Executive Summary of a scientific review An update

Regional Consultation on Nutrition and HIV/AIDS in South-East Asia:
Evidence, lessons and recommendations for action

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NUTRITION AND HIV/AIDS
Executive Summary Update

Introduction

In preparation for a regional consultation on nutrition and HIV/AIDS in 2005, six review papers were prepared to summarize the existing knowledge base and identify gaps in available evidence related to the complexities of the relationship between nutrition and HIV infection.

The executive summary provided at that time a synopsis of the content of the larger review. The summary, presented a consolidation of the main key findings and identified knowledge gaps in the six scientific review papers and, where appropriate, the relevant WHO recommendations. The summary also emphasized those issues that were relevant to programme and policy actions in resource-limited settings. The key findings were discussed at the Consultation on Nutrition and HIV/AIDS in Africa, in Durban, South Africa, 10-13 April 2005. Based on these reviews WHO finalized a consensus statement and recommendations for immediate action and implementation by countries.

The reviews were underpinned by the principle that nutritional support is an integral part of a comprehensive response to HIV/AIDS, but nutritional support of any kind cannot serve as a substitute for antiretroviral therapy. The focus on nutrition derives from the concern to determine what additional nutritional elements are required to be considered in the rapid scale up ART in high burden countries.

The technical report was divided into three major sections:

Section I covered knowledge about macronutrients and micronutrients.

Section II covered knowledge about nutritional needs and includes issues on infant feeding and HIV transmission, growth failure in HIV-infected children and nutrition of pregnant and lactating women.

Section III included a review of current knowledge about the effect of ART on nutrition, metabolism, growth and development.

In preparation for the **Regional consultation in South East Asia** (8-11 October, 2007) three out of the six sections in the "Executive Summary" were revised as the Scientific Committee for the Consultation recommended to take into account new scientific knowledge and recent research findings.

These were.

- HIV and micronutrients
- HIV and infant feeding
- Nutrition and ART

These three updated sections are included in this preliminary version for your information and consideration. After the Bangkok consultation the update of the scientific papers will be continued for all sections and revised Executive Summary completed. In this context, kindly consider these updates as preliminary versions.

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Micronutrients

Key Findings:

- Access to a diet providing adequate micronutrients is fundamental to human health.
- HIV infection may increase micronutrient requirements, and cause or exacerbate existing micronutrient deficiencies.
- Assessment of nutritional status and dietary intake, and possibly nutritional support to ensure adequate micronutrient status, should be an integrated component of the case-management of children and adults with HIV infection.
- Efforts to ensure adequate intakes of micronutrients through access to a diversified diet, fortified foods and supplements for the general population must remain a major public health priority, particularly where both undernutrition and HIV infection are widespread.
- Interventions to increase the intake of micronutrients may reduce – or even increase – the risks of transmission or progression of HIV infection, or morbidity associated with HIV.
- Due to methodological limitations of trials performed, as well as differences within and between study populations, there is a need for more well-designed trials to allow evidence-based recommendations specifically for HIV infected individuals.
- Current data suggest that interventions providing vitamins B, C, E may be beneficial, whereas vitamin A and iron and possibly other micronutrients – although essential – may be potentially harmful, depending on the dose, composition, form and route of administration, as well as nutritional and other characteristics of the individual with HIV.
- The current recommendation of regular large-dose vitamin A supplementation among children six months to five years of age, seems also to be beneficial for those with HIV infection.
- The current recommendation of iron-folic acid supplementation among pregnant women may be inadequate, as supplementation with high doses of vitamins B, C and E was found to reduce maternal HIV progression, and be beneficial with respect to pregnancy outcomes.
- Postpartum maternal and infant vitamin A supplementation may be harmful for uninfected children, but targeted vitamin A supplementation of HIV positive children may prolong survival.
- High-dose multi-micronutrient supplementation may also reduce mortality among HIV infected adults in general, and among HIV patients undergoing treatment for pulmonary tuberculosis, but more data are needed before recommendations can be made.
- Access to ART does not reduce the need for nutritional assessment and support, as commencement of ART may increase nutritional requirements, and inadequate intake may affect drug absorption, efficacy and safety.

Evidence Base:

The review of the scientific literature on micronutrients and HIV infection was presented in 2005 (WHO, 2005). It concluded that HIV infection impairs micronutrient intake and status, and that this becomes worse with increasing disease severity and superimposed opportunistic infections. Furthermore, micronutrient supplementation, and possibly interventions increasing micronutrient intake, may affect the risk of HIV transmission and progression. Since then, other reviews have been undertaken, discussing the methodological difficulties and limitations associated with nutrition intervention trials (Friis, 2006) and the research priorities (ASSAf, 2007), and reviewing more recent data.

However, due to methodological limitations even data from randomised trials may be difficult to interpret and translate into evidence-based programmes and policies. Such methodological difficulties include lack of data on baseline nutritional status. In the absence of such data, it is difficult to assess how background micronutrient intake and status modifies the effect of the intervention, and to understand inconsistencies between trials in different populations. For example, zinc deficiency seriously impairs immunity, but excessive intake of zinc may also be immunosuppressive. Hence, the same zinc supplement may be either beneficial, neutral or harmful when given to individuals and populations with inadequate, adequate or high intakes of zinc.

