

Nutritional considerations in the use of ART in resource-limited settings

Daniel J. Raiten, Steven Grinspoon and Stephen Arpadi

*Consultation on Nutrition and HIV/AIDS in Africa:
Evidence, lessons and recommendations for action*

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Contents

1. Introduction	1
2. Overview of drug metabolism: why does nutrition matter?	2
2.1. Specific examples of nutrient–drug interactions	4
2.2. Effect of nonnutrient components of food on drug metabolism.....	5
2.3. Food–drug interactions: specific effects on ART	6
3. Metabolic consequences of HIV/AIDS: before and after ARVs	7
3.1. Overview	8
3.2. Effect of ART on HIV-related wasting	9
4. Metabolic complications associated with ART	10
4.1. The ART metabolic syndrome	10
4.2. Bone mineral metabolism.....	14
4.3. Lactic acidemia, mitochondrial toxicity and use of NRTIs	16
4.4. Energy metabolism and ART	17
5. Gender-specific issues in HIV metabolism in adults.....	18
5.1. HIV, nutrition and pregnancy	20
5.2. HIV, nutrition and lactation.....	20
6. Effect of HIV infection on infants and children	22
6.1. Impact of ART on growth	23
6.2. Bone abnormalities in HIV-infected children and adolescents	25
6.3. The ART metabolic syndrome in infants and children.....	27
7. Research gaps	30
7.1. Nutrition and pharmacology	31
7.2. Metabolic consequences of ART	31
7.3. Pregnancy	32
7.4. Lactation	32
7.5. Children	32
8. Summary and conclusions	33
9. References	34

1. Introduction

As the HIV/AIDS pandemic continues to expand, the moral imperative to provide safe and efficacious treatment options becomes of paramount interest to the international health-care communities. The use of antiretroviral therapy (ART) has become the cornerstone of the clinical armamentarium available to prevent transmission and slow progression of the infection in people living with HIV/AIDS (PLWHA) worldwide. Efforts have begun for a significant scaling up of the use of antiretroviral drugs (ARVs) in settings such as sub-Saharan Africa where the epidemic has had its most devastating impact. However, questions have been raised about the use of ART against a background of health problems not often seen in the developed world.

Reynolds et al. (1) observed that access to effective therapies for HIV-positive persons is arguably one of the highest global public health priorities but that simply providing affordable access to ARVs is insufficient. Prevention should be combined with access to clinical care that clearly helps patients to live longer, healthier lives. These authors suggested that “the expansion of access to highly active antiretroviral therapy (HAART) should be accompanied by a more evidence-based approach to optimize HIV care guidelines locally.” With this philosophy in mind, the World Health Organization Technical Advisory Group on Nutrition and HIV/AIDS (TAG) has been asked to provide advice and guidance about one of the most critical factors affecting conditions in the local setting and one that presents significant obstacles to our ability to ensure longer and healthier lives for PLWHA.

Chronic malnutrition continues to be a major contributor to the burden of disease worldwide (2). It provides the baseline setting on which the HIV pandemic has been imposed in many areas of sub-Saharan Africa. Consequently, an enhanced appreciation of the potential interactions between nutrition and ART is critical for the promulgation of relevant evidence-based practice guidelines.

The interaction of HIV/AIDS with nutritional status has been a distinguishing characteristic of the disease course since the earliest days of the epidemic. The term “*slim disease*” was often used in endemic areas such as sub-Saharan Africa to reflect the wasting syndrome characteristically associated with HIV/AIDS and related diseases (3–5). The importance of this interaction and suggested recommendations for nutritional interventions are covered throughout the other sections of this technical report and will be cross-referenced as appropriate.

Among the tasks identified for TAG is the exploration of potential interactions between current and proposed treatment regimens (e.g., ARV regimens) and nutritional status (6). This paper provides an overview of current knowledge about the use of ART and suggests possible strategies to support the safe and efficacious use of ARVs in resource-limited settings.

2. Overview of drug metabolism: why does nutrition matter?

The efficient utilization of drugs and nutrients occurs through similar processes and it is therefore important to consider the potential interactions between nutrition and xenobiotics (defined here as substances foreign to the body, including ARVs). For this paper, nutrition is defined as processes involved in the taking in and utilization of food substances by which growth, repair and maintenance of the body or in any of its parts are accomplished (7). The processes of nutrition include ingestion, digestion, absorption and metabolism (including transport to and from target tissues and functional utilization/activation of dependent systems). The relationship between drugs and nutrients has been summarized (8,9). A conceptual model of the interrelationships among health, food, drugs, nutritional status and drug metabolism is presented in **Figure 1**.

Although consideration of the potential for food–drug interactions is most often limited to questions of bioavailability (i.e., specific physical interference of drug absorption due to the presence or absence of food or specific food components in the gastrointestinal tract), the metabolic fate of drugs, nutrients and other xenobiotics ultimately depends on nutritional factors. Interest has increased in the complexity of factors that affect all aspects of bioavailability of nutrients and other bioactive substances (10). However, drug–nutrient interactions, including the effects of drugs on nutritional status and the effects of nutritional status on drug absorption, efficacy or safety, are more complex than just the physical relationship that occurs in the gastrointestinal tract. **Table 1** contains a summary of the potential mechanisms for drug–nutrient interactions. **Table 2** includes some examples of specific nutritional effects on the function of the mixed function oxidase (MFO) system that along with the conjugase systems is responsible for the conversion of drugs and, in many cases, nutrients to their active or excretory forms.

Presystemic xenobiotic metabolism, occurring in the gastrointestinal tract and/or liver, is an important predictor of drug delivery and efficacy (11). A significant portion of drug metabolism

occurs in the gastrointestinal tract via nutrient-dependent enzyme systems historically viewed as limited to the liver (*12*). Thus, the view of the gastrointestinal tract as being only a potential barrier has evolved into one in which it is a pivotal locus of processes that affect the bioavailability of xenobiotics to the general system.

Xenobiotic metabolism consists of two essential phases: the oxidation-reduction reactions involving MFO systems and the conjugation steps. Components of the former, which occur in the gastrointestinal tract and liver, tend to be more susceptible to nutritional effects. Yang et al. (*13*) described several potential sites for dietary effects on the MFO systems. Nutrients may 1) interfere with the genetic transcription and translation steps for synthesis of the drug metabolizing enzymes; 2) influence the degradation of P450 mRNA and protein; or 3) nutrients may directly influence MFO enzymes, resulting in either increased or decreased enzymatic activity. The last effect demonstrates the delicate balance and exquisite responsiveness of the body to fluctuations in nutrient availability.

This balance is exemplified in the recent review by Ross and Zolfaghari (*14*) in which the importance of the status of a given nutrient, in this case vitamin A, on the subsequent metabolism of that nutrient was described. Many of the presystemic metabolic systems that regulate the availability of vitamin A to the body are subject to feedback regulation mediated by vitamin status (i.e., deficiency is associated with changes in metabolism to increase availability and decrease elimination). Thus, in addition to those substances discussed below (e.g., drugs), herbs, botanicals and nutrients themselves can affect their own metabolism. These relationships become important in areas of the world where vitamin A deficiency and the use of drugs, herbs and botanicals are endemic.

Developmental stage is an additional factor that needs to be considered both as it affects the pharmacology and toxicology of xenobiotics throughout the life cycle and in terms of potential influence of other aspects of systems biology, e.g., indirect impact on nutrient availability from changes in nutrient requirements to support other aspects of growth, development and/or response to disease (*8,11*). The potential importance of the drug metabolizing system (i.e., cytochrome P450) to biological development was recently described (*15*).

With regard to pharmacology and toxicology, a direct link has not been established between the changes in requirements for specific nutrients that occur during the life cycle and drug

bioavailability and metabolism. However, an evidence-based case can be made for developmental changes (e.g., increased activity during the neonatal period) in both stage I (oxidative processing associated with the MFO systems) and stage II (conjugation) (16,17). Sonawane et al. (18) observed that the adult progeny of rats fed diets differing in lipid content had changes in microsomal MFO-driven drug metabolism. Sonawane and Catz (19) further reviewed the research on the developmental aspects of the nutrient–drug relationship and concluded that children may be more susceptible than adults to the effects of malnutrition on drug metabolism. Of particular interest in the context of infant health are the interrelationships between lactation and drug metabolism and bioavailability (20).

2.1. Specific examples of nutrient–drug interactions

For a given macro- or micronutrient, the effect from an excess or a deficiency may be paradoxical (Table 2). As noted above, Ross and Zolfaghari (14) described the effect of vitamin A status on regulation of cytochrome P450 activity. Another example is riboflavin deficiency, which may result in either an increase or a decrease in the activity of particular components of the MFO system, and these effects may be contingent on the degree of insufficiency. A mild riboflavin deficiency may result in decreased activity of NADPH reductase along with increased activity of several other enzymes; a severe deficiency may result in decreased activity of several other MFO enzymes (13).

