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# Nutrition and Tuberculosis:

A review of the literature and considerations  
for TB control programs



April 2008

This publication was produced for review by the United States Agency for International Development. It was prepared by the Africa's Health in 2010 project, managed by AED.

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**Nutrition and Tuberculosis: A review of the literature and considerations for TB control programs** was produced for review by the United States Agency for International Development. It was prepared by Dr. Peggy Papatkakis, California Polytechnic State University, San Luis Obispo and Dr. Ellen Piwoz, Academy for Educational Development.

This publication is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of Contract No. RLA-C-00-05-00065-00, managed by the Academy for Educational Development (AED). The contents are the responsibility of the Africa's Health in 2010 project/AED and do not necessarily reflect the views of USAID or the United States Government.

The Africa's Health in 2010 project is implemented by the Academy for Educational Development and its partners—Abt Associates, Heartlands International Ltd., Population Reference Bureau, and Tulane University's School of Public Health and Tropical Medicine. The purpose of Africa's Health in 2010 is to provide strategic, analytical, communication and advocacy, monitoring and evaluation technical assistance to African institutions and networks to improve the health status of Africans.



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# Acknowledgments

We gratefully acknowledge the technical review and comments on earlier drafts of this paper made by the following individuals. Without their inputs, this work could not have been completed.

## **Africa's Health in 2010**

Doyin Oluwole  
Sambe Duale  
Justin Opoku  
Winston Allen  
Stephen Musau  
Silvio Waisbord

## **USAID**

Hope Sukin  
Tim Quick  
Christy Hanson  
Connelia Davis

## **UNICEF**

Anirban Chatterjee

## **World Health Organization**

Peter Eriki (Nigeria)  
Dermot Maher

## **World Food Programme**

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# Acronyms

<b>AED</b>	-	Academy for Educational Development
<b>ARV</b>	-	Antiretroviral
<b>BIA</b>	-	Bioelectric Impedance Analysis
<b>BCG</b>	-	Bacilli Calmette-Guérin
<b>BMI</b>	-	Body Mass Index
<b>CDC</b>	-	U.S. Centers for Disease Control and Prevention
<b>C-SAFE</b>	-	Consortium for the Southern Africa Food Security Emergency
<b>CSB</b>	-	Corn Soya Blend
<b>DOTS</b>	-	Directly Observed Treatment, Short-course
<b>INH</b>	-	Isoniazid
<b>MDR</b>	-	Multi-Drug Resistant
<b>MUAC</b>	-	Mid-Upper Arm Circumference
<b>PEM</b>	-	Protein-Energy Malnutrition
<b>PLP</b>	-	Pyridoxal Phosphate
<b>ROS</b>	-	Reactive Oxygen Species
<b>TB</b>	-	Tuberculosis
<b>TBARS</b>	-	Thiobarbituric Acid Reactive Substances
<b>USAID</b>	-	United States Agency for International Development
<b>WFA</b>	-	Weight-for-age
<b>WFP</b>	-	World Food Programme
<b>WHO</b>	-	World Health Organization
<b>XDR</b>	-	Extensively Drug Resistant



## Executive summary

In Africa, tuberculosis (TB) is the most common cause of death from a curable infectious disease. The nutritional consequences of active TB are well recognized by clinicians, yet little is known about effective nutritional management, nor of the interactions between TB treatment and nutritional status. The purpose of this paper is to review the scientific literature on the role of nutrition in TB disease, summarize key findings and knowledge gaps, and investigate related programmatic experience. The primary target audiences for this review are nutrition program managers in Africa and technical advisors in TB programs.

Based on the information summarized in this report, it is clear that TB affects nutritional status. Many patients with active TB experience severe weight loss and some show signs of vitamin and mineral deficiencies. Persons with TB/HIV co-infection are even worse off nutritionally. However, the evidence surrounding best practices for nutritional management is very limited.

The paper concludes with suggested approaches for addressing the nutritional needs of patients with active TB, based on nutritional principles and experience. Research priorities to provide the type of evidence needed to translate these suggestions into firmer evidence-based recommendations are also listed.

### Generalized malnutrition and TB

The association between TB and malnutrition has long been known. TB makes malnutrition worse and malnutrition weakens immunity, thereby increasing the likelihood that latent TB will develop into active disease. Unfortunately, few studies have been designed to examine the relationship between nutrition and the incidence of TB or its severity. It is very difficult to determine accurately what the nutritional status of individuals with active TB was before

the onset of the disease, making it impossible to determine whether malnutrition led to advancement of the disease or whether active TB led to malnutrition. Several studies report that patients with active TB are more likely to be wasted or have a lower body mass index ( $\text{BMI} = \text{kg}/\text{m}^2$ ) than healthy controls and that wasting is associated with increased mortality in TB patients.

TB affects protein metabolism and nutritional status through multiple mechanisms. With anti-TB drug treatment, nutritional status usually improves. This may be for a variety of reasons, including improved appetite and food intake, reduced energy/nutrient demands, and improved metabolic efficiency. However, most improvements are limited to increases in fat mass with little effect on muscle tissue. The evidence suggests that adequate nutritional intake during TB care and recovery is needed to fully restore nutritional status during and following TB treatment and microbial cure. There are few published studies on the optimum duration and effectiveness of nutritional support during and following TB treatment.

HIV is one of the most important factors contributing to the increase in active TB cases in sub-Saharan Africa. HIV infection increases the risk of rapid TB disease progression. Co-infection with HIV and TB poses an additional metabolic, physical, and nutritional burden, resulting in further increase in energy expenditure, malabsorption, and micronutrient deficiency. There is evidence that adults and children co-infected with HIV and TB are at greatest risk of malnutrition, poor treatment outcomes, and death. Efforts to prevent, manage, and treat HIV and TB have been largely separate endeavors, despite the overlapping epidemiology. Continued and improved collaboration between TB and HIV/AIDS programs is necessary to control TB more effectively

among HIV-positive people and to make significant public health gains.

### **Micronutrients and TB**

Reduced micronutrient intake, and especially intake of vitamins and minerals such as vitamins A, E, and C, zinc, and selenium, has been associated with an impaired immune response. There is evidence that at the time of diagnosis, patients with active TB have depressed blood concentrations of several micronutrients, including retinol, vitamins C and E, hemoglobin, zinc, iron, and selenium compared with healthy controls—in part due to the immune system response to infection. Anemia is commonly found in patients with pulmonary TB and appears to be more common among TB/HIV co-infected patients. Data on the impact of micronutrient supplementation on TB outcomes are limited. Studies suggest, however, that daily supplementation may have an added benefit among those who have deficiencies, especially during early months of anti-TB therapy. Additional research is warranted on the impact of multiple micronutrient supplements on TB-associated outcomes in settings where predominantly cereal-based local diets are unlikely to provide adequate micronutrient content due to low bioavailability and high fiber content.

### **Program experience**

Food assistance is a potentially influential means for increasing adherence to TB treatment, reducing the costs to patients of staying in treatment, and for improving nutritional status. Food assistance may

influence early case detection (encouraging patients to come sooner for diagnosis and treatment), and promote completion of the full course of treatment. Both are important to decrease TB transmission. Although most evidence of the impact of food support on TB patients' nutritional status, quality of life, treatment adherence, and outcome is anecdotal, there is reason to believe that such support will provide direct benefits to adults and children infected with TB both during and following drug therapy. However, the cost to programs of providing food support may be considerable. Other low-cost interventions, such as periodic nutritional assessment, counseling on diet, nutritional management of symptoms and drug side-effects, may help TB patient maintain or increase their food intake and adhere to TB treatment. But again, program and/or research evidence is limited.

### **Research priorities**

Many areas require further investigation to improve our understanding and management of malnutrition in TB and TB/HIV co-infection. Of particular priority are studies of the most effective approaches for treating malnutrition and improving overall nutritional status and muscle mass in TB and TB/HIV co-infected adults and children during and after TB treatment—taking into consideration local diets and food availability. Successful and varied models for integrating nutritional support into both TB and HIV/TB programs, and data on the cost-effectiveness of integrated nutritional support, are also needed.

# Introduction

The purpose of this paper is to review the scientific literature on the role of nutrition in Tuberculosis (TB) disease, summarize key findings and knowledge gaps, and investigate related programmatic experience. This review is intended to guide nutritionists and others working in TB control programs, with an aim to improve the nutritional management of those with active TB disease. A focus on nutrition is especially important where TB programs are increasing in scale to maximize TB diagnosis and treatment.