Furthermore, lack of attention to possible effect modification by background status or intake of other micronutrients as well as other factors (eg. infections, vaccines, drugs, genotypes) may further reduce the generalizability of findings from randomised trials. The existence of micronutrient-micronutrient interactions is well-documented, but only relatively few are described and understood. Vitamin A deficiency, for example, may partly be due to zinc deficiency impairing conversion of provitamin A carotenoids to preformed vitamin A. In that situation, even supplementation with preformed vitamin A may be ineffective, since zinc is also required to synthesize retinol binding protein and hence mobilize vitamin A from the stores. Interventions ensuring the required intake of not only a single micronutrient, but the whole range of essential micronutrients may therefore be important, both from a scientific and a public health point of view. Nevertheless, even then may micronutrient-micronutrient interactions occur, in that addition of one micronutrient may reduce or enhance the absorption of other micronutrients.

There is an urgent need to develop a firm evidence-base in order to inform policy decisions about the potential role of micronutrient interventions in populations severely affected by HIV, and in the case-management of people living with HIV upon any contact with the health system. While such evidence has to come from trials using clinical endpoints, there is also a need to obtain a better understanding of the causal pathways involved. Not least since harmful effects of increasing the micronutrient intake cannot be excluded, depending on the dose, composition, form and route of administration, as well as nutritional and other characteristics of the individual with HIV.

Unfortunately, despite the urgency of the matter, still very few randomised, placebo-controlled, double-blind trials have been conducted with HIV-specific clinical outcomes, such as transmission or progression of HIV, or mortality, as summarized below.

Review of trials with HIV-specific outcomes or mortality

Vitamin A

Daily supplementation with vitamin A, given as preformed provitamin A as well as β-carotene was found to increase mother-to-child HIV transmission in a randomised trial in Tanzania (Fawzi, 2002), although no such effect was observed in two other trials (). Single large dose vitamin A supplements to HIV-infected mothers and/or their infants postpartum had no effects on mother-to-child HIV infection or overall mortality up to 2 years of age (Humphrey, 2006). However, the effects of supplementation on infant mortality seemed to depend on the timing of infant HIV infection: in infants infected *in utero*, neither intervention had effects, in infants infected around delivery infant supplementation reduced mortality, whereas in infants escaping infection *in utero* and around delivery, but exposed to HIV through breast milk, both maternal and neonatal supplementation increased mortality.

Regular large-dose vitamin A supplementation to children between 6 months and five years of age, as currently recommended, was found to reduce mortality in randomised trials in Tanzania (Fawzi, 1999) and Uganda (Semba, 2005).

Since vitamin A is an essential nutrient and vitamin A deficiency is widespread in resource-limited settings where HIV is most prevalent, there is a need to understand the mechanism behind the reported adverse effects, and to find ways whereby adequate vitamin A intake can be ensured. This is essential to ensure that the global commitment to combat vitamin A deficiency may be continued without the risk of increasing HIV transmission and progression.

Iron

Despite concern that interventions to increase iron intake might adversely increase morbidity from HIV infection *per se* or from opportunistic infections, the efficacy and safety of current iron interventions has not been adequately examined. [However, low dose iron given twice weekly to Kenyan adults and inclusion of iron to a multi-micronutrient supplement given to female injection users in the US had no effects on viral load.]

Other individual micronutrients

Several other micronutrients are essential to immunity and other body function, and often deficient in HIV infected individuals. However, single micronutrient interventions, other than those of vitamin A and iron, are not usually recommended. Therefore, micronutrients such as zinc, selenium, copper, vitamin D, etc, should be studied, if possible using a factorial design, and given as part of multi-micronutrient interventions.

Multi-micronutrients

Daily supplementation with high-doses of B vitamins, and vitamin C and E to HIV infected women during pregnancy and lactation in Tanzania, only reduced mother-to-child HIV transmission in the most nutritionally and immunologically compromised women. However, with supplementation continued several years, it also reduced progression of HIV in the women, partially mediated by effects on viral load and CD4 counts. In addition, the multivitamin supplement had beneficial effects on various non-HIV-specific outcomes, such as adverse pregnancy outcome, and infant growth and nutritional status. Although encouraging, the generalizability of the findings remains to be determined. Furthermore, pregnant and lactating HIV infected women in low income countries are also likely to be deficient with respect to other important vitamins and minerals. Daily multi-micronutrient supplementation seemed to reduce mortality among adult HIV infected adults in Thailand, although only in those with advanced HIV infection (Jiamton et al. 2003). Among Tanzanian patients with pulmonary tuberculosis co-infected with HIV, high dose multi-

micronutrient supplementation during TB treatment increased weight gain and reduced mortality (Range et al. 2006). In contrast, daily multi-micronutrient supplementation of Malawian patients with pulmonary TB and HIV co-infection, during and after TB treatment, had no effect on mortality. However, most micronutrients were only provided at the RDA levels, which might be inadequate given the high requirements.

Knowledge gaps:

- Reliable, feasible and affordable methods are needed to assess micronutrient status, also in individuals with infectious diseases.
- There is a need for research to estimate the effect of HIV infection, taking the clinical stage and treatment into consideration, on requirements for individual micronutrients. Special attentions should be given to children, and pregnant and lactating women.
- There is a need for research to clarify the mechanism mediating the harmful effects of vitamin A supplementation in individuals with HIV observed in some studies, and to develop safe and effective interventions to ensure adequate intake and status of vitamin A.
- There is a need for research to assess the safety and efficacy of current recommendations about iron supplementation, and, if needed, to develop safe and effective interventions to ensure adequate iron intake and status.
- There is a need for research to develop safe and effective interventions to ensure adequate intake of micronutrients in populations affected by undernutrition and HIV infection.
- There is an urgent need for well-designed micronutrient intervention trials to develop micronutrient interventions, providing all needed micronutrients, for various groups of HIV infected individual (children, pregnant/women, before and during ART, etc), including those being co-infected with and treated for tuberculosis.