Riboflavin metabolism has been linked with the effectiveness of several drugs. In particular, the effectiveness of the antibiotic doxorubicin (used as an antineoplastic agent) and antimalarial drugs (e.g., quinacrine) has been associated with their activities in reducing riboflavin availability (21,22). The clinical trade-off for therapeutic efficacy in these cases may be an increased risk for riboflavin deficiency, particularly in the form of the active coenzymes flavin adenine dinucleotide and flavin mononucleotide. The consequence of this iatrogenic deficiency may be an increased toxicity of these drugs to specific tissues such as heart and skeletal muscle (22). Interestingly, riboflavin is a key component of the MFO systems. The relationship between riboflavin status and the mitochondrial aberrations associated with ARV-induced lactic acidosis has been of interest (discussed below). How a riboflavin deficiency induced by one drug may affect the safety and/or efficacy of other drugs such as ARVs has not been explored.

Niacin, riboflavin, pantothenic acid, iron and copper are required as cofactors in many of the oxidation-reduction reactions of the MFO system (23). Protein; lipid; calcium; zinc; magnesium; and vitamins A, E, C and B₆ are also required for the maintenance of membrane integrity and are critical supporting components of the MFO systems. Other nutrients, such as vitamin B₆ (through its action in heme synthesis), provide peripheral support for the MFO systems through their role in biosynthesis of MFO components. Evidence of changes in drug metabolism following changes in the availability of any of these nutrients may be found in numerous studies examining these relationships (24–28). To date none of these specific nutrient–drug relationships has been explored in the context of ARV use.

Drugs can also affect specific elements of nutrient metabolism. For example, the therapeutic efficacy of several classes of drugs involves the ability to act as an antimetabolite or antagonist for specific nutrients. Isoniazid and hydralazine are both vitamin B₆ antagonists (29–32), necessitating supplemental vitamin B₆ in cases of toxicity.

Another example of this type of interaction is between the anticoagulant, warfarin, and vitamin K. The coumarin anticoagulants function by interfering with vitamin K metabolism. Consequently, an increase in the intake of green leafy vegetables or use of vitamin K supplements would counteract the anticoagulant effects (33).

2.2. Effect of nonnutrient components of food on drug metabolism

Food, particularly of plant origin, can provide essential nutrients and toxic substances (8). Factors other than essential nutrients (e.g., vitamins and minerals) have been identified in foods that influence the activity of the drug-modifying conjugase and MFO systems. For example, substances found in cruciferous vegetables (e.g., broccoli, brussel sprouts, cabbage) and others found in charcoal-broiled meats were reported to increase the activity of the MFO systems via enzyme induction (34,35).

An additional concern is the growing use of dietary supplements, including herbal and botanical substances, and the potential for adverse interactions with therapeutic drugs (36,37). Components of St. John's wort have been implicated in the induction of enzymatic components of the MFO systems and a subsequent effect on the efficacy of certain classes of medications (38). Echinacea is another example of a commonly used herbal supplement with the potential to affect

safety and efficacy of therapeutic drugs (39). Both of these examples emphasize the importance of better understanding of the effects of herbal/botanical treatments on the metabolism of therapeutic drugs when both are being used concomitantly. These issues become even more important in settings where the use of traditional medicines is the norm.

Caffeine can increase the risk of adverse effects from theophylline, which is in the same family of chemicals (40,41). In addition, caffeine consumption has been linked to decreased therapeutic response to psychoactive medications such as neuroleptics. This may result from an induction of liver metabolism or the formation of insoluble precipitates. Because caffeine consumption in the form of coffee, tea and soft drinks is common, these interactions may have clinical importance if such substances are consumed excessively. In the context of ARV drugs or other therapeutics that might be used by PLWHA, the range caffeine intake beyond which problems might occur has not been defined. There are limited data regarding the effect of caffeine in HIV-positive patients. Caffeine has been found to exacerbate sleep disturbances in HIV-positive patients (42). There was one case report of a fatal interaction between a caffeine and ergotamine medication and protease inhibitors (PIs) (43), but this effect was more likely due to the well-documented interaction between ergotamine and related compounds used to treat severe headache and PIs (44) than to an effect from caffeine per se.

2.3. Food–drug interactions: specific effects on ART

Numerous studies have shown a direct interaction between food and herbal and botanical supplements and ARVs. Piscitelli et al. (45) documented a specific food–ARV interaction involving garlic and the PI saquinavir. Long-term use (twice daily for 20 days) of garlic supplements was reported to significantly decrease plasma concentrations of saquinavir in otherwise healthy humans. Saquinavir was selected because it is a substrate of the P450 system. Whether these results can be generalized to other members of this class of drugs remains to be seen.

Another commonly used traditional remedy particular in sub-Saharan Africa is *Hypoxis hemrocallidea*, commonly known as the African potato. Mills et al. (46) evaluated the impact of this botanical supplement and another, *Sutherlandia*, both commonly used for relief of HIV-related symptoms, on metabolism of ARVs. In these in vitro studies, both substances caused significant

decreases in cytochrome P450 activity as well as reductions in the expression of P glycoprotein, an important component of drug transport. These authors concluded that these findings indicate the potential for increased drug toxicity, viral resistance, and treatment failure when these botanicals are used in conjunction with ART.

As mentioned above, St. John's wort has received considerable attention recently because of its possible effect on drug efficacy and safety through its induction of P450 system. The relevance of this concern to PLWHA was reinforced by Piscitelli et al. (45) who reported significantly reduced plasma concentrations of indinavir, another PI.

Studies have evaluated the relationship between food and some selected nutrients (primarily macronutrients such as fat or protein) and the use of ARVs in terms of the pharmacokinetics and bioavailability of the drugs. For example, Aungst et al. (47) reported significantly higher circulating drug concentrations of the nonnucleoside reverse transcriptase inhibitor, efavirenz, in the fed versus fasted state in dogs. The recent review by Nerad et al. (48) offers a compendium of recommendations for general nutritional considerations for PLWHA, including a table summarizing current recommendations about administration of ARVs with foods, taking into account relevant food-ARV interactions. In addition, the recently published World Health Organization guidelines on the use of ARVs in resource-limited settings include specific suggestions about the importance of taking specific ARV regimens with or without food (49).

3. Metabolic consequences of HIV/AIDS: before and after ARVs

A number of metabolic consequences have been described in individuals receiving ART. These consequences include derangements in lipid metabolism (lipodystrophies), insulin resistance and glucose intolerance, lactic acidemia and derangements in bone mineral metabolism (50–54). Metabolic complications have been associated with each class of ARV drug (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs] and PIs). In addition, it is important to know the metabolic consequences of HIV infection per se, which may contribute to lipid, glucose and body composition changes. The review of the literature with regard to many aspects of the metabolic consequences of HIV/AIDS has been summarized in previous sections of this report (55–57).

It is often difficult to know where the effects of HIV end and those of the drugs begin. Of equal importance is the potential role of developmental and perhaps gender differences in the impact of HIV/AIDS. The following sections briefly explore what is known about the concomitant metabolic consequences of HIV/AIDS in the context of ART from both a developmental and a gender perspective.

3.1. Overview

Much of the early work on HIV/AIDS focused on the wasting syndrome identified as a distinguishing feature of AIDS as early as in the 1986 diagnostic criteria promulgated by the U.S. Centers for Disease Control and Prevention (CDC) (58). This early definition characterized wasting as involuntary loss of more than 10% of body weight. One of the core issues of the wasting syndrome is its etiology. The potential causes of this weight loss include decreased dietary intake, opportunistic infections (which could affect the processes of nutrition) and/or metabolic changes secondary to HIV infection itself. With regard to the clinical profile of the wasting patient, there is a preferential loss of lean body mass (muscle) particularly in men (59).

In resource-limited settings such as many areas of sub-Saharan Africa, HIV has been superimposed on conditions of severe malnutrition in areas such as sub-Saharan Africa. The metabolic sequelae associated with severe malnutrition, primarily protein-energy malnutrition, have been well characterized (60). Protein-energy malnutrition may be compared with cachexia, seen in conditions such as cancer and described as a mixture of metabolic abnormalities that lead to weight loss through accelerated wasting of lean body mass and failure of many of the processes of nutrition, including intake, absorption and metabolism. The essential difference between protein-energy malnutrition and cachexia is that in the former the body attempts to compensate metabolically for the nutrient deficits whereas in the latter the metabolic signals become uncoupled (7). The consequences of protein-energy malnutrition can be explained in terms of preservation of lean body mass and visceral organ function. By contrast the changes seen in cachexia include marked and almost immediate loss of muscle mass and may not be reversible by nutritional intervention (61,62). Other characteristics of cachexia include a lesser effect on body fat and extracellular water, increases in resting energy expenditure and increased cytokine production (62).