Studies included in this review were identified through a Medline search strategy, using the search words tuberculosis and nutrition; tuberculosis and HIV; tuberculosis and wasting or weight loss; and tuberculosis and vitamins, minerals, or micronutrients. Additional searches included TB and weight or body composition; and TB and protein. Abstracts of more than 2,000 citations were reviewed, with a focus on published studies carried out in Africa and other settings where malnutrition is endemic. In addition, websites for government and international agencies, such as the United States Agency for International Development (USAID), the World Health Organization (WHO), the World Food Programme, and U.S. Centers for Disease Control and Prevention (CDC) were searched for recommendations and nutrition programs.

## I. Tuberculosis

TB is one of the top ten causes of illness, death, and disability worldwide and is the leading cause of death from a curable infectious disease.<sup>4,5</sup> It is estimated that approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* (hereafter called latent TB), with 8.8 million new cases during 2005 alone.<sup>6,9</sup> Considering current trends, the annual number of new active TB cases is expected to increase to

9-10 million in the year 2010.<sup>4</sup> Smear-positive TB, the most infectious form of the disease, accounts for about 46% of these new cases.<sup>6,8</sup> Worldwide, about 10% of those with latent TB are expected to develop active TB disease.<sup>6,9</sup>

### Epidemiology

More than 80% of TB patients live in Asia and sub-Saharan Africa, considered by WHO to be “high burden countries.” Sub-Saharan Africa has the highest incidence of the disease.<sup>6,9,10</sup> India, China, Indonesia, Bangladesh, and Pakistan together account for more than half of the global estimate of active TB, as shown in **Figures 1-3**.<sup>6,11</sup> Population increases in South Asia and central Africa alone will account for ~75% of new cases of active TB in the next ten years.<sup>4</sup> For the most part, active TB cases have steadily declined in western and central Europe, North and South America, and in the Middle East, but are increasing in sub-Saharan Africa and the former Soviet Union.<sup>9,10</sup> HIV/AIDS is responsible for most of the recent increase in incidence in sub-Saharan Africa.<sup>6,8</sup> Co-infection with HIV greatly increases the lifetime risk that latent TB will develop into active disease.

Approximately 1.6 million people died from TB in 2005.<sup>6</sup> Deaths from active TB are expected to increase to five million a year by 2050. The main reasons for this increase in number of deaths have been suggested:<sup>4,10</sup>

- Increasing populations in countries where TB is highly prevalent
- Increasing poverty
- The spread of HIV/AIDS
- Weak health systems and TB program management
- Insecure funding
- TB drug resistance

The relationship between poverty and active TB is well established in both developed and

developing countries. Most cases of active TB (5-6 million annually) occur during the economically productive years of people's lives (19-49 years),<sup>11</sup> compromising earning capacity. Poverty is also an underlying risk factor for TB.

Other risk factors include HIV-infection, sharing a home with someone who has active TB, exposure to smoke from domestic stoves and cigarettes, poorly controlled diabetes, vitamin D deficiency, malnutrition, chemotherapy, and impaired immune function.<sup>4,11,14-16</sup> HIV is currently the single biggest risk factor for development of active TB disease.

The collapse of health infrastructure in countries experiencing economic crisis or civil unrest increases the global burden of active TB.<sup>10,12</sup> Poorly funded or organized TB control programs may not be able to offer the full course of treatment, possibly resulting in drug resistance. The emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB poses a great public health threat, particularly in countries with high HIV prevalence.

## Pathophysiology

*Mycobacterium tuberculosis* (latent TB) from an individual with active TB is spread through airborne droplets dispersed via coughing, sneezing, singing, or talking. These particles are very small and can remain airborne for minutes to hours.<sup>11</sup> TB infection occurs when the droplets are inhaled and lodge in passageways in the lungs. The bacterium is then taken up by macrophages, a type of white blood cell that ingests foreign substances, beginning a chain of responses that result in either containment of the infection or development of active disease.<sup>11</sup> A healthy immune system is very effective in containing TB but is not able to eradicate it,<sup>13</sup> because TB bacilli continue to exist in the macrophages.

Following TB exposure, healthy individuals mount a cell-mediated immune response

involving T-cells, macrophages, and cytokines.<sup>13</sup> The infection is usually controlled and active disease does not develop unless the immune function is weakened.<sup>11,14-16</sup> A positive tuberculin skin test indicates that there has been TB exposure and the body has developed cell-mediated immunity against TB.<sup>11</sup> Active TB disease can be caused by a recent infection, activation of latent TB, or a relapse following earlier treatment.<sup>5,10</sup>

In addition to the risk factors mentioned above, there is some evidence to suggest that genetic factors may play a role in both the susceptibility to infection and the development of active TB.<sup>17</sup> Research in the **Gambia** and **South Africa** among families containing two or more siblings developing active TB found two Y chromosomal regions linked to susceptibility to active TB, and one to the X chromosome. This may partially explain the higher incidence of active TB in males.<sup>18</sup>

The variety of genetic and other risk factors for developing active TB underscore the complex relationship between the host immune system and the TB bacillus in determining the outcome of TB infection.<sup>19</sup>

## Clinical presentation

### Diagnosis

Bacteriology remains the recommended method for diagnosing active TB, first through sputum smear microscopy and then culture testing.<sup>6,10</sup> Culturing TB bacteria is expensive and results are not immediately available.<sup>6,11</sup> In countries where the culture is not routinely available, sputum smear is the primary diagnostic tool for pulmonary TB. However, relying on sputum smears to diagnose TB has limitations. For example, TB smears detect 65-80% of infections confirmed by cultures in low HIV prevalence areas. HIV-positive individuals with culture-confirmed TB are generally less likely to have positive smear results than those who are HIV-negative, particularly in the later stages of HIV disease.<sup>20</sup>

### Active TB disease

TB bacteria grow in almost any organ system but infection occurs most often in the mid to lower lung. Symptoms of active TB include persistent cough, fever, night sweats, weight loss, shortness of breath, coughing up blood, and chest pain.<sup>11</sup>

Extra-pulmonary TB is found in about 20% of HIV-negative individuals. It is more common in HIV-positive individuals, in women, and in young children. Severe forms of extra-pulmonary TB include central nervous system TB and abdominal TB.<sup>11</sup>

In the era before effective TB treatment (and also the advent of the HIV epidemic), the TB case fatality rate was reported to be between 17-29% within the first year of diagnosis, and up to 42-55% after five years. With anti-TB therapy, fatalities in industrialized countries decreased dramatically so that death due to active TB became an unusual occurrence.<sup>21</sup>

### Treatment

TB treatment goals include:

- Cure of active TB disease without recurrence
- Prevention of transmission
- Prevention of drug resistance
- Improved survival

Standardized short course chemotherapy is used for 6-8 months in confirmed smear-positive cases.<sup>6</sup> Treatment with a combination of drugs and high adherence are necessary to attain a cure. Treatment usually takes place in two phases.

The initial phase of treatment, during which active and dormant bacilli are killed using daily drug therapy, lasts 2-3 months and shortens the duration of infectiousness in 80-90% of cases. At least three and preferably four antibacterial drugs, including isoniazid and rifampin, are used during the initial phase.

The continuation phase usually uses two drugs daily or three times a week and lasts 4-6 months.<sup>11</sup>

Directly observed treatment, short-course (DOTS) is an important approach to promote adherence to treatment.<sup>10</sup> This approach has proven successful in improving completion rates of anti-TB therapy, reducing multi-drug resistant disease, and preventing disease relapse. The strategy requires sputum smear microscopy for diagnosis of infectious patients, use of a standardized short course drug treatment with supervision and patient support (a trained observer is present when the patient takes each dose of medication), a secure drug supply and management system, a recording and reporting system, and political commitment.<sup>22,6</sup>

The Global Plan to Stop TB includes six main components, including expanding and enhancing high quality DOTS strategy, addressing TB/HIV co-infection and multi-drug resistant TB, strengthening health systems, engaging all providers, empowering individuals with TB and their communities, and promoting research.<sup>23</sup>

Worldwide, DOTS is the standard approach, with 187 countries implementing the strategy in 2005. A total of 26.5 million new and relapse cases were treated in DOTS strategy programs between 1995 and 2005.<sup>6</sup> On average, the rate of DOTS treatment success in 2004 was 77%, with 74% success in the African region.<sup>6</sup>

### TB in children

Children are usually infected with TB by a smear-positive family member or other close contact. Therefore, the most effective means to prevent childhood TB is early identification and proper treatment of infectious cases.<sup>12</sup> Children may also be infected from untreated cow's milk containing *Mycobacterium bovis*.<sup>12</sup> Although children may present with active TB at any age, infection is most common between the ages of one

and four years, most likely due to an under-developed immune response.