References:

HIV/AIDS, TB and Nutrition. 2007. Academy of Science of South Africa.

Coutsoudis, A., Pillay, K., Spooner, E., Kuhn, L., & Coovadia, H. M. 1999, "Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group", *AIDS*, vol. 13, no. 12, pp. 1517-1524.

Fawzi, W. W., Mbise, R. L., Hertzmark, E., Fataki, M. R., Herrera, M. G., Ndossi, G., & Spiegelman, D. 1999, "A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania", *Pediatr.Infect.Dis.J.*, vol. 18, no. 2, pp. 127-133.

Fawzi, W. W., Msamanga, G. I., Hunter, D., Renjifo, B., Antelman, G., Bang, H., Manji, K., Kapiga, S., Mwakagile, D., Essex, M., & Spiegelman, D. 2002, "Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality", *AIDS*, vol. 16, no. 14, pp. 1935-1944.

Fawzi, W. W., Msamanga, G. I., Spiegelman, D., Wei, R., Kapiga, S., Villamor, E., Mwakagile, D., Mugusi, F., Hertzmark, E., Essex, M., & Hunter, D. J. 2004, "A randomized trial of multivitamin supplements and HIV disease progression and mortality", *N.Engl.J.Med.*, vol. 351, no. 1, pp. 23-32.

Friis, H. 2006, "Micronutrient interventions and HIV infection: a review of current evidence", *Trop.Med.Int.Health*, vol. 11, no. 12, pp. 1849-1857.

Humphrey, J. H., Iliff, P. J., Marinda, E. T., Mutasa, K., Moulton, L. H., Chidawanyika, H., Ward, B. J., Nathoo, K. J., Malaba, L. C., Zijenah, L. S., Zvandasara, P., Ntozini, R., Mzengeza, F., Mahomva, A. I., Ruff, A. J., Mbizvo, M. T., & Zunguza, C. D. 2006, "Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality", *J.Infect.Dis.*, vol. 193, no. 6, pp. 860-871.

Jiamton, S., Pepin, J., Suttent, R., Filteau, S., Mahakkanukrauh, B., Hanshaoworakul, W., Chaisilwattana, P., Suthipinittharm, P., Shetty, P., & Jaffar, S. 2003, "A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok", *AIDS*, vol. 17, no. 17, pp. 2461-2469.

Kumwenda, N., Miotti, P. G., Taha, T. E., Broadhead, R., Biggar, R. J., Jackson, J. B., Melikian, G., & Semba, R. D. 2002, "Antenatal vitamin A supplementation increases birth weight and decreases anemia among infants born to human immunodeficiency virus-infected women in Malawi", *Clin.Infect.Dis.*, vol. 35, no. 5, pp. 618-624.

Range, N., Changalucha, J., Krarup, H., Magnussen, P., Andersen, A. B., & Friis, H. 2006, "The effect of multi-vitamin/mineral supplementation on mortality during treatment of pulmonary tuberculosis: a randomised two-by-two factorial trial in Mwanza, Tanzania", *Br.J.Nutr.*, vol. 95, no. 4, pp. 762-770.

Semba, R. D., Ndugwa, C., Perry, R. T., Clark, T. D., Jackson, J. B., Melikian, G., Tielsch, J., & Mmiro, F. 2005, "Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: A controlled clinical trial", *Nutrition*, vol. 21, no. 1, pp. 25-31.

Semba, R. D., Kumwenda, J., Zijlstra, E., Ricks, M. O., van, L. M., Whalen, C., Clark, T. D., Jorgensen, L., Kohler, J., Kumwenda, N., Taha, T. E., & Harries, A. D. 2007, "Micronutrient supplements and mortality of HIV-infected adults with pulmonary TB: a controlled clinical trial", *Int.J.Tuberc.Lung Dis.*, vol. 11, no. 8, pp. 854-859.

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5. Infant Feeding and HIV Transmission

Key Findings:

- The overall risk of mother-to-child HIV transmission by a nonbreastfeeding mother is 15–25% (without interventions to reduce transmission) and of a breastfeeding mother is 20–45%.
- The most effective intervention for reducing HIV transmission is through the use of ARV prophylaxis in a PMTCT programme which should include access to ART for the mother when indicated.
- Exclusive breastfeeding carries a lower risk of HIV transmission in the first months of life than mixed feeding, that is, giving other liquids or foods in addition to breast milk.
- Because human milk can transmit HIV at any time during lactation, the rate of HIV-infection in breastfed infants is cumulative and increases with duration of breastfeeding.
- Recent HIV infection, disease progression and clinical or sub-clinical mastitis are among the factors associated with HIV transmission through breastfeeding.
- The most appropriate infant feeding option for an HIV infected mother depends on her individual circumstances, including her health status and the local situation, but should take consideration of the health services available and the counselling and support she is likely to receive.
- Exclusive breastfeeding is recommended for HIV-infected women for the first six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time.
- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended.
- When suitable replacement foods are not accessible, early breastfeeding cessation may increase malnutrition in infants and young children; malnutrition significantly increases the risk of child mortality from infectious diseases.
- Guiding principles for feeding the non-breastfed child after six months are available from WHO. The Global Strategy for Infant and Young Child Feeding, adopted by WHO and the United Nations Children's Fund, provides the context for feeding of children in exceptionally difficult circumstances, including those born to HIV-positive women.