Additional considerations in both protein-energy malnutrition and cachexia—as discussed in this technical report in the context of both macronutrients and micronutrients (55,56)—are the complications associated with the acute phase response, most often associated with concomitant infections. The acute phase response includes changes in concentrations of circulating proteins that can affect binding of drugs and thus active drug concentrations in the plasma as well as the ability to reliably assess nutritional status. The relevance of the acute phase response to nutritional assessment in PLWHA was demonstrated by Baeten et al. (63), who reported significant differences in vitamin A status in HIV-positive women experiencing an acute phase response compared with both HIV-infected and uninfected women who were not experiencing an acute phase response. Baeten et al. speculated that these differences, which they attributed to viral load and infection, might account for the disparity between observational studies and randomized trials of vitamin A in PLWHA.

It is important to distinguish between the clinical states of starvation, cachexia, and an acute phase response, as the most appropriate course of treatment for the HIV-positive individual may differ depending on which condition(s) are present. Each of these conditions has the potential to directly or indirectly effect the pharmacokinetics of certain antiretroviral drugs and could result in drug levels that are higher or lower than anticipated or an increased risk of toxicity. Complicating this assessment is the knowledge that each or all of these conditions can coexist in an individual patient. As noted by Macallan (64), the complexity of wasting in HIV disease defies adequate description in terms of either etiology or pathophysiology. He cautioned that it is important to distinguish between weight loss associated with HIV infection (a diffuse multifactorial condition with an episodic nature) and AIDS wasting syndrome (a more well-defined circumstance with an inexorable path occurring at the end stages of the natural history of HIV infection).

3.2. Effect of ART on HIV-related wasting

Before ART the prevalence of wasting was high in HIV-infected patients. Since the use of ART became commonplace in the developed world, the prevalence of wasting has diminished but not disappeared. HIV-associated wasting was recently reviewed (65,66).

There have been a number of studies of wasting before and after the era of ART. Batterham et al. (67) evaluated prevalence and predictors of wasting in a cohort of 122 HIV-positive adults (100 on

HAART and 22 drug naïve) and reported that 40% had documented weight loss. A comparison of those on drugs versus the naïve patients showed a significant difference in prevalence of weight loss (34% versus 68% respectively). A multivariate analysis demonstrated that only HIV viral load independently predicted weight loss; dietary intake was not an independent predictor in these analyses. Tang et al. (68) reported that in their cohort (n=552) taken from their larger study (Nutrition for Healthy Living Study), wasting (defined as involuntary weight loss of >10%, unintended weight loss >5% in previous 6 months and/or body mass index <20) was the strongest predictor of mortality.

Thus, at this point in our understanding of the clinical significance of HIV-related wasting, it appears that ART has made a difference in the prevalence of wasting, probably through the reduction in viral load. Although the exact mechanisms of wasting (e.g., reduced intake and/or increased resting energy expenditure mediated by factors such as cytokine or androgenic hormones) remain elusive, it is clear that weight loss (using CDC or more specific criteria) remains a major problem and may be the best predictor of mortality in PLWHA.

4. Metabolic complications associated with ART

4.1. The ART metabolic syndrome

A constellation of symptoms associated with derangements in intermediary metabolism potentially secondary to ART have been described in recent years. The metabolic syndrome that has been described in connection with HIV infection and ART includes lipodystrophy (aberrant mobilization and deposition of lipids); dyslipidaemia (elevated circulating concentrations of total cholesterol and triglycerides and disadvantageous shifts in the ratio of high- to low-density lipoprotein cholesterol); and insulin resistance, glucose intolerance and diabetes in PLWHA. Numerous reviews of these conditions were published (50,69–72).

Many putative mechanisms for these derangements are being investigated. As many of the clinical sequelae of the metabolic syndrome resemble symptoms seen with endocrine system diseases. A number of investigators have explored whether endocrinologic abnormalities exist in HIV-infected patients with symptoms of the metabolic syndrome. For example, Yanovski et al. (73) have demonstrated that there are not elevated cortisol levels in HIV-infected individuals with the metabolic

syndrome, and therefore the syndrome is not analogous to Cushing's Syndrome. Much of the work of this investigative group has focused on the molecular biology of specific HIV viral proteins, the potential interaction of these proteins with endocrine receptors, and consequent metabolic outcomes (74). In response to a question about why the severity of the metabolic changes associated with HIV seem greatest in patients with the lowest viral load (as a result of treatment with ARVs), Dr. George Chrousos, suggested (Chrousos, personal communication, 2003) that it could be due to differential expression of the virus in different tissues (e.g., differential responses in subcutaneous versus visceral fat deposits). This is a basic research question that warrants further investigation.

Because HIV has become a chronic disease as a result of the efficacious use of ART, discussion has turned to questions about how to address the metabolic changes that in the absence of HIV would warrant aggressive intervention to protect against the development of chronic diseases such as diabetes, cardiovascular disease (CVD) and osteoporosis. The need to determine whether and how to treat these potential risk factors for disease in HIV-infected individuals is an issue not only of short- and long-term health and the quality of life but also one that may affect patient compliance with ART and consequently the success of available interventions. As with the any condition, the development of strategies for prevention involves estimates of the relative risk of the disease in a given population followed by an evaluation of the safety and efficacy of available interventions. The question of cardiovascular risk in HIV patients is typical of that process. The dyslipidaemias seen in HIV-positive patients may increase the risk for CVD. If risk factors exist in HIV-positive people that would otherwise warrant interventions—dietary, pharmaceutical or both—in HIV-uninfected people, what is the best approach to prevention or reduction in risk in an HIV-infected individual who is receiving ART?

The relative risk of CVD and related adverse events (e.g., ischemic heart disease or stroke) has been shown to be higher in HIV-infected individuals receiving ART and has been explored extensively (75–80). Although differences exist as to the relative contribution of HIV per se, ART (PI, NRTI or combined therapies), lifestyle, or all of the above (81), there is little doubt that CVD risk is elevated in HIV-positive patients, particularly those receiving ART (75,80). However, how to reduce this risk and how to do so safely needs study.

This issue was the focus of a recent effort to bring those with expertise in cardiovascular medicine together with the HIV clinical community. In recommending a multidisciplinary and multi-pronged strategy to address CVD risk in PLWHA, the authors of the Pavia Consensus Statement on CVD and HIV management (81) concluded that the “the interconnection of CVD and HIV infection is common and complex, yet inadequately understood. Considering and managing actual or potential cardiovascular illness in patients with HIV infection are important aspects of HIV care. As the diagnosis and management of CVD is itself complex, specialists in this area of medicine may need to be consulted. They, in turn, need to be aware of the complex manifestations of HIV infections and the cardiovascular implications of HIV therapy.”

The use of lipid-lowering therapies is increasing in HIV-positive people at an apparently much greater rate than the general population (82). In addition to the multidisciplinary clinical and lifestyle recommendations outlined in the Pavia Consensus Statement (81), numerous reports were published in which potential drug–drug interactions between currently available interventions for prevention of CVD and ART were explored (82–88). These interactions occur secondary to the effect of the PI or NNRTI drugs on the cytochrome P450-enzyme system. All PIs are substrates for and inhibitors of CYP3A4 (ritonavir having the greatest inhibitory effect and saquinavir the least); some PIs (e.g., amprenavir and ritonavir) also act as inducers of certain cytochrome P450 isoenzymes. The NNRTIs are also substrates of cytochrome P450 enzymes and can act as inducers (nevirapine), inhibitors (delavirdine), or a mixed induced and inhibitor (efavirenz). Inhibition of the cytochrome P450 enzymes will result in inhibition of statin metabolism, resulting in markedly elevated statin levels, which can result in toxicity; induction of enzymes would lead to increased statin metabolism and decreased statin levels, potentially lowering the efficacy of the statin in reducing cholesterol levels.

The complexity of these interactions is illustrated by a trial reported by Wanke (89) that was designed to assess the interactions between PIs (ritonavir and saquinavir) and statins in HIV-uninfected subjects (ACTG protocol A5047). The PIs had the expected effect of delaying the metabolism of several of the statins (simvastatin, lovastatin and atorvastatin). However, the same PIs actually reduced the therapeutic levels of another of the statins, pravastatin, presumably through an induction of its metabolism. Thus, knowledge of these drug–drug interactions are critical in determining

which statin drug to use in patients receiving specific ART. The conclusions of the study investigators included several cautionary caveats about the use of specific statins by PLWHA using specific ART (90).

Although evidence indicates that the lipid-lowering therapies can be efficacious in PLWHA taking ARVs (83,86), the use of lipid-lowering medications in this population requires further evaluation in terms of both safety and efficacy. These concerns were further reinforced by the observations of Visnegarwala et al. (87) who analyzed clinical data from a cohort of 103 HIV-positive adults taking ART and concluded that the use of the cholesterol-lowering drugs may have only modest effects while adding to the complexity of HIV care.