In Africa, an estimated 10% of new active TB cases occur in children.<sup>5</sup> This estimate is likely to be low because many sick children are not brought to health facilities, and there is limited diagnostic capacity in many treatment centers.<sup>24</sup> Furthermore, since active TB in children often affects more than one organ system, signs and symptoms are vague, making diagnosis difficult. (See **Box 1**)

It is estimated that more than 95% of children with active TB would have a negative sputum smear. Studies in hospital settings have found that extra-pulmonary TB is as or more common than pulmonary TB and missed diagnosis is as common as over-diagnosis.<sup>7,12</sup> Poverty is the strongest risk factor for childhood TB infection since it is associated with both poor nutrition and household overcrowding, resulting in close contact with infectious cases.

The majority of children with latent TB do not develop active TB. Immunosuppressive factors such as HIV infection, measles, and malnutrition are risk factors for development of active disease.<sup>12</sup> The risk of active TB is five times higher in children with HIV.<sup>7</sup> Progression to active disease is also influenced by age. If the child is infected in the first two years of life, disease is more likely to progress than if infected between ages five and ten years.

Children under five years of age are at increased risk of TB meningitis, which can present as headache, fever, and altered mental status.<sup>7</sup> BCG, or bacille Calmette-Guérin, is a vaccine used to prevent childhood TB meningitis and miliary disease (small nodules or lesions resembling millet seeds). WHO recommends the use of neonatal BCG as a means to prevent TB meningitis.<sup>25</sup> This vaccination does not prevent TB infection, but prevents the spread of the bacteria to extra-pulmonary locations.<sup>7</sup>

<b>Box 1. Symptoms of pulmonary tuberculosis in children compared with adults<sup>7</sup></b>		
<b>Feature</b>	<b>Adults</b>	<b>Children</b>
Symptoms	Cough, fever, chest pain, hemoptysis (spitting up blood), weight loss	
Lesions	Apical, upper lobes of lungs most commonly involved	Peripheral, often middle and lower lobes of lungs
Cavitation*	Common	Uncommon, seen during infancy and adolescence
Dissemination (extra-pulmonary disease)	Uncommon	Common
Infectivity	Patients with smear-positive pulmonary TB are infectious	Usually not infectious

\*Cavities form in the lung tissue when necrosis involves the wall of an airway



## II. TB/HIV co-infection

### Epidemiology

HIV is responsible for the increase in active TB cases in sub-Saharan Africa and increases the risk of rapid TB disease progression.<sup>8,24</sup> Worldwide, more than 13 million individuals are co-infected with HIV and TB, or about one-third of the 40 million people currently living with HIV. Approximately 70% of those co-infected reside in sub-Saharan Africa.<sup>9</sup>

The incidence of active TB is more than eight times higher in HIV-positive than HIV-negative Africans.<sup>9,26</sup> In Africa, the countries with the largest numbers of co-infected adults are South Africa (2 million) and Nigeria (0.9 million).<sup>8</sup> Between 30-50% of those infected with HIV will develop active TB, while up to 75% of those infected with TB are HIV-positive.<sup>21,27</sup>

In many individuals infected with HIV, development of active TB disease is the first sign of AIDS. Active TB often occurs at a higher CD4+ lymphocyte count than other HIV-related illnesses. TB is a potent factor in the progression of HIV disease.<sup>28,29</sup> Both diseases accelerate the progress of the other. Active TB often decreases the number of CD4+ lymphocytes, increases HIV viral replication and shortens the lives of HIV-positive persons.<sup>30,21</sup> The case fatality rate for HIV-related TB has been estimated to be over 50% in developing countries.<sup>8</sup>

HIV infection impairs cell-mediated immunity, increasing the risks of TB infection and the reactivation of latent TB in adults and children.<sup>31</sup> When TB infection occurs early in the course of HIV disease, before the immune system has been compromised, its characteristic features are similar to those in HIV-negative patients. However, when TB occurs among persons with advanced immune deficiency, the majority of patients (~70%) present with atypical pulmonary disease and about 30% present with extra-pulmonary (or disseminated) TB.<sup>31,32</sup>

### The clinical context

#### Diagnosis

Although most HIV-positive patients with pulmonary TB are sputum smear-positive, the occurrence of negative smears is more frequent among the co-infected, making TB diagnosis difficult in areas with limited laboratory support. In those with extra-pulmonary TB, the disease may be regularly missed.<sup>31</sup> In children, almost all pulmonary TB cases are smear-negative and diagnosis is made according to clinical and radiological criteria.

Smear-negative TB has a worse outcome than smear-positive disease in HIV-positive persons, with a case fatality rate of about 50% in Africa.<sup>26</sup> The high mortality associated with co-infection and a sputum-negative smear is most likely caused by missed diagnosis and delayed initiation of treatment. Management of opportunistic infections in TB/HIV patients is challenging in many regions due to inadequate capacity to make early diagnosis and the lack of proper medications.<sup>10</sup>

The number of TB deaths in a population is an important marker of the severity of HIV's impact.<sup>21</sup> Currently less than 10% of TB patients in Africa are tested for HIV. HIV testing is usually not available in TB clinics.<sup>26</sup> However, most countries have recently begun to implement collaborative TB/HIV activities. While 58% of African countries have national policies to offer HIV testing for TB patients, only 17% provide HIV surveillance of TB patients.<sup>10</sup> There is an urgent need to improve the scaling up of TB/HIV collaborative activities including coordination between HIV and TB programs in Africa.

#### Treatment

Provision of antiretroviral (ARV) drugs can reduce TB incidence in HIV-positive persons by 70-80%. (Even so, the incidence

of TB in this group remains higher than among HIV-negative persons.<sup>26,33</sup> TB is an opportunistic infection that occurs at a higher level of immune function than most other opportunistic infections. Thus, the potential of ARV treatment to prevent TB is highest when ARV therapy is started in the earlier stages of immune deficiency.<sup>26,33</sup>

Although most HIV-positive patients with active TB respond to anti-TB therapeutic drug regimens, it is speculated that drug absorption may be suboptimal in patients with gastrointestinal symptoms—leading to reduced effectiveness of treatment.<sup>21</sup> However the evidence is conflicting and

study sample sizes are small (**Box 2**). There are also interactions between some TB and ARV drugs, which are addressed in WHO treatment guidelines.<sup>26,34</sup>

### HIV-TB co-infection in children

HIV is a major risk factor for childhood TB. Children may contract both infections from their mothers. The clinical criteria used to diagnose active TB are also the most frequent signs and symptoms associated with HIV infection (failure to thrive, chronic cough, recurrent fever, lymphadenopathy), making correct diagnosis even more difficult.<sup>2</sup> WHO provides guidelines

<b>Box 2. Conflicting studies on TB drug absorption in individuals co-infected with HIV</b>		
<b>Author</b>	<b>Subjects</b>	<b>Findings</b>
Gurumurthy <i>et al.</i> <sup>35</sup> <b>India</b>	1. 23 subjects HIV-negative with TB 2. 40 subjects AIDS with diarrhea* 3. 26 subjects AIDS with TB* 4. 10 subjects healthy * <b>not on antiretroviral treatment</b>	TB drug absorption not different in groups 1 and 4 but a 24-37% reduction in TB drug absorption in both AIDS groups (2 and 3)
Gurumurthy <i>et al.</i> <sup>36</sup> <b>India</b>	1. 13 subjects HIV-negative with TB 2. 13 subjects advanced AIDS with diarrhea 3. 15 subjects HIV-positive and TB with diarrhea	Compared to group 1, 35-48% decreased TB drug absorption in group 2; 19-43% decreased TB drug absorption in group 3
Choudhri <i>et al.</i> <sup>37</sup> <b>Kenya</b>	1. 14 subjects HIV-positive with TB 2. 15 subjects HIV-negative with TB	No relationship between diarrhea and HIV and TB drug absorption
Taylor <i>et al.</i> <sup>38</sup> <b>South Africa</b>	1. 13 subjects HIV-positive with TB 2. 14 subjects HIV-negative with TB	No differences between groups in absorption and no evidence that HIV reduced plasma concentrations of TB drugs

### TB/HIV co-infection in children

Palme *et al.*<sup>2</sup> studied 517 HIV-positive and HIV-negative Ethiopian children presenting at a TB clinic. None of the HIV/TB co-infected children had been diagnosed with HIV prior to the study. On average, the HIV-positive children had been brought to medical clinics 5.6 times before TB diagnosis. Among HIV/TB co-infected children 41% died, compared with 7% of the HIV-negative TB patients. Among both groups, 90% of the deaths occurred in the first two months of TB treatment. Age and low weight-for-age were the only variables predicting death in the HIV co-infected group. The lowest weight-for-age scores were amongst the youngest children, who also had the highest mortality. The authors conclude that although HIV/TB-co-infected children have a six-times higher risk of death than HIV-negative children with TB, the majority of the HIV-positive children (58%) completed treatment and were considered cured.

on the diagnosis and treatment of children with TB/HIV co-infection.<sup>39</sup>

There have been several studies of the impact of TB/HIV co-infection on the clinical presentation and treatment outcomes of children in Africa.<sup>2,40,41</sup> These studies indicate that mortality is higher in those with TB/HIV co-infection, that mortality tends to be highest in the youngest children, that most of the deaths occurred during TB treatment, and that malnutrition was a strong predictor of death.