- In making the right choice women should receive counselling, including general information about the risks and benefits of the various infant-feeding options and specific guidance in selecting the option most likely to suit their circumstances. The mother's choice should always be respected and supported.

- HIV-positive women should have access to follow-up care and support, including family planning and nutritional support.

Evidence Base:

Without specific interventions, HIV-infected women will pass the virus to their infants during pregnancy or delivery in about 15–25% of cases; and an additional 5–20% of infants may become infected postnatally during breastfeeding, for an overall risk of 30–45%. Breastfeeding may thus be responsible for one third to one half of HIV infections in infants in settings where interventions are not available.

HIV has been detected in breast milk in cell-free and cell-associated compartments and there is now evidence that both compartments are involved in transmission of HIV through breast milk. Following ingestion of HIV infected breast milk, infant gut mucosal surfaces are the most likely site at which transmission occurs.

Transmission of HIV continues throughout the breastfeeding period. Data from a meta-analysis show that the cumulative probability of late postnatal transmission at 18 months is 9.3% (95% confidence interval, CI, 3.8–14.8%). Late postnatal transmission, therefore, could contribute as much as 42% to the overall rate of MTCT. Analysis indicates that late postnatal transmission risk is around 1% per month of breastfeeding and is constant over time from between four and six weeks to 18 months. Transmission can take place at any point during breastfeeding, and the longer the duration of breastfeeding, the greater the cumulative additional risk. When breastfeeding is prolonged beyond 18–24 months, the additional cumulative postnatal HIV risk varies from 4% to 16% across studies, depending on breastfeeding duration.

The risk of postnatal transmission through breastfeeding is associated with clinical, immunological and virological maternal factors and infant feeding patterns. Maternal seroconversion during breastfeeding, low maternal CD4 cell count, increased maternal RNA viral load in plasma and breast milk and a lack of persistence of HIV-specific IgM in breast-milk at 18 months are strongly associated with increased risk of transmission through breastfeeding. Breast pathologies such as clinical and subclinical mastitis, nipple bleeding, and abscesses, fissures or lesions are also associated with a higher risk of transmission through breastfeeding.

Exclusive breastfeeding for up to six months is associated with a three to fourfold decreased risk of transmission of HIV compared to non-exclusive breastfeeding; mixed feeding, therefore, appears to be a clear risk factor for postnatal transmission. One study found that about 4% of exclusively breastfed infants became infected through exclusive breastfeeding from six weeks to six months.

The duration of breastfeeding is confirmed to be one of the main risk factors for HIV transmission through breastfeeding. In Zimbabwe, among the children exposed to HIV through breastfeeding, the overall risk of postnatal transmission was 12%, of which 68% occurred after six months.

Prevention of MTCT of HIV using available peripartum antiretroviral interventions can be achieved leading to peripartum HIV transmission rates below 5%, even in breastfed populations, and considerable effort is ongoing to expand these interventions to a wider population.

The incidence of HIV infection among women during the postpartum period is high in some parts of the world. The overall risk of MTCT is increased in recently-infected lactating women and estimated to be 29% (95% CI, 16–42%), illustrating the importance of prevention of primary infection throughout the breastfeeding period.

Early cessation of breastfeeding could prevent a sizable proportion of postnatal HIV infections but several studies have reported that it was associated with an increased risk of infant morbidity (especially diarrhoea) and mortality in HIV-exposed children. Recent data show that prolonged breastfeeding of children already infected with HIV is associated with improved survival compared to early cessation of breastfeeding.

Knowledge Gaps:

- Identifying approaches to treating expressed breast milk to eliminate the risk of transmission while preserving the milk's nutritional content and protective qualities.

- Practical tools that can be used routinely – especially around the time of early breastfeeding cessation – to contribute to the assessment of the nutritional adequacy of complementary feeding and guide efficiently the nutritional counselling of children exposed to HIV.

- Whether HAART to women during breastfeeding (whether or not necessary for the mother's health) and post-exposure prophylaxis to the infant are effective and safe for the infant.

- The potential role of passive and active immunization strategies of breastfed newborns.

- Finding effective means of preventing HIV transmission during breastfeeding with appropriate interventions is an urgent priority in resource-limited settings.

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Section III: Nutrition and Antiretroviral Therapies (ART)

The overriding principles for evidence-based guidelines regarding the importance of nutrition for people living with HIV and AIDS (PLWHA) are:

- Antiretroviral drugs (ARV) are essential to prolong lives and halt the spread of HIV/AIDS
- Food is essential to life for all people

The challenge is how to apply sound principles of clinical care and nutrition science to the safe and efficacious implementation of ARV's and long-term care for PLWHA. The goal of this review is to update the original review with new data that can have an impact on current approaches to care and treatment.

The fundamental questions in resource-limited settings where food insecurity/malnutrition and HIV co-exist are:

- What is the role of diet/nutrition in HIV/AIDS and related conditions that would require special consideration above and beyond provision of food to ensure a well balanced diet?
- How might the potential impact of nutrition on drug metabolism and vice versa be played out with specific reference to the use of ART?

The review prepared in 2005 (Raiten et al., 2005) addressed these concerns and outlined a research agenda to help answer outstanding questions. This update includes an overview of those initial findings and a brief review of evidence developed in the ensuing 2 years. As this update is being prepared in the context of the convening of the WHO consultation on nutrition and HIV/AIDS in Southeast Asia Region (SEAR) it also contains data on the condition upon which the HIV epidemic and ART scale-up have been superimposed in this region.