A well-established approach used to address hyperlipidemias and related cardiovascular risk factors has been dietary counselling. Only one clinical trial was specifically designed to address this issue in the context of HIV and ART. Moyle et al. (88) conducted a randomized open-label 24-week trial of dietary advice alone or with a lipid-lowering drug (pravastatin) in 31 men receiving PIs. They reported no adverse effects or problems with compliance in either group. Dietary advice alone was significantly less effective than dietary advice plus statin in effecting positive changes in lipid profiles.

An important question that needs to be addressed is how the metabolic complications of ART observed in developed countries in well-nourished HIV-infected individuals receiving ART might be manifested in the context of conditions that exist in endemic areas such as sub-Saharan Africa (e.g., high prevalence of malnutrition)? In addition, are there genetic or racial differences in the development of metabolic complications to ART?

Chang et al. (91) observed the metabolic syndrome (specifically lipodystrophy, hyperlipidaemia and insulin resistance) in a much lower than usually reported percentage of Korean HIV-positive patients receiving ART. This raises the possibility that race-specific factors may influence responses to ART. Gender differences may also exist in HAART-related lipodystrophies (92) that will need to be further explored in terms of mechanism, clinical outcomes and treatment.

4.2. Bone mineral metabolism

A range of bone-related conditions from osteonecrosis to osteopenia and osteoporosis has been reported in HIV-infected adults and children (54,93–96). In addition to the traditional risk factors for these bone-related conditions (i.e., age, gender, weight), the relative contribution of HIV and/or treatments has emerged as an additional risk factor (94,96). Evidence indicates that HIV per se causes problems with bone mineralization (93,94,97). What is less clear is the relative contribution of ART to these problems (98). This lack of clarity is in part due to the complexity of bone mineralization processes and the nature and the range in quality of the studies that examined these relationships in HIV-positive people. In addition, the effect of ART on bone may vary between classes of drugs as well as among drugs within the same class (99). Consequently, a disparity exists within the literature examining the bone–ART relationship; some investigators have reported no effect (compared with HIV-positive drug-naïve subjects [100]), a negative effect (101) and a beneficial effect (102) of ARV therapies.

Several studies of bone turnover in HIV-positive patients suggest low rates of bone formation with high levels of bone resorption, an uncoupling of turnover and formation that may be deleterious (102). Some studies have compared HIV0-infected men and women with and without lipodystrophy and have reported an association between bone loss and visceral fat or lipodystrophy (103,104). Huang et al. (105) in a further evaluation of these relationships in women identified hormonal status (specifically androgen deficiency) as a distinguishing concomitant of bone loss. Carr et al. (106) reported that osteopenia in their cohort of 221 HIV-positive men (32 drug naïve, 42 receiving NRTIs and 147 receiving NRTIs and PIs) was associated with lower weight before initiation of therapy and NRTI-associated lacticacidemia but not lipodystrophy.

Aside from the already established risk factors for decreased bone mineralization and related conditions in individuals without HIV infection (e.g., poor calcium and vitamin D status, age, gender), specific nutritional factors have been examined in relation to the potential adverse effects of HIV and ART on bone health. In an in vitro study aimed at exploring the effects of PIs on vitamin D metabolism, indinavir and ritonavir reduced the rate of conversion of 25-hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D₃ in a dose-dependent manner (107).

Haug et al. (108) evaluated the relationship between low circulating concentrations of 1,25-dihydroxyvitamin D₃ and clinical status of adult HIV-positive patients (44 men and 10 women) and reported that 54% had concentrations of 1,25-hydroxyvitamin D₃ well below the lowest reference limit (18 had undetectable concentrations); these levels were associated with reduced CD4+ counts and high levels of tumor necrosis factor- α . The HIV-positive subjects had levels of 25-hydroxyvitamin D that were comparable with normal values, which led these investigators to conclude that a derangement exists in the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D₃.

In a larger cohort study, Madeddu et al. (109) evaluated the association between ART and bone health in 172 HIV-positive patients (112 men and 60 women). Of these patients 92 were receiving HAART with PIs, 60 were receiving NNRTIs or triple combination NRTIs but no PIs and 20 were drug naïve. There were 64 HIV-uninfected control subjects. Bone mineral density and 1,25-dihydroxyvitamin D₃ were measured. Circulating 1,25-dihydroxyvitamin D₃ levels were lower in all three HIV-positive groups than in HIV-uninfected control patients, but were lowest in the HIV-infected individuals receiving PI-containing therapy, and levels were positively correlated with bone mineral density in all HIV-positive groups. The incidence of osteopenia was greater than 30% in all HIV-positive groups (higher in ART groups than the naïve group). Osteoporosis was documented only in the group receiving PIs. Although 25-hydroxyvitamin D was not assessed, these investigators concluded that ART has a negative effect on vitamin metabolism that contributes to bone problems in HIV-positive patients.

Teichmann et al. (95) evaluated these relationships specifically as they exist in HIV-positive women. They measured bone mineral density and related bone variables including vitamin D in 50 HIV-positive women who were not receiving ART during the study. Compared with age-matched healthy HIV-negative control women, the HIV-positive women had significantly lower bone density measures and circulating concentrations of 1,25-dihydroxyvitamin D₃. They also reported a significant positive correlation between CD4+ counts and vitamin D levels. Dolan et al. (110) reported lower bone density in HIV-positive women compared with control subjects matched for age

and body mass index. Decreased levels of 1,25-dihydroxyvitamin D₃ were also seen but did not correlate with bone density.

Data are limited with regard to the issue of bone health in PLWHA in resource-limited settings with or without ART. However, the recent paper by Mody et al. (*111*) provides evidence that the pre-ART conditions associated with HIV infection in Africa are something to be considered in this context. These authors report a direct interaction between HIV infection and the development of a variety of adverse bone- and joint-related effects (e.g., persistent and progressive arthritis). Although no data could be found for the interaction between poor nutritional status of bone-related nutrients (e.g., calcium and vitamin D) and ART use in HIV-infected individuals in resource-limited settings, data are available on the overall prevalence of poor calcium and vitamin D status (*112*) and their importance to bone health in the developing world (*113*). Thus, it is strongly recommended that both calcium and vitamin D status be considered in the context of care and treatment of PLWHA, particularly mothers and their children.

It is unclear whether bone problems are due to metabolic derangement resulting primarily from HIV infection, use of ART or a combination of both. Nonetheless, bone loss is a potentially serious problem that affects the long-term health and quality of life of PLWHA, and assessment of bone health should become part of the clinical care of PLWHA. As discussed below, of particular concern are the implications for perinatally infected children who experience years of exposure to both HIV and ART. To prevent these complications and to ensure an enhanced quality of life, strategies will be needed for the incorporation of assessment of not only bone health but also risk factors that can be controlled—including diet—into clinical care. Availability and applicability of procedures and technologies for the assessment of bone status and factors that may contribute to bone health will be contingent on the setting and the clinical capacity of the caregivers.

4.3. Lactic acidemia, mitochondrial toxicity and use of NRTIs

Lactic acidemia has been associated with mitochondrial toxicity secondary to NRTI therapy and can result in adverse health outcomes including life-threatening lactic acidosis (*114*) and, may be involved in, the pathogenesis of bone mineral changes in PLWHA (*53,106*). Prevalence of hyperlactatemia was reported to be as high as 36% in patients receiving ART (*115*). Of particular

relevance to the discussion of nutrition and ART in resource-limited settings is the implication of deficiencies of specific micronutrients—thiamin, riboflavin and carnitine—in the pathogenesis and treatment of this condition (*116*). The evidence for a role for such micronutrients in lactic acidaemia independent of HIV or ART is extensive and is exemplified by a CDC report (*117*).

Because of the limited storage capacity in the body, deficiencies of these essential nutrients are common and particularly sensitive to conditions affecting food distribution (e.g., seasonality of food supplies, food insecurity) in resource-limited areas such as those with endemic HIV infection. Despite the association of deficiencies in these nutrients with several adverse health outcomes, including preeclampsia in Zimbabwe (*118*), neither surveillance nor systematic trial data are available in the developed world on either the prevalence of deficiency of these nutrients in the context of ART or their potential efficacy in treatment of NRTI toxicity. Assessment of these nutrients by dietary and/or biochemical means (as dictated by clinical setting, technical capacity and resources) should be included in the care and treatment of PLWHA.

4.4. Energy metabolism and ART

Studies in HIV-positive patients generally suggest an increased resting energy expenditure and resting energy expenditure adjusted for lean body mass. The data on resting energy expenditure in HIV-positive patients with malabsorption are mixed, but at least two studies suggest that it is increased (*119,120*). Energy balance in HIV-positive patients with secondary infection and weight loss has been carefully evaluated. Grunfeld et al. (*121*) observed that resting energy expenditure increased and energy intake decreased sharply in HIV-positive patients with active secondary infection. Macallan et al. (*122*) demonstrated that total energy expenditure decreased appropriately in HIV-positive patients with rapid weight loss whose energy intake decreased substantially, contributing toward a state of negative energy balance. Data from children suggest appropriately decreased resting energy expenditure in children with decreased growth (*123*).