### **Food insecurity, poverty, and vulnerability to HIV and TB**

Food insecurity and hunger are common among populations throughout Africa and are caused by a combination of climatic, economic, policy, and political factors, and exacerbated by the HIV/AIDS epidemic. Since most high HIV-prevalence African countries rely on agriculture for food security, long-term strategies for food security and

poverty reduction are challenged, with up to 25% of the labor force infected in some countries.<sup>42</sup> As the epidemic progresses, human capital is depleted, agricultural resources may be diverted, and farm and non-farm income can be lost, affecting overall agricultural production—resulting in lack of food and lack of access to food.<sup>43</sup>

Traditionally the victims of famine are largely the young and the elderly. HIV/AIDS alters this picture to include productive adults among those affected by food shortages. The resurgence of TB in conjunction with the HIV/AIDS epidemic in Africa has had a multifaceted impact on the economic and social fabrics of society.

In order to develop strategies to manage TB and HIV better it is important to consider factors that affect vulnerability to infection and progression of disease. Vulnerability is defined as the individual and community factors that lead to variability in the impact of disease including capabilities to anticipate, resist, cope with, and recover from the event or illness.<sup>24</sup> Individual, household and community, and environmental vulnerabilities are summarized in **Box 3**.

For more information on nutrition and HIV, readers are referred to the papers produced by the World Health Organization *Consultation on Nutrition and HIV/AIDS in Africa: Evidence, lessons and recommendations for action*.<sup>45,46</sup>

Since there is some evidence in areas of Africa that TB stigma and other beliefs may delay seeking medical treatment or interfere with completion of treatment<sup>47</sup>, it is important to consider these—especially if the individual has TB/HIV co-infection.<sup>48</sup> Unfortunately, there is little published evidence to document appropriate interventions to address TB and HIV stigma, and additional study is needed to fully understand and address stigma in programs.<sup>4</sup>

### **Disease profile of poverty – Uganda**

Hospital discharge records from 1992 to 2002 were used to describe disease patterns in northern Uganda where the population was debilitated by war, internal conflict, and epidemics. About 70% of the population in the region was internally displaced and living in protected camps. During this time period yearly admissions doubled, with the pediatric ward accounting for most of the increase. Young children (<4 years) and women accounted for 79.5% of all admissions. The admissions due to malnutrition peaked at the height of civil conflict. The largest number of “bed-days” was for patients with active TB (accounting for 20.8% of all bed-days), though there was a sharp decline after initiation of DOTS in 2001. HIV/AIDS and TB were the leading causes of death in persons aged 15-54 years. The authors conclude that long-term war and population displacement—with collapse of social structures and health systems—result in food shortages, social inequities, and humanitarian crises. These increase the risk of HIV, TB, emerging infections, and malnutrition—all contributing to the “disease profile of poverty.”<sup>73</sup>

**Box 3. Vulnerability factors related to progression of disease (Adapted from <sup>24</sup>)**

Individual	Household/community	Environment/institution
Age	Socioeconomic status	Geography/physical terrain
Sex	Migration	Availability of health services
Nutritional status	Access to treatment	Quality of health care
Immunity		Availability of appropriate treatment
Genetics		Emergence of drug resistance
Interactions with other diseases (such as HIV, diabetes)		Development of infrastructure/ other services
Behavior		Public policy
Poverty		
Education		
Knowledge		
Diet		
Livelihood		

**Box 4 compares some of the individual conditions that affect vulnerability for TB and HIV**

**Box 4. Biological and disease-related vulnerability factors (Adapted from <sup>44</sup>)**

Vulnerability factor	Tuberculosis	HIV/AIDS
Age	Affects < 5 yr olds and adults	Primarily affects young adults
Sex	Children: males=females Adults: males>females	Adolescents/young adults: females > males Adults: males = females
Genetic influence	Ethnic traits Vitamin D genes	Chemokine receptors HIV sub-type, clades
Disease vulnerability interactions	Co-infection with HIV increases disease progression	Sexually transmitted diseases increase infectiousness
Nutritional status	May affect incidence, progression, and treatment outcome	May affect incidence, progression, and treatment outcome
Tuberculosis		Increases the rate of HIV disease progression

### III. Malnutrition, immunity, and TB

#### Malnutrition and immunity

Nutritional status is one of the most important determinants of resistance to infection. It is well established that nutritional deficiency is associated with impaired immune functions.<sup>30</sup> While malnutrition limits cell mediated immunity and increases susceptibility to infection, infection can lead to nutritional stress and weight loss, thereby weakening immune function and nutritional status.<sup>50</sup>

Generalized malnutrition manifests itself as low weight-for-height (thinness), and in children it is sometimes measured as low weight-for-age (underweight) or low height-for-age (stunting). These conditions, which often co-exist with micronutrient deficiencies, are often referred to as protein-energy malnutrition (PEM) or simply as clinical malnutrition. Generalized malnutrition can cause significant impairment of several important mechanisms of immune protection, including cell-mediated immunity, phagocytic function, antibody concentration, and cytokine production.

#### Malnutrition and TB

It has long been known that there is an association between TB and malnutrition. Malnutrition enhances the development of active TB, and active TB makes malnutrition worse.<sup>51,52</sup> It has been suggested that generalized malnutrition—by reducing the expression of gamma interferon, tumor necrosis factor alpha, and other mycobactericidal substances—may selectively compromise portions of the cell-mediated response that are important for containing and restricting TB.<sup>30</sup>

Unfortunately, very few studies have been designed to examine the relationship between nutrition and the incidence of TB or its severity. It is very difficult to determine accurately what the nutritional status

of individuals with active TB was *before* the onset of the disease, making it impossible to determine whether malnutrition led to development of active TB or active TB led to malnutrition.<sup>1</sup> Furthermore, randomized trials—the gold-standard in evidenced-based medicine—can be difficult to carry out in food insecure regions due to ethical considerations.

Several studies report that patients with active TB are more likely to be very thin (wasted) or have a lower body mass index ( $BMI = wt(kg)/ht(m^2)$ ) than healthy controls.<sup>51,53,54</sup> World Health Organization classifications for nutritional status based on BMI are shown in **Box 5**. During the wasting process, there is usually a loss of both fat and lean (muscle) tissue, with loss persisting for several months after the initiation of anti-TB therapy.<sup>55</sup>

For example, in a cross-sectional study, Paton and Ng compared the body composition of recently diagnosed and wasted TB patients to individuals without TB. They found that, on average, the body composition difference between groups was almost equally distributed between fat mass and lean body mass (6.4kg, 6.0kg respectively) compartments. Interestingly, they also found that depletion of lean tissue occurred mainly in the limbs, while the reduction of fat mass was mainly found in the trunk.<sup>56</sup>

The wasting commonly found in patients with active TB is most likely the result of a combination of factors, including decreased appetite and food intake, and increased losses and altered metabolism associated with the inflammatory and immune response.<sup>54</sup>

#### Effects of TB on nutritional status

During active TB, catabolic processes that cause wasting usually begin before the patient is diagnosed; therefore more is known about nutritional status at the time

of diagnosis than of the wasting process *per se*.<sup>52</sup> As with HIV infection, at the time of diagnosis the metabolic rate or resting energy expenditure is increased, resulting in increased energy needs to meet the basic demands for body function. At the same time, energy intakes are likely to decline as a result of illness-associated anorexia.<sup>57</sup> This combination of conditions results in weight loss with eventual wasting if energy intakes are not increased or energy expenditures decreased. Utilization of amino acids and protein synthesis may be inhibited due to the presence of pro-inflammatory cytokines.