The overarching conclusions of the review were:

- ARV/ART/HAART save lives, but their use may cause metabolic changes, including insulin resistance, dyslipidemia, fat redistribution, bone related problems. These conditions may place patients at risk for other diseases.
- Switching drugs is one response to addressing these concerns. However, the role of dietary and/or nutritional management should also be considered.
- Knowledge of these effects is critical in the implementation of appropriate nutritional policies in conjunction with HAART use

Key Findings from the 2005 review on ART:

- HIV-infected adults and children being considered for ART and while on ART need to be screened and assessed for nutritional problems:basic anthropometry and dietary assessment are appropriate.
- Documentation is needed of dietary supplement use including use of herbal and botanical therapies (that can potentially cause drug/supplement interactions which in turn affect the efficacy, safety and/or compliance with ART) and participation in government-sponsored food and/or micronutrient supplementation programmes.
- ART can reverse but not rectify the loss of body mass (including muscle mass) that results from HIV infection.
- Metabolic complications of long-term ART are documented in HIV-infected adults, infants and children include lipodystrophy, dyslipidaemia, insulin resistance, derangements in glucose tolerance, lacticacidaemia and mitochondrial toxicity, and problems with bone mineral metabolism.
- Risk estimates vary for lipodystrophy and the ART metabolic syndrome but there is a consensus that although nucleoside reverse-transcriptase inhibitors drugs (NRTIs) such as stavudine have also been implicated, protease inhibitors (PI) are the class of drugs most commonly associated with these effects.
- These effects appear in men, women, and children, and present risks in terms of adherence with ART protocols, long-term health and quality-of-life issues and increased risk of chronic diseases including cardiovascular disease and diabetes.
- Bone problems have been associated with ART in HIV-infected adults and children. However the implication and importance of this is yet unknown and at present this does not effect the current recommendation for selection of first and second level therapies in resource-limited settings.

Knowledge Gaps:

Wasting and Energy Metabolism:

A number of knowledge gaps were identified that continue to be of concern in the context of ART. With regard to the overarching issue of wasting, data continue to support the conclusion that although ART reduces many of the contributing factors, wasting continues to be an issue in the era of ART including highly active anti-retroviral therapies (HAART). The reasons are not known but potential factors identified pre-HAART still are in play and need to be monitored (Tang et al., 2005; Mangili et al., 2006). Further, van der Sande et al. (2004) have reported that BMI (weight/height2) is a strong predictor of mortality in PLWHA (van der Sande et al, 2004). Responsiveness to both ART and dietary interventions are affected by similar conditions, including stage of disease when initiated, BMI, body composition (lean versus adipose mass), and presence or absence of OI

Although data suggest increased resting energy expenditure in low-weight HIV-positive patients taking ARV's, especially those with active secondary infection, a need exists to study this effect in HIV-infected people living under conditions of malnutrition or severe food insecurity. To date there are insufficient data to address this issue.

An additional question is the impact of ART on work capacity of HIV-infected people. At this time there are several non-ART strategies for improving LBM and work capacity, e.g., hGH (Esposito et al., 2005), but these may not be available or practical in many settings in the developing world where the epidemic has hit hardest.

In 2003, WHO issued its first set of recommendations with regard to the nutritional needs of PLWHA. Paramount among those recommendations was the increased energy needs in both asymptomatic and symptomatic HIV-infected adults and children (WHO, 2003). Since that time several reports have confirmed increased resting energy expenditure (REE) in HIV infection (Betterham, 2005).

With specific regard to the impact of ART on energy requirements Shevitz AH, et al. (1999) published some of the first evidence documenting elevated resting energy expenditure among HIV-infected persons receiving HAART. A number of studies subsequently provided further confirmation of this relationship Kosmiski et al. 2001; Batterham et al., 2003).

There have been some recent attempts to expand our understanding of potential mechanisms that can account for changes in energy regulation in HIV infected patients. For example, Sutinen and Yki-Jarvinen (2007) examined the interaction between energy metabolism, ART, fat oxidation and changes in dietary intake and reported a positive association with increased REE and lipid oxidation and increased caloric and fat intake in patients with ART related lipodystrophy. At this time however the precise mechanism for the changes in energy metabolism associated with HIV per se and ART remains an elusive target. The potential mechanisms including the role of ART in energy dysregulation in HIV infected people was recently reviewed by Chang et al. (2007).

Nutrition and ART:

It is clear that metabolic complications do occur in people exposed to ART. It is less clear whether being chronically malnourished has an impact on drug safety and effectiveness. Thus a key question in addressing these problems is whether nutritional status somehow can predict and/or influence ART outcome: The answer is yes; nutritional status matters.

In a seminal study, Paton et al. (2006) evaluated the impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting ART in Singapore. Moderate to severe malnutrition was present in 16% of patients at the time of starting ART, and was found to be a significant independent predictor of death [hazard ratio (HR) 2.19, 95% confidence interval (CI) 1.29–3.73, P<0.004 for those with a body mass index (BMI) <17 compared with those with BMI>18.5]. Based on their observations, these authors concluded that, “Malnutrition at the time of starting ART was significantly associated with decreased survival, but the effect appeared not to be mediated by impaired immune reconstitution. Given the increasing access to ART in developing countries and the high frequency of HIV-associated wasting, studies of nutritional therapy as an adjunct to the initiation of HAART are urgently needed. “

Zachariah et al. (2006) evaluated risk factors for high early mortality in patients on ART in a rural district of Malawi. They reported significant risk factors associated with mortality included WHO stage IV disease, a baseline CD4 cell count <50 cells/ml and increasing grades of malnutrition. A linear trend in mortality was observed with

increasing grades of malnutrition and decreasing CD4 cell counts. Individuals who were severely malnourished (BMI)<16.0 kg/m2) had a six times higher risk of dying in the first 3 months than those with a normal nutritional status.

