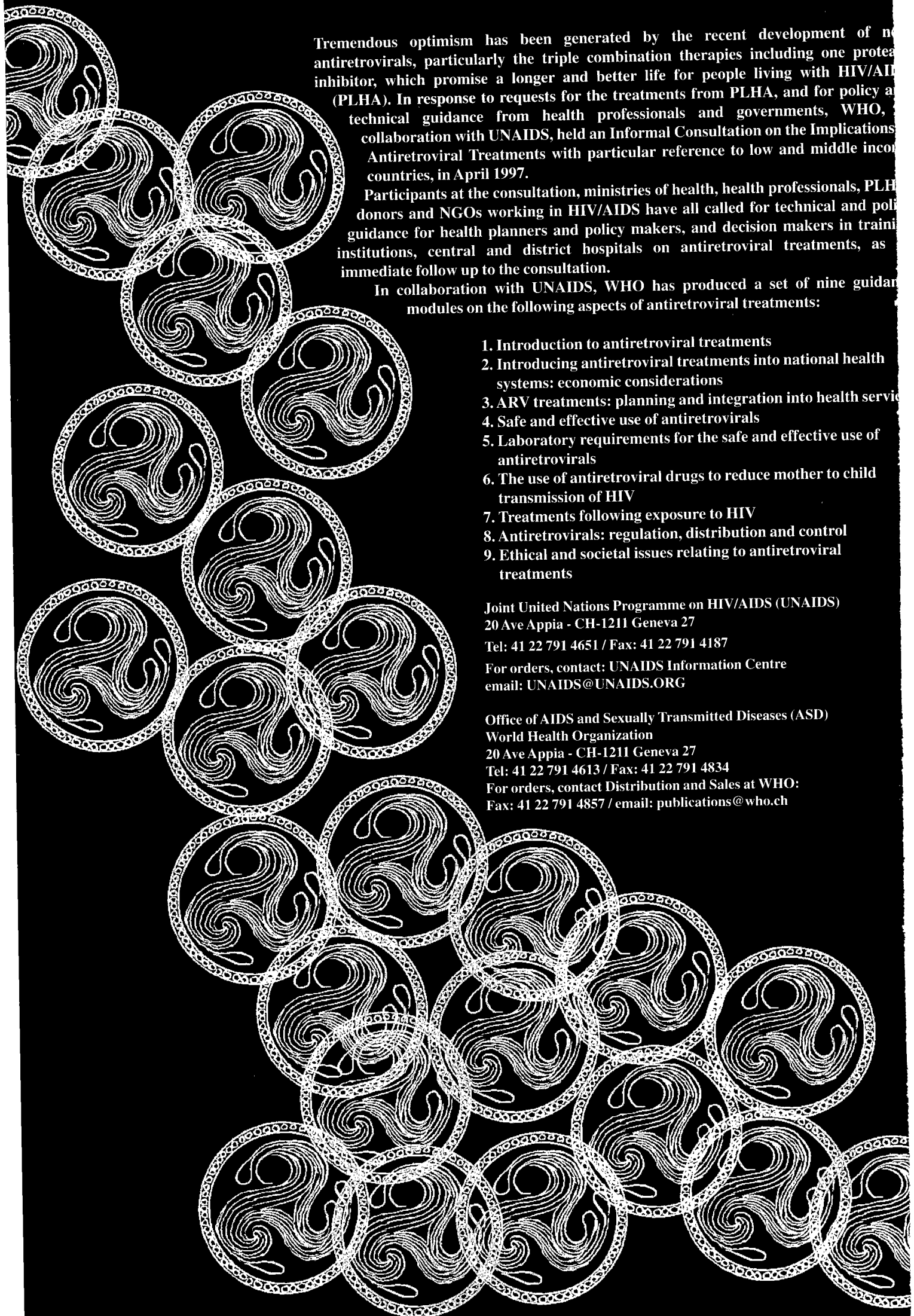
Classification:

- A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the foetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters)
- B: Animal reproduction studies fail to demonstrate a risk to the foetus but well controlled studies of pregnant women have not been conducted
- C: Safety in human pregnancy has not been determined, animal studies are either positive for foetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the foetus
- D: Positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
- X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit

DRUG	FDA CATEGORY
<i>Nucleoside Reverse Transcriptase Inhibitors</i>	
Zidovudine (ZDV, AZT)	C
Zalcitabine (ddC)	C
Didanosine (ddI)	B
Stavudine (d4T)	C
Lamivudine (3TC)	C
<i>Non-nucleoside Reverse Transcriptase Inhibitors</i>	
Nevirapine	C
Delavirdine	C
<i>Protease Inhibitors</i>	
Indinavir	C
Ritonavir	B
Saquinavir	B
Nelfinavir	B







Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

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