Several nutritional parameters are worse among newly diagnosed TB patients compared to healthy controls:

- In a study of patients with active TB in the **United Kingdom**, BMI, muscle mass, and subcutaneous fat stores were 13%, 13%, and 20% lower, respectively, in those with TB compared with healthy age-, sex-, and ethnic-matched controls.<sup>58</sup>
- Similarly, in a study conducted in **Malawi**, these same parameters were 20% (BMI), 35% (muscle mass), and 19% (subcutaneous fat) less in subjects with active TB, with a larger decrease in muscle mass than among the United Kingdom patients.<sup>53</sup>
- In **Indonesia**, the mean BMI of patients with active TB recently admitted for treatment was 20% lower than in controls (BMI of  $18.5 \pm 3.2$  vs.  $21.9 \pm 2.8$  in male,  $17.8 \pm 3.1$  vs.  $21.9 \pm 3.5$  in female patients vs. controls respectively,  $p < 0.01$ ). 66% of patients had a BMI  $< 18.5$  (6 times more frequent than in controls). In addition, weight, skin-fold thicknesses, mid-upper arm circumference (MUAC), fat mass, and fat free mass were all significantly lower in those with active TB.<sup>15</sup>

### Box 5. International classification of adult underweight, overweight, and obesity according to BMI

Classification	BMI (kg/m <sup>2</sup> ) Principal cut-off points
Underweight	$< 18.50$
Severe thinness	$< 16.00$
Moderate thinness	16.00–16.99
Mild thinness	17.00–18.49
Normal range	18.50–24.99
Overweight	$\geq 25.00$
Pre-obese	25.00–29.99
Obese	$\geq 30.00$
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	$\geq 40.00$

Source: Adapted from WHO, 1995; WHO, 2000 and WHO, 2004.

- In an **Ethiopian** study of 155 patients with active TB (81 HIV-negative and 74 TB/HIV co-infected) and 31 controls, BMI  $< 18.5$  was common (65.4% of TB patients, 71.6% of TB/HIV co-infected), and severe malnutrition (BMI  $< 16$ ) was more common in those co-infected.<sup>59</sup>
- Wasting is associated with increased mortality in those with active TB. In a study of 1,181 newly diagnosed TB patients in rural **Malawi**, 57% were underweight (BMI  $< 18.5$ ), including 21% with BMI  $< 16$ . A BMI  $< 17.0$ , indicating moderate to severe malnutrition, was associated with a two-fold increased risk of early death.<sup>60</sup> Advanced lung disease was associated with low BMI and fat mass in another **Malawian** study.<sup>51</sup>

### Effect of nutritional status on TB

Cell mediated immunity is the most important defense against TB. An already malnourished individual is more likely to become infected with TB, and latent infec-

tion is more likely to become active TB when the cell mediated immunity response is impaired. In fact, among individuals with latent TB, the occurrence of malnutrition may be an important trigger for active TB development.<sup>1</sup>

Most data on the relationship between the nutritional status and the development of active TB come from studies carried out in the 1950s to 1970s in developed countries. One longitudinal study of participants in a BCG vaccine trial conducted in the **United States** found the incidence of active TB was 2.2 times higher in children with low subcutaneous fat stores (skin-fold thicknesses between 0 and 4mm) compared with those with 10mm subcutaneous fat.<sup>61</sup> In a large study conducted in **Norway**, the incidence of smear-positive and smear-negative TB declined significantly with increasing BMI in all age groups. New TB diagnosis was 5 times higher in the lowest BMI group compared with the highest BMI group.<sup>62</sup>

### Nutritional status changes during TB treatment

Body weight is made up of fat free mass (muscle) and fat mass. Adequate muscle is generally related to physical function. Nutrient partitioning is defined as the relative distribution of weight loss or gain between fat and fat free (muscle/protein) stores. During drug treatment of active TB without supplementary nutrition, nutritional status usually improves. This is most likely for a variety of reasons including improved appetite and food intake, reduced energy/nutrient demands, and improved metabolic efficiency. Most improvements, however, are limited to increases in fat mass.<sup>52</sup>

For example, Schwenk *et al.* investigated the changes in fat mass and protein mass in 40 TB patients in **England** receiving standard TB treatment. The patients reported loss of  $10.1 \pm 6.8\%$  of body weight in the five months before diagnosis. After six months

of treatment, the patients had gained  $9.5 \pm 8.9\%$  body weight, mainly due to gain in fat mass with no significant change in protein mass. The authors suggest that clinical recovery from TB does not guarantee protein mass restoration, even though weight gain is significant.<sup>63</sup> This finding may support the idea that protein metabolism continues to be altered even during treatment, and that clinical and functional recovery from TB lags behind microbial cure. Alternately, diet during treatment may have been inadequate in relationship to increased requirements during treatment and recovery, thereby limiting development of lean body mass.

Although nutritional support during TB treatment is often recommended, there are few published studies on the effectiveness of such support. Three studies are summarized below. However, only the first one was a randomized trial:

- Paton *et al.* conducted a nutritional support study in **Singapore** that randomized 36 patients who recently started anti-TB drug treatment to a high energy-protein supplement (600-900kcal/d, 25-37.5gm protein/d) for six weeks compared with a control TB group not receiving the supplement. All participants were given nutrition counseling to correct imbalances noted in reported dietary intake. Food intake was assessed via recall, and was reported to not differ between groups at baseline. At six weeks, the subjects in the nutrition supplement group had a significant increase in body weight compared with controls ( $2.6 \pm 1.8$  vs.  $0.8 \pm 0.9$ kg,  $p=0.001$ ), and in lean mass ( $1.2 \pm 0.9$  vs.  $0.04 \pm 1.3$ kg,  $p=0.006$ ). Fat mass increased in both groups. In addition, there was a significant increase in grip strength in the supplement group. At 12 weeks, the supplement group had a greater increase in body weight than the control group, but the difference was no longer statistically significant by 24 weeks ( $4.4 \pm 2.7$  vs.  $2.7 \pm 2.5$ ,  $p=0.07$ ).

However, it is important to note that the sample size may have been too small to detect a statistical difference after supplementation ceased and the 1.7kg difference may be of clinical importance. Nearly half of the early weight gain in the supplemented group was lean tissue, suggesting that TB patients are able to build muscle mass during recovery. The authors suggest that accelerating the recovery of lean tissue through nutrition support may help restore physical functioning earlier, shortening the convalescent period and allowing earlier return to productive work. They also suggest that since poor nutrition in TB patients is associated with mortality, a more rapid reversal of malnutrition may help to improve TB patients' survival.<sup>54</sup>

- In an early nutrition study of 30 TB patients in **England** followed for one year after anti-TB treatment, drug treatment was associated with progressive nutritional recovery of BMI, fat stores, and iron status. At 12 months however, MUAC and serum albumin remained low, suggesting that repletion of muscle mass may take longer than 12 months.<sup>58</sup> Alternately, diet during convalescence may have been inadequate to support repletion.
- In a study of 174 smear-positive pulmonary TB patients in **Tanzania** followed for one year, most patients lost weight after discharge from hospital treatment. At 12 months 32% of males and 19% of females considered cured of their TB continued to have a BMI <18.5, indicating malnutrition continued after TB treatment.<sup>64</sup>

### Nutritional status and TB relapse

Nutritional status may have an effect on relapse of active TB. To investigate the relationship between change in weight during anti-TB drug therapy and active disease relapse, Khan *et al.* monitored 857 HIV-negative patients with active TB during, and two years after, their drug treatment.

Relapse risk was increased amongst those who were  $\leq 90\%$  of ideal body weight (19.1% vs. 4.8%,  $p < 0.001$ ; RR 3.99; 95% CI 2.3-6.76,  $p < 0.001$ ) or had a BMI  $\leq 18.5$  (19.5% vs. 5.8%,  $p < 0.001$ ; RR 3.92; 95% CI 2.22-6.91,  $p < 0.001$ ) at the time of diagnosis. Using multivariate logistic regression, in those who were underweight at diagnosis, weight gain of less than 5% between diagnosis and completion of the initiation phase of therapy was significantly associated with relapse (OR 2.4,  $p = 0.03$ ).<sup>65</sup> Additional study is needed to determine whether nutritional support to underweight patients with active disease prevents relapse following anti-TB treatment.