Resting energy expenditure is increased in patients with HIV lipodystrophy (*124*) but data on changes with HAART are mixed, with reports of decreased, increased and neutral effects of HAART introduction on resting energy expenditure (*125–127*). Differences among studies may be secondary to differences in study populations (e.g., nutritional status, wasting status) or specific drugs used.

Taken together, the data suggest increased and inappropriate increases in resting energy expenditure in low-weight HIV-positive patients, especially those with active secondary infection for whom particular care must be paid to increase energy intake to prevent further weight loss.

5. Gender-specific issues in HIV metabolism in adults

The impact of HIV per se on energy metabolism and body composition was reviewed previously in this paper and in this report (55). One of the more interesting observations is the reputed difference between men and women. It is against this background that a discussion of those stages in a woman's life that present more severe physiological and metabolic demands than men experience (e.g., pregnancy, child birth and lactation) must be viewed. Thus, it is useful to revisit some of our fundamental knowledge about the possible difference between men and women in terms of the effect of HIV infection on metabolism pre-ART to provide context for what we are learning about the use of ART throughout a woman's life.

In 1985 Kotler et al. (128) reported that compared with normal values (derived from a previous survey of 3000 adult men), body fat was depleted in HIV-positive patients albeit in a manner that was similar in both HIV-positive and -negative (matched control) men. However, compared with the same data, the HIV-positive women (n=6) had significantly less fat (29% of the control value) than did the HIV-positive men (71% of control value). The pattern in the HIV-positive women was similar to that seen in women with eating disorders. In contrast to the HIV-positive women, HIV-positive men experienced a greater relative depletion of body potassium (reflective of lean body tissue) than fat. The conclusion was that weight loss in HIV-positive women resembled protein-energy malnutrition whereas weight loss in men resembled cachexia.

Grinspoon et al. (129) observed that changes seen in HIV-positive women include increased resting energy expenditure, with fat-free mass as the primary determinant of these changes. The apparent preferential loss of body fat over lean body mass by women was reinforced by the observations of Swanson et al. (130). An important distinction made in both studies is that the women evaluated were underweight. More than 50% (29/56) of the racially heterogeneous group of HIV-positive women in the study by Swanson et al. were receiving either single or combined ART.

Swanson et al. suggested that the distinction between men and women may result from higher premonitory fat stores and hormonal differences.

The role of endocrine factors in HIV-related changes in body composition has become an area of active investigation. In a series of studies, Grinspoon and colleagues (105,131,132) evaluated the potential role of androgen hormones in the wasting syndrome in HIV-positive women both in terms of describing a possible mechanism for wasting in women and as a potential treatment. Grinspoon et al. (132) described a shunting of adrenal steroid metabolism away from androgenic pathways and toward cortisol production as a possible mechanism. Huang et al. (105) reported a significant association between hormonal and body composition factors and decreased bone density in HIV-positive women with wasting.

With regard to potential efficacy as a treatment, this same group (131) reported the result of a pilot study showing a positive effect of testosterone on body composition changes associated with HIV wasting in women. Kong and Edmonds (133) conducted a systematic review and meta-analysis of the data on efficacy of testosterone for the treatment of HIV-related wasting and reported that based on the eight trials and 417 subjects included in their analysis, testosterone therapy increases lean body mass more than placebo does. They noted that the limitations of their analysis were the total number of studies and the heterogeneity of the patient populations. Kong and Edmonds also added several caveats about the generalizability of the data including concerns about the long-term safety of this treatment. None of the studies in the final analysis involved subjects in resource-limited settings.

From the review of the metabolic consequences of HIV infection in women, it is apparent that as with men, body weight is a strong predictor of morbidity and mortality in HIV-positive women. Recent data indicate that body composition will change in proportion to initial levels of fat and lean mass. The differences in the composition of weight loss between males and females may therefore be the consequence of a higher percent body fat in women than men. Thus, it would not be surprising that women would lose fat first. It appears that once the fat reserve is lost, lean body mass wasting ensues and the wasting of HIV/AIDS is indeed, contrary to earlier belief, the same pattern as occurs in starvation.

An emerging area of interest is the role of androgen hormones in the metabolic changes associated with HIV/AIDS in women. Specifically, the effect of reduced testosterone concentrations in HIV-positive women was reported. In a trial to assess the efficacy of a testosterone patch (slow release of a nonsynthetic form of testosterone), muscle mass and function and bone formation increased (*134*). The hypothalamic-pituitary-adrenal axis should receive increased research attention in the effort to understand and elucidate the mechanisms of wasting in HIV/AIDS.

5.1. HIV, nutrition and pregnancy

As summarized previously in this report (*56,57*), several studies have involved the assessment of micronutrient status and interventions on birth outcomes in HIV-positive women. Nutritional status, irrespective of HIV, will have significant effects on the child as well as the mother. These effects are well documented for a range of conditions and outcomes including complications of pregnancy such as preeclampsia (*135*), impaired glucose tolerance (*136*), adverse birth outcomes (*137,138*) and subsequent health throughout the life cycle (*139,140*). HIV/AIDS brings its own set of nutritional concerns, and the combined effects of poor nutrition and HIV/AIDS have the potential to substantially affect both the safety and the efficacy of ART.

5.2. HIV, nutrition and lactation

Historically and as reviewed elsewhere in this report (*57,141*), the question of mother-to-child transmission of HIV via breastfeeding has focused primarily on the virus, both in terms of mechanism of transmission and strategies for prevention (*142,143*). In addition, knowledge about the safety and toxicity of ART during pregnancy, the perinatal period and lactation is evolving (*143–146*). Concerns have been raised about the potential health effect of lactation on HIV-positive mothers. The study by Nduati et al. (*147*) implicating that breastfeeding by HIV-positive women results in adverse health outcomes has stimulated considerable discussion and research to determine the reproducibility and generalizability of these findings (*148*). However, aside from the issues of mortality, toxicity, metabolic effects and HIV disease progression, no studies have specifically addressed issues pertaining to nutritional needs of HIV-positive women before, during or after pregnancy or during lactation.

Maternal nutritional requirements are greater during pregnancy and lactation (*149–152*). These requirements are quantitatively greater during lactation than pregnancy (*153*). For some nutrients, milk concentrations depend directly on intake whereas for others, maternal reserves will be used to maintain milk levels (*153*). As the composition of milk has been known for some time to vary with, among other influences, time of day, time during feeding and most importantly stage of lactation, assessment of the effect of any environmental factor including HIV status and ART must be done with due consideration of these factors (*154*). Of all the nutrients in human milk, fat may be most susceptible to variation (*154*); the fat composition of human milk mirrors diet composition. For example, consumption of a fat-free diet will result in an increase in medium-chain triglycerides through endogenous metabolism and mobilization of body fat stores (*153,155*).

The importance of diet and nutrition to the health of lactating women and their infants has been well described (*156*). However, few data address the specific relationships among nutrition, lactation, maternal health and HIV status. Clearly, irrespective of HIV status, the importance of maternal nutritional status including that of specific micronutrients (as reflected by maternal intake and subsequent concentrations in human milk) must be considered particularly in resource-limited settings because of the dependency of milk content on maternal intake.

Maternal nutritional status is intimately and inextricably linked to successful breastfeeding, both in terms of the ability to sustain breastfeeding over time and short- and long-term changes in human milk composition (*153*). This linkage is codified in such documents as the U.S. Dietary Reference Intakes (*149–152*), which contain recommendations for the specific dietary needs of women during pregnancy and lactation. Aside from issues pertaining to viral transmission, data are minimal regarding the specific nutritional needs of HIV-infected women during lactation. Moreover, there are no data on the effect of ART on maternal nutritional status or lactation (duration or milk composition).

The fat content of human milk is not only a critically important contributor of nutrients and other bioactive components but also is the component most susceptible to variation (*157*). It may be of particular concern in ART in the context of the well-described lipodystrophy syndrome discussed above.

The relationship between lactation and changes in body composition (primarily related to the fat mass with a reported preservation of lean body mass) in well-nourished HIV-negative women has been described (*158–160*). However, this relationship has not been studied in lactating HIV-positive women. The use of ART has been associated with significant breast enlargement in nonlactating HIV-positive women. This effect is presumably attributable to the well-documented regional changes in fat distribution observed in HIV-positive people receiving ART (*161*). The changes in body composition that may occur in HIV-infected women with or without ART could reflect changes in milk composition as changes in fat or lean body mass could reflect changes in available sources of macronutrients needed for milk production. Clearly, data on these relationships in poorly nourished women are needed. The functional ramifications of these phenomena in lactating HIV-positive women are unknown.