In a similar study, Ferradini et al. (2006) evaluated predictors of survival and compliance with a HAART scale-up initiative in a rural population in Malawi Consistent with the findings above, these authors reported that along with CD4 count and WHO Stage IV diagnosis, BMI was an independent predictor of mortality.

ART in SEAR:

As the HIV pandemic has matured, a data base has emerged with regard to the impact of ART in SEAR. Chuapai Y, et al. (2007) reported a high prevalence of dyslipidemia (53.6%) and lipodystrophy (66.1%) detected in their small survey of HIV-infected adults. Hiransuthikul et al. (2007) reported similar prevalence of dyslipidemias associated with protease inhibitors (PI) and HAART in a cohort of HIV-infected adults in Thailand. The findings of both these reports are consistence with those from US and elsewhere.

As the HIV pandemic has spread globally the question of genetic differences in response to both the disease and its treatment has emerged as an important concern for care. Chang et al. (2002) asked whether the prevalence of metabolic complications, particularly lipodystrophy was similar in a cohort of Korean HIV infected adults as values reported for Caucasians populations. They observed that in comparison of metabolic indices in ART, ART naïve HIV-infected and HIV uninfected Korean patients (total n=156) only HDL-chol was significantly lower in the HIV patients. They concluded that lipodystrophy, hyperlipidemia, and insulin resistance are rare metabolic complications of HAART in this cohort suggesting the need for additional studies of race-specific metabolic complication studies in HIV-infected subjects receiving HAART

In contrast, Pujari et al. (2005) reported that in a comparison of ART and ART naïve patients in India, the prevalence of lipodystrophy was 46.1%, and lipoatrophy was significantly associated with stavudine (d4T) use. The prevalence of dyslipidemia and fasting hyperglycemia was significantly higher in the treatment groups and not dissimilar to that found in populations in the US and Europe..

ART and the Metabolic Syndrome (MetSyn):

Coincident with the spread of HIV has been an alarming global increase in the constellation of conditions now referred to as the metabolic syndrome.(MetSyn) Because of the high prevalence of the MetSyn, it is important to ask the question in the context of what we see in response to ART, are these complications due to HIV, ART, nature, or a combination of all?

According to Misra et al. (2007), “approximately 20-25 per cent of urban South Asians have evidence of the metabolic syndrome. Furthermore, insulin resistance was reported to be present in nearly 30 per cent of children and adolescents in India, more so in girls. At the same time many young individuals have clustering of other risk factors/conditions related to insulin resistance (e.g.,non-alcoholic fatty liver disease, obstructive sleep apnoea, etc.). Rapid nutritional and lifestyle transition in urbanized areas in various countries in South Asia are prime reasons for increasing prevalence of obesity and the metabolic syndrome.”

Although studies have reported no differences in metabolic complications between HIV-infected and uninfected populations (Mondy et al. 2007; Brar et al. (2007)); some have reported higher prevalence (Estrada et al.2006; , Shikuma et al (2007)).

So, what is it? Part of the problem is our definition of the MetSyn. Samaras et al (2007) reported that HIV-infected patients had lower incidence of MetSyn than controls depending on the definition used but, almost 50% had at least two components (using missing waist-to-hip criteria). Those patients with Met Syn were on PI.

Deepa et al. 2007 in a comparison of the prevalence of the MetSyn using WHO, ATPIII and IDF definitions in Asian Indians reported that out of a total sample of 2400 randomly screened adults >20 yrs.(not tested for HIV status) the range of MetSyn differed considerably based on the criteria used: WHO criteria n = 546 (23.2%), IDF criteria n = 607 (25.8%), NCEP ATPIII criteria n= 430 (18.3%), and 224 met the criteria for all three.

While the clinical significance of being diagnosed with the MetSyn remains unclear, its constituent parts, i.e., dyslipidemia, hypertension. obesity etc. each present significant risk for adverse health outcomes and should be considered before and during ART. In light of the high prevalence of all of these conditions in SEAR, it becomes an important consideration in the context of ART scale in this region. Table 1 outlines the different criteria for defining the MetSyn.

The research agenda with regard to the HIV MetSyn includes the following:

- Does HIV-infection place patients at ↑ risk for CVD, diabetes, MetSyn?
- Are there genetic differences in predisposition?
- Do ARV further ↑ that risk or are they independent risk factors?
- Are HIV infected patients already at risk for MetSyn because of inherent risk independent of HIV status, i.e., would they develop MetSyn even without HIV?
- Does ART accelerate risk of MetSyn in patients already at risk, i.e. is it a trigger?
- What is the role of nutritional status as either a predictor or modulator of MetSyn in HIV?

<u>ART and Bone</u>:

Aside from the metabolic complications discussed above another significant concomitant of HIV and ART highlighted in the 2005 report was bone-related problems. Again, the fundamental question is whether the bone problems observed in HIV infected adults and children are due to a metabolic derangement resulting primarily from the HIV infection, the use of ART, poor nutrition or some combination of all? The status of our understanding of this question is that it's probably the latter, i.e., combined effects

Gallant et al. (2004) reported high baseline prevalence of osteopenia in both treatment arms (23 and 28%) of their study of ART; these rates are significantly higher than rates found in uninfected populations.