### Serum albumin levels and TB

Many studies have reported low concentrations of serum albumin ( $< 35\text{g/L}$ ), an indicator of protein status, at the time of active TB diagnosis.<sup>66</sup> However, cytokines present during the acute phase response to active infection down-regulate serum albumin levels. Low albumin in patients with active infection is therefore difficult to interpret without another laboratory measure of an acute phase process. Low levels of albumin may reflect the presence of inflammation rather than a protein deficient state.<sup>67</sup> Taking this important limitation into account, studies reporting the correlation between serum albumin levels and active TB are summarized below.

- Researchers in **Ethiopia** reported that serum albumin was significantly lower in TB patients compared to healthy controls ( $29.7 \pm 7.7$  vs.  $42.2 \pm 2.9$ ,  $p < 0.001$ ).<sup>68</sup>
- Likewise in **Malawi**, researchers found that serum albumin was low in newly diagnosed TB patients compared with healthy controls ( $31.4 \pm 8.1$  vs.  $39.9 \pm 6.3$ ,  $p < 0.001$ ). After two months of anti-TB treatment, mean serum albumin increased significantly to the level of the healthy controls at  $39.6 \pm 5.8$ , ( $p < 0.0001$ ).<sup>69</sup>



- In **South Africa**, median serum albumin in newly diagnosed TB patients before isoniazid (INH) treatment was initiated was low (median 30.5 g/L, IQR 27.5-33.5). After seven days of INH treatment, albumin concentrations increased significantly (median 32g/L,  $p < 0.001$ ).<sup>70</sup>

### Malnutrition and TB/HIV co-infection in adults

TB and HIV infections are both independently associated with malnutrition. TB/HIV co-infection poses an additional metabolic, physical, and nutritional burden, resulting in potential further increase in energy expenditure, malabsorption, micronutrient deficiency, and increased production of pro-inflammatory cytokines resulting in breakdown of body lipids and proteins.<sup>71,66</sup> Co-infection may lead to poor appetite with decreased nutrient intake, which may interact with the altered metabolism associated with both infections as part of the immune and inflammatory responses.<sup>72</sup> The combination of TB/HIV co-infection and malnutrition has been termed “triple trouble.”<sup>66</sup> Studies on differences in nutritional status (BMI) among HIV-positive and HIV-negative TB patients are summarized in Annex 1.

To investigate the impact of HIV on nutritional status in patients with active TB, Niyongabo *et al.* compared the nutritional status of HIV-positive and HIV-negative hospitalized TB patients in **Burundi** in a cross-sectional study. Mean anthropometric measures were all significantly less in the TB/HIV co-infected compared with the HIV-negative TB patients (BMI  $15.6 \pm 3.4$  vs.  $18.5 \pm 2.5$  kg/m<sup>2</sup>, arm fat area  $17.9 \pm 2.3$  vs.  $19.7 \pm 3.2$  cm<sup>2</sup>, arm muscle area  $29.3 \pm 8.5$  vs.  $37.5 \pm 10.3$  cm<sup>2</sup> respectively,  $p = 0.01$ ), indicating lower body weight, fat mass, and fat free mass in the HIV co-infected cases. Anthropometric indices tended to underestimate the severity of malnutrition in comparison to bioelectrical impedance measures of body composition. Co-infected patients also had significantly lower mean

serum albumin compared with HIV-negative TB patients ( $18.9 \pm 6.1$  vs.  $28.9 \pm 6.9$  g/L respectively,  $p = 0.01$ ) and lower pre-albumin ( $0.08 \pm 0.05$  vs.  $0.13 \pm 0.06$  g/L respectively,  $p = 0.01$ ). The authors suggest that the TB/HIV co-infected patients may have either more severe malnutrition or increased inflammation, and that these proteins may have a useful prognostic value in HIV-positive TB patients.<sup>71</sup>

- In **Tanzania**, Villamor *et al.* conducted a large cross-sectional study to evaluate the role of HIV in wasting among 2,231 patients with active TB, and to identify correlates of wasting including socioeconomic factors. MUAC and arm muscle area were significantly lower in TB/HIV co-infected patients compared to HIV-negative TB patients, but there was no difference between groups in BMI.<sup>67</sup> Mean serum albumin concentrations were significantly lower in the TB/HIV co-infected patients ( $28.0 \pm 10$  in co-infected vs.  $32.0 \pm 11$  in active TB only patients;  $p = 0.004$ ). Interestingly, the Tanzanian TB/HIV co-infected patients had higher BMI than the Burundi patients described above. The mean BMI of the TB/HIV co-infected men in the Tanzanian study ( $19.0 \pm 2.4$  in HIV-positive vs.  $18.9 \pm 2.2$  in HIV-negative) was about 21% higher than in the Burundi study. Additionally, wasting was positively associated with the severity of TB, while BMI, MUAC, and arm skin-fold thicknesses were positively associated with socioeconomic status and Karnofsky score (a higher score indicating increased physical functioning) and negatively associated with bacillary density.<sup>67</sup>
- In another study carried out in **Tanzania**, Venkatesh *et al.* examined predictors of incident active TB in 1,078 HIV-positive women attending antenatal clinics and found that 8.7% developed active TB during the follow-up period. Baseline

CD4+ counts were lower and plasma viral load higher in those who developed TB. Women with CD4+ counts <200cells/mm<sup>3</sup> were at the greatest risk of developing TB, as were those with baseline MUAC <22cm. Death rates were higher in HIV co-infected women (63% in TB/HIV co-infected vs. 23% in HIV-positive only).<sup>73</sup>

- To understand protein metabolism better in TB/HIV co-infected patients, Paton *et al.* conducted a small metabolic study in **Singapore** of ten patients with HIV alone, ten patients with active TB alone, eight TB/HIV co-infected patients, and compared them with 11 healthy controls. They found that patients with only TB had lower BMI than patients with only HIV and the healthy controls. In both TB groups, wasting was characterized by overall loss of body fat and lean tissue in arms and legs, and there was evidence of ongoing inflammation based on elevated erythrocyte sedimentation rate and C-reactive protein concentrations. Protein change and degradation was lower in the HIV alone group.
- The rates of protein change, synthesis, and degradation were not different between the TB alone and the healthy control group, but in the TB/HIV co-infected group the net protein balance was close to zero and lower than the other groups, perhaps due to the metabolic disturbances associated with a secondary infection and more advanced disease. The authors conclude that their findings support the case for providing additional nutrition for TB/HIV co-infected patients during treatment.<sup>72</sup>

### Malnutrition and TB/HIV co-infection in children

Several studies have documented an increased risk of malnutrition among TB/HIV co-infected children. No studies of the impact of nutritional support among TB/HIV co-infected children were identified.

- In a study of **Ethiopian** children, 60% of the co-infected children aged one month to 14 years had weight-for-age (WFA) z-scores <-2.00 (i.e., z-scores were more two standard deviations below the reference median), compared with 46% of the HIV-negative and 19% of healthy children.<sup>2</sup>
- In a study of **South African** children co-infected with HIV at TB diagnosis, 25% had WFA z-scores <-3.00 and 47% had WFA z-scores <-2.00.<sup>41</sup>
- Another **South African** study of 250 children <15 years old with active TB reported that underweight (WFA z-score <-2.00) was more common in those co-infected with HIV (77%) compared to those with TB alone (56%) (OR 2.62; 95% CI 1.08-6.43). TB/HIV co-infected children were also more likely to have severe malnutrition (OR 2.57; 95% CI 1.02-6.50). The nutritional status of all children improved during hospitalization, but WFA remained lowest in the TB/HIV co-infected children. At discharge from the hospital, 47% of the co-infected remained underweight (WFA z-score <-2.00).<sup>40</sup>

## Generalized malnutrition, immunity, and TB summary

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- The above studies highlight the complex relationships between generalized malnutrition and active TB but few studies have been carried out to assess the direct benefits of providing nutritional support to malnourished TB patients.
- Randomized trials are difficult to carry out due to ethical considerations.
- Although the evidence is limited, available data suggest that malnutrition affects cell-mediated immunity, which is critical for controlling TB infection, and may increase the risk of active TB disease development by six to ten times.<sup>1</sup>
- Targeting nutritional support to malnourished populations at high risk for TB could potentially reduce the incidence of active TB in these groups, although this has not been directly proven.
- It is important to note that mild-to-moderate malnutrition typically affects larger segments of the population than severe malnutrition, so prevention efforts most likely will not be successful if they only target the severely undernourished.
- TB treatment improves nutritional status but treatment alone is probably not sufficient to achieve adequate nutrition among patients living in food insecure areas.
- Active TB affects protein metabolism and nutritional status through multiple mechanisms and, examined together, the evidence suggests that adequate nutritional intake during TB care and recovery will be needed to fully restore nutritional status during and following TB treatment and microbial cure.
- Adults and children co-infected with HIV and TB are at greatest risk of malnutrition, poor treatment outcomes, and death.
- Efforts to prevent, manage, and treat TB and HIV have been largely separate endeavors, despite the overlapping epidemiology. Although progress is being made, improved collaboration between TB and HIV/AIDS programs is necessary to control TB more effectively among HIV-positive people and to make significant public health gains.