6. Effect of HIV infection on infants and children

The importance of nutrition in the context of growth, development and health of HIV-infected and -affected infants and children is covered elsewhere in this report (*162*). The key elements of that relationship may be summarized as follows: Maternal HIV infection is associated with increased prevalence of adverse birth outcomes including increases in the prevalence of intrauterine growth retardation in small-for-gestational age infants and premature births. Higher viral load and lower CD4+ counts are associated with poorer birth outcomes. ART currently recommended for prophylaxis to prevent mother-to-child transmission of HIV has no apparent effects on fetal growth or pregnancy outcomes. No evidence indicates that single-dose nevirapine causes adverse short-term birth outcomes. However, there are no data regarding potential long-term effect on child health and development. Prenatal transmission of HIV is associated with decreased body weight, length and head circumference. Children infected prenatally and intrapartum have deceleration of growth that is detectable by ages 3–4 months. High rates of stunting are reported throughout childhood in the United States and European studies. Limited data support the existence of stunting in HIV-positive children in Africa albeit with more pronounced wasting. The pattern of the composition of the body weight changes in children and adults with ready access to adequate food is similar, with a preferential loss of fat-free (muscle) tissue. Poor growth in children is associated with increased mortality. The

relationship between body composition, viral load and adverse health outcomes and mortality appears to be the same in adults and children. Growth velocity is inversely related to viral load as is dietary intake. Children reach a point where they can no longer take in sufficient calories to support growth. Supplemental feeding is efficacious in improving weight and fat losses but there are no apparent compensatory gains in height or lean body mass.

An emerging literature has begun to shed some light on various aspects of the interaction of ART with infant and child health and development (*163*). The following is a review of the data on issues ranging from the impact of ART on growth and birth outcomes to risk for chronic diseases of adulthood including CVD, diabetes and osteoporosis.

6.1. Impact of ART on growth

As with many aspects of the metabolic consequences of HIV and related treatments, there are some conflicting data with regard to the relative contributions of the infection and the treatment. Miller et al. (*164*) explored maternal and infant risk factors for failure to thrive in HIV-infected infants and reported that exposure to ART (but not PIs) before age 3 months was a risk factor. Morris et al. (*165*) reported that intrauterine exposure to ARVs either as a maternal therapy or as chemoprophylaxis to prevent mother-to-child HIV transmission did not appear to significantly affect birth outcomes. Both Miller et al. (*164*) and Morris et al. (*165*) noted a higher rate of premature births in the HIV-positive women studied.

Lambert et al. (*166*) found no difference in risk factors for adverse pregnancy outcomes related to either measures of HIV status or use of ARVs (predominantly single-drug therapy with azidothymidine) between HIV-positive and -negative women. Culnane et al. (*167*) reported that intrauterine and postnatal growth in HIV-negative children with in utero and neonatal azidothymidine exposure was normal. Goldstein et al. (*168*) reported a higher rate of low birth weight in infants of HIV-positive mothers who received either azidothymidine or PIs. More recently, Tuomala et al. (*169*) reported a higher incidence of very low birth weight associated with the use of combination ART with PIs.

As noted throughout this paper, not only does the direct effect of HIV or treatment on nutritional status and related outcomes such as growth need to be considered: the effect of the disease

and interventions on the processes of nutrition also needs to be considered. Canani et al. (170) evaluated the effect of ART on gastrointestinal function in HIV-infected children (n=10) and found that combination therapy including the PI ritonavir improved intestinal function and resulted in weight gain. In another study examining this PI, Nachman et al. (171) performed a secondary analysis on data from a cohort of 197 children who had been randomly assigned to receive combination therapies of either ritonavir plus stavudine or ritonavir plus zidovudine and lamivudine. In this case a significant decline in height and weight Z-scores was associated with the PI (171). There was also a paradoxical significant association between viral load and growth; children in whom viral load was better controlled had poorer growth than those in whom viral load was less controlled. No differences in incidence of severe gastrointestinal complications were reported. There were no other data with regard to any other aspect of nutrition included in this report.

Timing is important with regard to the effect of any intervention on an infant or a child. This is exemplified by the results reported by Steiner et al. (172) on the effect of PIs (ritonavir or nelfinavir) on growth of HIV-infected children aged 0–17 years. They observed significant catch-up growth in children who had been stunted before initiation of the PI therapy, which was most pronounced in children less than 3 years of age. No data were presented about any aspect of diet or nutritional status beyond anthropometry. These findings imply the existence of a critical period in growth response to ART in HIV-infected children.

With regard to the question of whether viral suppression after the use of ART reverses growth and body composition abnormalities, data are becoming available that, while generally favourable, are mixed. Buchacz et al. (173) conducted a prospective cohort study in the United States of 906 HIV-infected children (aged 3 months to 18 years) before and after receiving PI-containing regimens. Although there was no significant growth retardation, PI use resulted in only a minor incremental increase in growth across this sample. There was a more significant deficit in age-adjusted height than weight in the HIV-infected children at baseline. Gender (girls tended to be taller than boys), age (children younger than 3 years were less affected than older children) and immune status (children who were less immunosuppressed were less affected) were associated with better growth based on height and weight Z-scores. Most of the subjects had received zidovudine before enrolling in the

study. Data were not stratified by age group (e.g., less than 3 versus greater than 3 years) and no data on any aspect of nutrition were included in these analyses.

Treatment with ARV regimens containing PIs significantly affected weight and weight-for-height ratio and had a marginal effect on height (174). Conversely, two studies found no overall improvement in growth in children receiving regimens containing PIs despite improvements in viral load (174). Children with a very high entry viral load (e.g., >200 RNA copies/cc³) who subsequently experienced a decline of more than 2.0 log had an improved height-for-age Z-score (175). Again, a potentially important issue in studies of this nature is whether HIV treatments, many of which have significant gastrointestinal toxicities (e.g., nausea, vomiting, diarrhoea), negatively affect appetite and dietary intake, resulting in a blunting of growth improvement potentially achieved through viral suppression. Only Miller et al. (175) were able to account for this through measurement of dietary intake.

Virtually all of the experience to date has been in settings where food is readily accessible and although risk for poor nutrition may be higher in certain high groups with a high risk of HIV, underlying levels of severe undernutrition are relatively negligible. This is not the case in many areas of the world where HIV infection is highly prevalent. As the pandemic is in many cases superimposed on preexisting conditions of food insecurity and poor nutritional status, evaluating the effect of potent antiviral drugs on somatic growth of children in developing countries will need to take these conditions into consideration.

A number of limitations characterize the data regarding the impact of ART on growth in infants and children including nonstandard measurements used in large multicenter studies; pretreatment growth rates not routinely measured in clinical studies; the power of the studies not sufficient for determining growth outcome; inadequate assessment of nutritional status, including a lack of biochemical and/or dietary intake data; and inconsistent results from analyses of viral load (e.g., responders versus nonresponders).

6.2. Bone abnormalities in HIV-infected children and adolescents

An obvious corollary to the question of the impact of ART on growth is the potential impact on bone health. Childhood is a critical period for bone development, accounting for more than 50% of

ultimate adult bone mineral content. Inhibition of bone mineral accrual either by disease or drug has potentially serious implications not only for growth but also for future risk of osteoporosis and related complications.

As reviewed above, a range of bone-related conditions has been reported in adults and children (93). For example, osteonecrosis, a severe debilitating condition that affects the ends of long bones, was reported in children (176). Various degrees of derangements in bone mineral content (e.g., reduced bone mineral content, osteopenia through to osteoporosis) were also reported in children (96,177,178). Adverse bone health outcomes related to the use of ART in children were reported (179,180); as for adults, the question of the relative contribution of HIV and treatments remains an unresolved but clearly multifactorial issue in clinical care.

A critical aspect of bone mineralization is the role of vitamin D in calcium homeostasis. Vitamin D has been implicated in some of the adverse effects of HIV and ART on bone health. As reviewed above, there have been several reports of derangements in vitamin D metabolism following the use of ART in adults. Few data have been published with regard to this relationship in children. One report included two case studies of male African American HIV-infected children (aged 13 and 14 years) living in an urban setting in the United States (181). In both cases the children were found to be hypocalcemic and bone scans revealed reduced bone density. Vitamin D status was not assessed. The children were both given oral 1,25-dihydroxyvitamin D₃ (2000 IU/day initially for the first patient and 800 IU/day for the second patient) and calcium (600 mg/day initially for the second patient). Bone scans and calcium levels improved significantly in both cases. Notwithstanding the shortcomings of over-reliance on case studies, this report nevertheless supports the importance of these types of assessments.