The study by Cozzolino et al. (2003) suggested a mechanism for the bone problems related to certain PI. The reported that in their in vitro study, ritonavir, indinavir, and

nelfinavir decreased hepatic 25-hydroxylase and macrophage 1-hydroxylase activity and led to calcitriol degradation, all with a final effect of decreased macrophage-based calcitriol activity. The bottom line is that vitamin D is metabolized via the same cytochrome P450 enzymes stimulated by these PI. Thus the use of PI can result in impaired vitamin D activation.

Is vitamin D an issue in SEAR?

Several reports indicate that it is and therefore both HIV infection and the use of ART may be superimposed on a population already at risk for problems with this essential nutrient. In a survey of urban and rural men and women in India Harinarayan et al. (2007) found high prevalence of vitamin D deficiency (<20 ng/mL 25 OH D) in the rural, and vitamin D-insufficient (20-30 ng/mL) in 44%, 39.5% of the men and 70%, 29% of the women, respectively. In the urban subjects, 25(OH)D-deficiency and insufficient were seen in 62% and 26% of the men and 75% and 19% of the women.

Vitamin D status is a problem in other countries of the SEAR as well. For example, Islam, et al.(2006) surveyed women (n=121) ages 18–60 and found a prevalence of vitamin D insufficiency of 35% in Bangladesh. Lips (2007) reviewed the literature and confirmed a high prevalence of vitamin D deficiency India (> 30%), with highest risk in school children, pregnant women and large cities. He also reported that there is a range of status across Asia, e.g., vitamin D status was much better in Malaysia and Singapore but lower serum 25(OH)D was observed in Japan and China (apparently associated with seasonal variations).

Micronutrients and ART:

The role of micronutrients in HIV has been covered in Section 1 of this report. With specific regard to the potential for interactions between micronutrient status and ART there are limited data. Drain et al. (2007) reviewed the extant data and observed that, “most of these studies had some major limitations, including a small sample size, a short duration of follow-up, a lack of adjustment for inflammatory markers, and an inadequate assessment of HIV-related outcomes. Therefore, few data are available to determine whether HAART ameliorates micronutrient deficiencies or to recommend or refute the benefit of providing micronutrient supplements to HIV-positive persons receiving HAART. Because micronutrient supplementation may cause harm, randomized placebo-controlled trials are needed..”

Current Knowledge Gaps and Research Agenda

Outstanding questions regarding treatment of metabolic consequence of ART include the following case management issues

- Do risk factors for chronic diseases observed in PLWHA warrant the same response as in non-infected adults and children? If not, why not? The statin story
- Does being chronically malnourished present different conditions for care? For example, can we utilize current care recommendations for lowering CVD risk in pop at risk for severe caloric deprivation?
- How can we manage complications to avoid impact on compliance?
- What is the impact of micronutrients in the context of ART?
- What are the effects (if any) of ART on the nutritional needs of lactating women particularly in resource-limited settings
- What is the impact of ART on nutrient composition of human milk? What is the impact of malnutrition on drug pharmacokinetics, metabolism, efficacy/safety?
- Potential interactions of ARV with Traditional medicines?
- Operational issues: what to do in different settings?

Additional research and clinical care challenges:

- The “triangulation” of malnutrition, ART and treatments for opportunities infections (OI) and co-morbidities of HIV.
- The interface between ART implementation and programs aimed at addressing food insecurity or malnutrition at a macro-level.
- Prophylaxis versus care: assessment needs and site-specific guidelines.
- Customizing guidelines based on indigenous conditions.
- Capacity needs to implement clinical guidelines.

Conclusion:

The conclusions remain the same, ARV/ART/HAART save lives, but their use may cause metabolic changes, including insulin resistance, dyslipidemia, fat redistribution, bone related problems. These conditions may place patients at risk for other diseases.

What we have learned is that nutritional status matters, patients who are severely malnourished have increased risk for poor outcomes even with ART. Further, the metabolic complications that have been associated with ART already exist in the general population. Thus the use of ARV is being superimposed on populations that are already at risk for these problems. Consequently, we must be increasingly vigilant about clinical assessment before and during treatment to be able to respond most effectively to not only save but improve the quality of life of PLWHA.

References Cited:

Batterham MJ, Morgan-Jones J, Greenop P, Garsia R, Gold J, Caterson I. 2003. Calculating energy requirements for men with HIV/AIDS in the era of highly active antiretroviral therapy.Eur J Clin Nutr.57(2):209-17

Betterham, MJ.2005. Investigating heterogeneity in studies of resting energy expenditure in persons with HIV/AIDS: a meta-analysis. Am.J.Clin. Nutr. 81: 702-713.

Brar I, Shuter J, Thomas A, Daniels E, Absalon J; Minorities and Women's Task Force of Terry Beirn Community Programs for Clinical Research on AIDS. 2007. A comparison of factors associated with prevalent diabetes mellitus among HIV-Infected antiretroviral-naive individuals versus individuals in the National Health and Nutritional Examination Survey cohort. JAIDS. 45(1):66-71.

Chang E, Sekhar R, Patel S, Balasubramanyam A. 2007. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. Clin Infect Dis. 44(11):1509-17

Chang KH, Kim JM, Song YG, Hong SK, Lee HC, Lim SK.2002. Does race protect an oriental population from developing lipodystrophy in HIV-infected individuals on HAART? J Infect. 44(1):33-8.