## IV. Micronutrients and TB

Although generalized malnutrition, as reviewed above, has been commonly described in those with active TB, less is known about micronutrient status and the TB disease process.<sup>66</sup> Vitamins A, C, E, B<sub>6</sub> and folic acid and minerals zinc, copper, selenium, and iron all have key roles in metabolic pathways, cellular function, and immune competence.<sup>74</sup> The concentration of these may have a role in host defense against TB.<sup>15</sup> Deficiency of single or multiple nutrients can reduce an individual's resistance to any infection.<sup>50,74-76</sup> In the era before drug management of active TB, administering cod liver oil (rich in vitamins A and D) was a common therapy to improve host defense.<sup>66</sup>

### Vitamin A and antioxidants

Reduced micronutrient intake, and especially intake of vitamin A and antioxidant vitamins and minerals such as pro-vitamin A carotenoids, vitamins E and C, zinc, and selenium, has been associated with an impaired immune response.<sup>50</sup> Antioxidants neutralize free radicals by sacrificing one of their own electrons. (Free radicals are unbound electrons that react quickly in an effort to capture another unbound electron and thus gain stability.) TB may induce oxidative substances such as reactive oxygen species (ROS) derived from free radicals, which in turn can promote tissue injury and inflammation. ROS are highly toxic to all types of cells, but especially to lipids (fat cells) causing peroxidation, resulting in damage to cell membranes, and are also associated with the pathogenesis of lung fibrosis and dysfunction in pulmonary TB.<sup>68,77</sup> Antioxidants scavenge free radicals and suppress the actions of ROS, protecting the host from tissue inflammation.

Vitamin A, which is usually assessed using serum retinol, also plays important roles in lymphocyte proliferation, generation of

antibody responses, and maintenance of mucosal surfaces and epithelial function.<sup>50</sup> Vitamin E protects cell membranes against lipid peroxidation and oxidative stress by scavenging free radicals and by stabilizing cell membranes. In animals, vitamin E is mobilized from tissues and diverted to the lungs during oxidative stress.<sup>77</sup> Zinc is essential for DNA synthesis and cell differentiation. Zinc deficiency is associated with recurrent infections, decreased phagocytosis, decreased B and T lymphocyte production,<sup>78</sup> and depressed macrophage activity.<sup>79</sup> Selenium is an essential part of antioxidative enzymes, such as glutathione peroxidase, which protects cells from oxidative damage.<sup>59</sup>

It must be noted that blood micronutrient status is difficult to assess in the presence of infection because biochemical indicators of several micronutrients are affected by the immune system's acute phase response. Serum ferritin (a measure of iron status) and copper are "positive" acute phase reactants that increase when the immune system responds to an infection, while albumin, retinol, and zinc are "negative" reactants. Thus, results of some studies on the relationship between micronutrient status and TB infection may be confounded by increased rates of acute phase response.

In people with infections, measurement of "positive" acute phase reactants, such as serum ferritin and copper, may underestimate nutrient deficiency, while measurement of negative responders, such as serum albumin, retinol, and zinc, may lead to an overestimation of underlying deficiencies. To give a specific example, during the acute phase response to infection, retinol is excreted in the urine and the liver's production of retinol-binding protein required to mobilize vitamin A from tissue stores is also reduced, resulting in low serum retinol levels. These levels may lead some reserches

to conclude that there is vitamin A deficiency when in fact the low serum value is primarily an indicator of the presence or severity of disease. Thus, researchers should also collect markers of the acute phase response—although they frequently do not.

### Studies of micronutrient status and TB

As expected, there is evidence that at the time of diagnosis active TB patients have lower blood concentrations of several micronutrients including retinol, vitamins C and E, hemoglobin, zinc, iron, and selenium compared with healthy controls. Studies on the relationship between micronutrient status and TB are summarized in **Annex 2**.

- The micronutrient status of 41 adult **Indonesian** patients with active pulmonary TB prior to anti-TB treatment was compared with an equal number of healthy matched controls. The mean plasma retinol, hemoglobin, and zinc concentrations were significantly lower in the TB patients. More TB patients were classified as having marginal or deficient micronutrient status (33% TB patients with retinol  $<0.70\mu\text{mol/L}$  vs. 13% controls,  $p<0.05$ ; 58% TB patients with hemoglobin  $<12\text{g/L}$  compared with 22% controls,  $p<0.05$ ; 21.1% TB patients with zinc  $<10.7\mu\text{mol/L}$  vs. 5.1% of controls,  $p<0.01$ ). More than half of all subjects had tocopherol (vitamin E) concentrations below normal ( $11.5\mu\text{mol/L}$ ), but it was not different by group.<sup>15</sup> No markers of an acute phase response were used in the analysis.
- In a study of circulating antioxidants and a marker of oxidative stress, 125 **Ethiopian** patients with active TB (before starting drug treatment) were compared with **Norwegian** and Ethiopian healthy controls. Karnofsky score, a simple scale used to categorize physical ability, was also measured. The TB patients had significantly lower

serum concentrations of vitamins C and E compared with controls, while malondialdehyde concentration, a measure of lipid peroxidation and oxidative stress, was significantly higher in the TB patients.<sup>68</sup> A higher malondialdehyde concentration was also associated with poor Karnofsky physical performance scores, indicating increased clinical severity.<sup>68</sup> These results indicate that the TB patients had higher oxidative stress and lipid peroxidation but low antioxidant capacity.

- In another study of lipid peroxidation and antioxidants, 30 newly diagnosed and untreated pulmonary TB patients from **India** were compared with healthy matched controls. Thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation, was significantly increased in the TB patients compared with controls, while the plasma levels of vitamins C and E were significantly decreased.<sup>77</sup>

### Vitamin A

As anticipated, because of the acute phase response, serum retinol levels are generally lower in patients with active TB, particularly those who are TB/HIV co-infected, and tend to improve with anti-TB therapy.

- In a study of vitamin A deficiency in **Tanzania**, serum measurements were obtained from patients with pulmonary TB upon admission to the hospital and after two months of TB treatment and compared with blood donor controls. At baseline, mean serum vitamin A was significantly lower in the TB patients than in controls, with TB/HIV co-infected patients having the lowest concentrations ( $13.1 \pm 5.6\mu\text{g/dl}$  in the co-infected vs.  $26.6 \pm 5.4\mu\text{g/dl}$  in the controls). Almost 90% of TB patients were classified as vitamin A deficient ( $<20\mu\text{g/dl}$ ), with a higher proportion of the TB/HIV co-infected considered

vitamin A deficient compared with controls (43% vs. 26% respectively,  $p < 0.001$ ). After two months of TB treatment, mean vitamin A status improved in the HIV-negative TB patients with fewer classified as vitamin A deficient, but was slightly worse in the co-infected patients with a larger proportion deficient. HIV infection was the strongest predictor of low vitamin A at baseline and at two months.<sup>69</sup>

- The vitamin A status of newly diagnosed pulmonary TB patients in **India** was compared with a similar number of close family contacts without illness and healthy normal controls. At the start of TB treatment, 81% of the patients were considered low in vitamin A (in this study defined as a retinol concentration  $< 30 \mu\text{g}/\text{dl}$ ) compared with 24% of household contacts and 7% of controls. The TB patients' mean vitamin A ( $21.2 \mu\text{g}/\text{dl}$ ) was significantly lower than household contacts or healthy controls ( $42.2$  and  $48.1 \mu\text{g}/\text{dl}$ ,  $p < 0.001$ ). After six months of anti-TB treatment, 93% of TB patients had improved serum vitamin A concentrations, but 32% remained abnormally low. The authors note that after six months of treatment, the mean serum vitamin A concentration of the TB patients was similar to the household contacts and normal control group, presumably due to control of the acute response to infection rather than because of improved vitamin A status.<sup>80</sup>

### **Ascorbic acid (vitamin C)**

In the first half of the twentieth century, before drug treatment for active TB was available, low vitamin C intake and lower plasma vitamin C concentrations were associated with increased TB incidence.<sup>81</sup> Vitamin C, together with vitamin E and glutathione, are important for pulmonary antioxidant defense.<sup>82</sup> Since the lung is exposed to many oxidizing chemicals during normal breathing, an inadequate concentration of

vitamin C in the lung and blood can lead to an imbalance between antioxidants and oxidants. In spite of this long-established relationship, there are few studies on vitamin C status and active TB risk and outcomes. No studies in HIV/TB co-infected patients were identified.