The study by O'Brien et al. (182) provides further support for the consideration of nutritional status in the care and treatment of children with HIV. In this report various bone variables were measured in 19 girls (aged 6–15 years, all receiving ART of an undisclosed nature) who had been infected perinatally with HIV. O'Brien et al. reported that in this predominantly African American sample, both 1,25-dihydroxyvitamin D₃ and parathyroid hormone levels were elevated compared with a geographical- and aged-matched reference sample of girls. Paradoxically, calcium excretion was

also elevated despite dietary intakes below the age requirements. All markers indicated significant differences in bone resorption between the HIV-infected girls and the girls in the reference sample. The combination of decreased bone mass and dietary calcium insufficiency place these girls at increased risk for short- and long-term bone-related problems.

A recent analysis of current U.S. national surveillance data indicates that African American girls and young women are at particular risk for vitamin D insufficiency (183). Although dietary data were collected, neither intake nor biochemical assessment of vitamin D (only the 1,25-dihydroxyvitamin D₃ form was measured, which does not reflect intake or exposure per se) were included by O'Brien et al. (182). No analyses by drug use were included. So although these girls were clearly at risk for dietary insufficiencies that could have contributed to the adverse bone marker outcomes, the relative contributions of HIV and ARVs could not be ascertained.

Although the relative roles of HIV and ARVs in bone problems remain to be defined, the prevalence of poor calcium and vitamin D status (184) and nutritional rickets associated with calcium and/or vitamin D deficiency is known to be high in many areas where HIV has become endemic, including Africa (113). Furthermore, vitamin D requirements independent of HIV status may be significantly higher in highly pigmented populations (185,186) such as those in sub-Saharan Africa. Thus, in light of the evidence indicating problems with calcium and vitamin D homeostasis in HIV-positive people before and during ART and the evidence indicating specific risks for calcium and vitamin D deficiency in populations at high risk for HIV infection, assessing bone health and these essential nutrients as part of the clinical care for PLWHA, including children, seems appropriate.

6.3. The ART metabolic syndrome in infants and children

An emerging body of evidence shows significant metabolic consequences associated with the use of ART in children as with adults (187). The question of prevention becomes even more important as ART use continues to change the natural history of HIV infection in infants and children to one more closely resembling a chronic disease. The same issues with regard to the nature and timing of interventions to prevent the onset of chronic disease that have been the focus of debate about the general population also confront those treating children with HIV infection (e.g., age at which such dietary interventions as fat reduction should be considered, level of intervention). The difference with

regard to HIV infection is the management of the health of these children in the context of their HIV status and concomitant treatment.

Alterations in regional body fat, insulin sensitivity and dyslipidemia have been documented in HIV-infected children and adolescents and are primarily associated with the use of ART especially those containing PIs or those with stavudine (188–193). Most of these studies lacked dietary intake data, assessment of nutritional status or anthropometry (calculated body mass index or any other measure of body composition beyond physical examination to document fat redistribution).

Although data are limited, the effects of ART on glucose and insulin metabolism appears to be less in children than those observed on lipid metabolism. Bitmun et al. (194) reported significantly higher total cholesterol, LDL cholesterol and triglycerides but no difference in serum glucose, insulin, proinsulin, insulin-glucose ratio or the homeostatic model assessment-insulin resistance (HOMA-IR) in HIV-positive children treated with PI-containing ART (n=30) compared with PI-naïve children (n=20). Although there were no significant differences between groups, the best predictor of fasting serum insulin and the HOMA-IR was Tanner stage, and age was the best predictor of visceral subcutaneous adipose tissue ratio in this cohort of predominantly prepubescent children.

In a subsequent study, Bitnun et al. (195) reported that prepubescent HIV-positive children receiving PI (n= 33; mean age 9.1 yr) had reduced insulin sensitivity and an impaired β -cell response to that insensitivity compared with HIV-positive PI naïve children (n=15; mean age 8.7 yr). Bitnun et al concluded that these findings which were a refinement of their previous assessments of glucose/insulin metabolism, could be indicative of early signs of the metabolic syndrome that has emerged as a predictor of long-term adverse health outcomes in the general HIV-negative population.

Brambilla et al. (188) published one of the few studies that focused on anthropometry rather than relying on subjective assessment of fat redistribution. In this study HIV-infected children (n=34) were pair matched with HIV-uninfected children for age, sex and body mass index. The primary comparison was of whole-body dual-energy x-ray absorptiometry and magnetic resonance imaging scans. These investigators were able to document an increased central fat deposition and peripheral redistribution on all children receiving ART containing PIs. They also observed changes in fat distribution (detectable by absorptiometry) in children without frank lipodystrophy.

The study by Lainka et al. (193) was unique in that children receiving NRTI-based therapies were compared only with those receiving combination therapy containing PIs, and fasting and nonfasting concentrations of lipids were measured. In both the fed and fasting states, children receiving regimens containing PIs had significantly higher blood concentrations of total cholesterol, low-density lipoproteins and triglycerides—all risk factors for CVD.

The European Pediatric Lipodystrophy Group (196) performed studies in 280 children, representing one of the larger published reports to date, and encountered an overall prevalence of either hypercholesterolaemia (total cholesterol greater than 5.20 mmol/L or hypertriglyceridaemia (triglycerides greater than 1501.69 mmol/L) of 38% (95% CI 32, 44). The prevalence estimate of hypercholesterolaemia was 27% (95% CI 21.6, 32.7), of hypertriglyceridaemia was 21% (95% CI 16.4, 26.6) and of both was 10%.

Although PIs have been the class of ARVs most implicated in the lipodystrophy syndrome, the recent report of McComsey and Leonard (187) offers a potentially important alternative to this dilemma. In what was referred to as the “paediatric switch study”, PIs were replaced with a new regimen containing efavirenz (a new NNRTI) the effect on lipid variables (primarily serum cholesterol, triglycerides and lipoprotein profiles) in HIV-infected children was evaluated. The trial involved 17 children (aged about 2–13 years) all of whom had been receiving combination therapies containing NRTIs and PIs. All children were switched from their respective PI regimens to the NNRTI while maintaining the NRTI regimen. After 48 weeks of the new treatment, there were significant decreases in serum total cholesterol, triglycerides and low-density lipoprotein. No changes in glucose or insulin were noted. In addition, no changes in dietary intake were seen throughout the trial. An additional finding was that although body fat content did not change, lean body mass significantly increased. Whether this observed effect reflected normal growth in these children or an improvement in body composition is not clear. This well-designed trial offers encouraging data about how to address the metabolic consequences of ART while still maintaining viral control in children.

The report by Cheseaux et al. (197) is important with regard not only to documentation of the existence of these metabolic anomalies in HIV-infected children but also to the question of how best

to address these risks to health and quality of life. A chart review was done of all plasma lipid levels of children (n=66) in Switzerland before and after receiving PIs in 1995–2001. A comparison of those levels with levels seen in children with familial hypercholesterolaemia revealed that children treated with PIs had lipid levels that were comparable with those in the contrast group (children heterozygous for familial hypercholesterolaemia) and analogous to changes reported for adults. The authors concluded that although serum lipids were clearly elevated, the risk for CVD was minimal as shown by the absence of evidence of CVD in HIV-positive children. The effect of long-term elevations in serum lipids on development of subsequent disease in adulthood was not considered. The authors concluded that long-term monitoring of these children would be necessary. No intervention—dietary or other—was suggested. In light of the well-established role of these risk factors in the subsequent development of a myriad of chronic diseases, including CVD, diabetes mellitus and cancer, this interpretation of these data is disconcerting and raises questions about the need for a more comprehensive approach to the care and long-term health of HIV-infected children. No studies of treatments for lipodystrophy and related conditions (e.g., statins or diet and lifestyle) in children were found. Similarly, no reports were found that included studies of these relationships in children living in resource-limited settings or who were assessed for nutritional status.

7. Research gaps

As noted throughout this technical report, there is a tremendous need for basic, clinical and operational research on the myriad of potential intersections between nutritional status and prevention, care and treatment of HIV/AIDS particularly in the context of high prevalence of food insecurity. Aside from the universal need for better (more specific and sensitive and field appropriate) assessment tools and capacity needs at all levels of health-care delivery, specific research questions will need to be addressed in the context of the use of ART in resource-limited settings. The following is a brief listing of topics requiring research, listed in the order of the materials presented in this review.

7.1. Nutrition and pharmacology

- The potential impact of macronutrient (e.g., protein-energy malnutrition) and micronutrient (vitamin/mineral) insufficiency or imbalance on the safety and efficacy of ART and related therapies.
- The prevalence of use and potential impact of traditional therapies (e.g., herbal/botanical) on safety and efficacy of ART.
- Potential interactions with ongoing or planned interventions (e.g., national vitamin A or iron supplementation programs) to ameliorate micronutrient insufficiency in areas where malnutrition and HIV coexist.
- Developmental differences (in utero and beyond) in drug metabolism and their potential role in nutrient–drug interactions, if any.
- Guidelines for counselling PLWHA with regard to potential nutrient–drug interactions that are suitable for various settings and levels of understanding.