Chuapai Y, Kiertiburanakul S, Malathum K, Sungkanuparph S.2007. Lipodystrophy and dyslipidemia in human immunodeficiency virus-infected Thai patients receiving antiretroviral therapy. J Med Assoc Thai.90(3):452-8.

Cozzolino M, Vidal M, Arcidiacono MV, Tebas P, Yarasheski KE, Dusso AS 2003. HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D. AIDS 17:513 20

Deepa M, Farooq S, Datta M, Deepa R, Mohan V. 2007 Prevalence of metabolic syndrome using WHO, ATPIII and IDF definitions in Asian Indians: the Chennai Urban Rural Epidemiology Study (CURES-34).Diabetes Metab Res Rev. 23(2):127-34

Drain PK, Kupka R, Mugusi F, Fawzi WW. 2007. Micronutrients in HIV-positive persons receiving highly active antiretroviral therapy. Am J Clin Nutr 85:333– 45

Elevated resting energy expenditure among HIV-seropositive persons receiving highly active antiretroviral therapy. AIDS. 13(11):1351-7.

Esposito JG, Thomas SG, Kingdon L., Ezzat S. 2005.Anabolic growth hormone action improves submaximal measures of physical performance in patients with HIV-associated wasting. Am J Physiol Endocrinol Metab 289: E494–E503

Estrada V, Martinez-Larrad MT, Gonzalez-Sanchez JL, de Villar NG, Zabena C, Fernandez C, Serrano-Rios M..2006.Lipodystrophy and metabolic syndrome in HIV-infected patients treated with antiretroviral therapy. Metabolism.55(7):940-5.

Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, Karungi G, Szumilin E, Balandine S, Fedida G, Carrieri MP, Spire B, Ford N, Tassie JM, Guerin PJ, Brasher C 2006. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. Lancet. 367(9519):1335-42

Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK; 903 Study Group 2004. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 292:191 201.

Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, Kumar EG. 2007. High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians.Am J Clin Nutr. 85(4):1062-7

Hiransuthikul N, Hiransuthikul P, Kanasook Y 2007. Lipid profiles of Thai adult HIV-infected patients receiving protease inhibitors. Southeast Asian J Trop Med Public Health. 38(1):69-77

Islam MZ, Akhtaruzzaman M, Lamberg-Allardt C. 2006. Hypovitaminosis D is common in both veiled and non-veiled Bangladeshi women, Asia Pac. J. Clin. Nutr. 15: 81–87.

J Acquir Immune Defic Syndr. 40(1):70-6.

Kosmiski LA, Kuritzkes DR, Lichtenstein KA, Glueck DH, Gourley PJ, Stamm ER, Scherzinger AL, Eckel RH. 2001. Fat distribution and metabolic changes are strongly correlated and energy expenditure is increased in the HIV lipodystrophy syndrome. AIDS. 15(15):1993-2000.

Lips P. 2007. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Mol Biol.103(3-5):620-5.

Mangili A, Murman DH, Zampini AM, Wanke CA. 2006. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. Clin Infect Dis. 42(6):836-42.

Misra A, Misra R, Wijesuriya M, Banerjee D 2007 The metabolic syndrome in South Asians: continuing escalation & possible solutions. Indian J Med Res. 125(3):345-54

Mondy K, Overton ET, Grubb J, Tong S, Seyfried W, Powderly W, Yarasheski K. 2007. Metabolic syndrome in HIV-infected patients from an urban, mid-western US outpatient population.Clin Infect Dis. 44(5):726-34

Paton NI, Sangeetha S, Earnest A, Bellamy R 2006. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Medicine 7, 323–330.

performance in patients with HIV-associated wasting. Am J Physiol Endocrinol Metab 289: E494–E503.

Pujari SN, Dravid A, Naik E, Bhagat S, Tash K, Nadler JP, Sinnott JT. 2005. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. J Acquir Immune Defic Syndr. 2005 Jun 1;39(2):199-202

Raiten, DJ, Grinspoon S., Arpadi S. 2005. Nutritional considerations in the use of ART in resource-limited settings. WHO/NHD publication.

Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A.Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. Diabetes Care. 2007 Jan;30(1):113-9.

Shevitz AH, Knox TA, Spiegelman D, Roubenoff R, Gorbach SL, Skolnik PR. 1999.

Shikuma CM, Yang Y, Glesby MJ, Meyer WA 3rd, Tashima KT, Ribaudo HJ, Webb N, Bastow B, Kuritzkes DR, Gulick RM. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 Infection (AIDS Clinical Trials Group Study A5095).JAIDS. 44(5):540-50.

Sutinen J, Yki-Jarvinen H. 2007. Increased resting energy expenditure, fat oxidation, and food intake in patients with highly active antiretroviral therapy-associated lipodystrophy.

Am J Physiol Endocrinol Metab. 292(3):E687-92

Tang AM, Jacobson DL, Spiegelman D, Knox TA, Wanke C. 2005. Increasing risk of 5% or greater unintentional weight loss in a cohort of HIV-infected patients, 1995 to 2003.

van der Sande MA, Schim van der Loeff MF, Aveika AA, Sabally S, Togun T, Sarge-Njie R, Alabi AS, Jaye A, Corrah T, Whittle HC. 2004. Body mass index at time of HIV diagnosis: a strong and independent predictor of survival. J Acquir Immune Defic Syndr. 37(2):1288-94.

Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, Harries AD. 2006. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS. 20(18):2355-60.