7.2. Metabolic consequences of ART

- Mechanisms contributing to the lipodystrophy syndrome, bone problems and other effects of ART to enable predictions about who might be at risk and the development of more effective strategies for prevention.
- Relative roles of diet, nutrition and lifestyle in these effects particularly for PLWHA in resource-limited settings with high prevalence of food insecurity.
- Within the context of the metabolic effect of ART, the risk factors related to reduced compliance in developing countries that might differ from those seen in developed countries and/or that could be affected by diet and nutrition care and counselling.
- The potential role for specific micronutrient in the onset of metabolic complications of ART.
- The role of preexisting malnutrition in the onset, natural history and treatment of these metabolic complications of ART.
- Indigenous gender differences, if any, in metabolic response to ART and what role nutrition might play in such differences.

- Social and cultural behavioural factors that contribute to gender differences in dietary intake and how they can they best be addressed in the context of delivery of care for women treated for HIV/AIDS.
- Setting-specific dietary and nutritional guidance specific to ART.

7.3. Pregnancy

- The potential interaction of nutritional state and response to ART during pregnancy.
- The effect of nutritional state and ART on the fetal environment and the implications for fetal intrauterine needs for growth and development.
- The effect of ART on maternal nutritional status and risk for morbidity and mortality, and the potential contribution of ART when malnutrition is endemic.

7.4. Lactation

- The effect of ART on lactation performance, both in terms of successful extended breastfeeding and milk composition (short and long term).
- The potential effect of ART on maternal nutrition status.
- Evidence-based guidance that adapts current programs and policies with regard to breastfeeding and complementary feeding within the specific context of ART and the nutritional needs of the mother and infant.

7.5. Children

- A better understanding of the nutritional needs of HIV-exposed infants and children.
- The effect of ART on nutritional needs.
- Within the context of the metabolic consequences of ART, critical periods before which dietary interventions might have a greater effect on prevention and long-term outcomes.
- The timing of such strategies as dietary interventions to reduce cardiovascular risk factors particularly for potential interactions with ART.
- Evidence-based guidance for nutritional care and management of HIV-infected children receiving ART.

8. Summary and conclusions

This paper reviews our knowledge about the importance of diet and nutritional status to pharmacology in general and the potential interaction between HIV status and current treatment for HIV and related conditions. There is no reason to expect that the intimate relationships between nutrition and drug metabolism should be different in PLWHA than in uninfected populations. What is not known are the specifics of the association among the natural history of HIV infection, consequent effect on the full range of nutrition processes, and pharmacology of ARVs. What has emerged from the limited number of studies is that a real potential exists for these interactions and that PLWHA need to receive appropriate counselling to ensure safe and efficacious delivery of ARVs.

Given the intimate and inextricable role of nutrition and specific nutrients in the bioavailability (absorption, digestion, metabolism and transport) of drugs, it is essential that PLWHA being considered for ART be screened for nutritional problems. The extent of such screening would depend on the level of support at the clinical care setting. At a minimum, basic anthropometry (weight, skinfold measurements reflecting regional adiposity and lipodystrophy) to obtain some appreciation of lean body mass and adiposity, and height and length measurements in infants and children) along with an assessment of normal diet (food frequency to assess normal dietary constituents and patterns) would be appropriate. Such intake assessments should also include documentation of dietary supplement use including use of herbal and botanical therapies and participation in government-sponsored micronutrient supplementation programs.

Assessment of PLWHA before the initiation of ART will be essential to if not avoid at least develop individualized programs to mitigate potential adverse effects. A specific set of circumstances may define conditions under which patients respond to interventions—nutritional and pharmacologic. Responsiveness to nutritional interventions appears to be contingent on viral load, stage of disease, body mass index (and probably relative body composition) and presence or absence of opportunistic infections. Few data exist on the direct effect of dietary intake on these variables in HIV-positive individuals. Thus, a hierarchical progression of diagnosis needs to occur in order to determine the appropriate intervention. For making a differential diagnosis of starvation versus wasting or cachexia

in PLWHA, it would be useful to develop a set of sensitive and reliable biomarkers and include assessment of dietary intake and biochemical measures of nutritional status that are not subject to fluctuation after the acute phase response. These considerations will be particularly critical in areas where food insecurity and chronic malnutrition are prevalent. Wild et al. (198) reviewed issues pertaining to the development and choice of appropriate biomarkers to assess diet and health relationships.

In conclusion, an intimate link exists between pharmacology and nutrition that is affected by stage of development and physiological differences (i.e., gender, physiological state). The HIV pandemic has been superimposed on these relationships. The currently available treatments for HIV/AIDS come with their own unique issues and consequences. A full appreciation of the potential interplay of all these factors will be essential as the global community moves forward to most effectively address this pandemic. In areas where malnutrition and HIV infection coexist, it will be essential to incorporate a full appreciation of the important role of diet and nutrition in the implementation of those strategies designed to prevent and treat HIV/AIDS in adults, infants and children.

9. References

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Table 1: Mechanisms by which nutrients and drugs can influence each other

PROCESS	MECHANISM
Ingestion	Both drugs and disease can cause changes in appetite and nutrient intake; resultant malnutrition can affect drug efficacy.
Absorption	Drugs and foods can have mechanical effect, via binding or adsorption that can influence the absorptive processes resulting in \uparrow or \downarrow drug and nutrient absorption. Some drugs can affect gastrointestinal motility thereby \uparrow or \downarrow absorption of nutrients. Chemical factors, in particular pH of the stomach contents and the influence of foods therein, can affect the subsequent absorption of drugs.
Translumenal transport	The ability of drugs and nutrients to be transported can depend on such factors as lipid solubility and competition for amino acid transport systems.
Metabolism	The effectiveness of the mixed function oxidase (MFO) and conjugase systems in the liver and elsewhere for converting drugs and nutrients into their active and, ultimately, excretory forms depends on the availability of specific nutrient cofactors. In addition, certain drugs can increase the activity of the MFO systems required to convert nutrient precursors into their active forms. Nonnutritive components in foods can induce MFO activity, thereby affecting drug metabolism.
Distribution	The utilization of both drugs and nutrients depends on body composition, the availability and functional integrity of transport proteins, receptor integrity and intracellular metabolic machinery.
Elimination	Drugs and nutrients can synergistically and competitively interact to cause increased or decreased excretion. Systemic factors such pH and physiological state (e.g., sweating) can dictate whether a drug or nutrient is excreted or resorbed.

Table 2: Examples of the effect of specific nutrients on MFO metabolism

NUTRIENT	EFFECT ON MFO METABOLISM	POTENTIAL MECHANISMS
Protein	Deficiency: ↓ rate of metabolism Excess: can ↑ rate of metabolism	↓ Protein synthesis; ↓ in synthesis of other elements, such as hormones, involved in enzyme induction.
Lipids	Deficiency (or diet high in saturated fatty acids): ↓ Excess (or diet high in polyunsaturated fatty acids): ↑ activity and inducibility of MFO enzymes	↓ Activity of MFO possibly connected to the requirement for polyunsaturated fatty acid in the β-position of phosphatidylcholine (lecithin), which is an essential component of the MFO system.
Carbohydrates	Excess: ↓	Secondary effect due to ↓ protein or possibly inhibition of P450 via ↓ in supporting enzyme components.
Vitamin C	Deficiency: ↓ Excess: ↓ MFO activity	Alterations in activities of P450 and P450 reductase.
Vitamin B ₆	Deficiency: ↓	↓ Synthesis of heme; possible impairment of protein synthesis.
Thiamin	Deficiency: ↑ activity of cytochrome P450 Excess: ↓ (both reductase and P450)	↑ Activity of specific P450 isozymes and perhaps other enzymes in deficiency by an unknown mechanism. Effect of excess may be due to □ substrate binding.
Riboflavin	Deficiency: ↑ or ↓ depending on the severity	↓ Reductase activity but ↑ P450 activity such that metabolism of some drugs will be ↑ while others may be ↓.
Vitamin E	Deficiency: ↓	Because activities of P450 and reductase are unaffected it may be due to maintenance of the lecithin/long-chain polyunsaturated fatty acid component.
Iron	Deficiency: ↑ and ↓ Excess: ↑ in microsomal lipid peroxidation	Differential effects on various components of the MFO system. ↑ Lipid peroxidation could lead to damage to the integrity of the system.
Vitamin A	Deficiency: ↓ liver P450 activity Excess: ↑ liver P450 activity	Availability of circulating vitamin A is regulated at the liver via an vitamin A status dependent on up or down regulation of P450.

Figure legend

Figure 1: Conceptual model of the relationships among nutrients, food, health and drugs. ARVs, antiretroviral drugs.