- Researchers in **Russia** studied 159 patients with pulmonary TB who smoked cigarettes and 20 smokers without TB to measure metabolic changes in vitamin C and its metabolites. The levels of serum ascorbic acid in the TB patients were significantly lower than in the controls. The authors suggest that the presence of TB lung inflammation leads to decreases in serum ascorbic acid levels and that the reduced metabolites indicate a slowing metabolism of ascorbic acid in this population. The authors raise the possibility that use of supplemental vitamin C in cigarette-smoking TB patients may not be helpful, as it is poorly utilized, and that dehydroascorbic acid, another form of vitamin C, as a supplement may need to be considered.<sup>82</sup>
- Researchers in **Finland** studied whether an intake of vitamin C and foods high in vitamin C were related to the incidence of active TB among smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. Median dietary intakes were 90 mg/d vitamin C, and 183 g/d of fruits, vegetables, and berries. There were 167 incident cases of active TB between 1985 and 1993. Higher vitamin C intakes were not associated with reduced risk of active TB when consumption of fruits, vegetables, and berries was fixed, suggesting that compounds in these foods other than vitamin C affect susceptibility to active TB. In fact, increased intakes of fruits, vegetables, and berries low in vitamin C content were associated with a reduced risk of TB.<sup>81</sup>

### Pyridoxine (vitamin B<sub>6</sub>)

Shortly after isoniazid (INH) treatment for active TB was introduced in 1952, it was noted that patients treated with the drug developed peripheral neuropathy (symptoms include numbness, pain, and burning sensation in the feet), a wide-ranging condition referring to disorders of peripheral nerves that branch out from the spinal cord to all parts of the body. Pyridoxal phosphate (PLP) is a co-enzyme required for the synthesis of neurotransmitters. INH inhibits the phosphorylation of pyridoxine, which results in increased excretion of vitamin B<sub>6</sub>.<sup>70</sup> Therefore, current treatment guidelines recommend that patients on INH with burning feet symptoms take supplemental pyridoxine.<sup>12</sup> It should be noted that INH is just one of the medications that may be used in TB treatment. INH prophylaxis is given if an individual has been recently infected with TB and the risk for progression to active disease is high (for example, in young children and in HIV-positive individuals).

- Visser *et al.* measured PLP in newly diagnosed active TB patients before and one week after initiation of INH therapy in Cape Town, **South Africa**. At study entry, only two out of 29 had normal plasma PLP (>24.3nmol/L) and all but one patient had a significant further reduction of PLP concentration one week after initiation of INH therapy. The authors conclude that most patients with newly diagnosed pulmonary TB have suboptimal levels of plasma PLP when they are diagnosed, which worsens with INH treatment, and that routine pyridoxine supplementation is warranted.<sup>70</sup>

Vitamin B<sub>6</sub> status in TB/HIV co-infected patients has not yet been described.

### Vitamin D

Susceptibility to TB and severity of active TB may be increased by vitamin D deficiency.<sup>83,84</sup> Humans have two main means to obtain vitamin D. Vitamin D

can be consumed as cholecalciferol (or D<sub>3</sub>) in fish, meat, and vitamin D fortified foods, and it can be formed via exposure to sunlight, which converts a form of cholesterol into pre-vitamin D, which is then activated by the liver and kidney.<sup>84</sup>

The role of vitamin D in resistance to active TB has been known for more than 100 years, as vitamin D-rich cod liver oil and exposure to sunlight were once part of regular therapy for TB.<sup>19</sup> Vitamin D is required for macrophage activation, which is essential for keeping TB in the latent phase. In addition, vitamin D down-regulates the transcription of a substance that is needed for the intracellular survival of TB bacillus in macrophages, further containing the bacilli.<sup>84,85</sup> Vitamin D deficiency allows the disease to progress to the active form.

- More recently, the role of vitamin D in the TB disease process re-emerged with the increased incidence of active TB in the winter months among individuals from the **Indian** subcontinent after moving to the **United Kingdom**. It was hypothesized that immigrants from tropical countries, where latent TB is common, had a marked decrease in their serum vitamin D levels when they lived in cold and cloudy England, with considerably less opportunity for exposure to sunshine.<sup>19</sup> Poverty is not considered to be a factor as these immigrant communities are generally prosperous.<sup>14</sup> To test this hypothesis among immigrants in London, the plasma vitamin D<sub>3</sub> levels of 210 patients diagnosed with active TB were regularly measured. Of all subjects, 76% were deficient in vitamin D (<22 nmol/L) and 56% had undetectable concentrations.<sup>85</sup>
- Another study conducted among Gujarati **Indians** living in London, **England**, found a high prevalence of vitamin D<sub>3</sub> deficiency, with the lowest concentrations found in those with active TB. The odds ratio of active TB increased with decreasing vitamin D<sub>3</sub>

concentrations (OR 2.9; 95% CI 1.3-6.5 in those with vitamin D<sub>3</sub> <10 nmol/L; OR 9.9; 95% CI 1.3-76.2 in those with vitamin D<sub>3</sub> undetectable, p<0.01).<sup>14</sup> The authors conclude that low dietary intake of vitamin D combined with lack of exposure to sunshine are the main factors in vitamin D deficiency that contribute to the acquired susceptibility to active TB in this population.<sup>14</sup>

The combination of a specific genotype with vitamin D deficiency is suggested to strongly predispose a person with latent TB to active disease.<sup>19</sup> Resistance to infection may be determined genetically through the ability of vitamin D to activate macrophages to consume and destroy the TB bacilli. Effects of vitamin D are mainly determined through a vitamin D receptor, which has common polymorphisms (minute variations of a trait that occur in human DNA) that influence vitamin D receptor activity. These polymorphisms are potentially the means of genetic susceptibility to active TB.<sup>86</sup>

- In a **Peruvian** study of pulmonary TB patients living in a community with high TB incidence, certain vitamin D receptor polymorphisms were associated with significantly faster resolution of pulmonary TB with DOTS strategy treatment, while another polymorphism was associated with a more aggressive disease process and a slower response to treatment. The authors also note that rifampin and isoniazid treatments may alter vitamin D metabolism and influence the polymorphisms during treatment as well. They suggest that vitamin D supplementation may be beneficial and that further study on this is warranted.<sup>85</sup>

Vitamin D status in HIV/TB co-infected patients has not yet been described.

### **Trace elements**

Trace element blood concentrations in persons with active TB are not well documented.

- A study was conducted examining serum concentrations of zinc, iron, copper, and selenium in 155 patients with active TB in **Ethiopia** before and after anti-TB drug treatment, compared with 31 healthy control subjects. At baseline before drug treatment, mean serum zinc, iron, and selenium in TB patients were lower than in controls, and a higher proportion was considered to be deficient (zinc deficient 47.1% in TB patients vs. 25.8% in controls, iron deficient 14.8% in TB patients vs. 3.2% in controls, selenium deficient 35.5% in TB patients vs. 22.6% in controls). After two months of anti-TB drug treatment, the mean zinc concentration increased significantly in TB patients ( $87.3 \pm 26.8$  before vs.  $118.3 \pm 59.6$  µg/dl after treatment, p<0.05), but not in HIV-co-infected subjects, nor for the other trace elements measured. The low serum zinc at baseline was probably due to redistribution of zinc from serum to other tissues or an alteration in transport proteins, both associated with an acute phase response.<sup>59</sup> Since serum concentrations of iron, zinc, and copper are altered with infection and an acute phase response, a limitation of this study is that the presence of an acute phase process was not measured.

### **Iron and anemia**

Anemia is common in patients with pulmonary TB, and appears to be more common among TB/HIV co-infected patients. Proposed reasons for this include increased blood loss from hemoptysis (blood in sputum for TB patients), bone marrow involvement (decreased red blood cell production), inadequate intake (poor appetite and food intake) resulting in poor micronutrient status, and anemia of chronic inflammation (decreased circulating iron with increased storage iron, making iron less available to microbes).<sup>87, 88</sup>



- In a study of micronutrient status and anemia conducted in **Malawi** among 500 newly diagnosed pulmonary TB patients (including 370 co-infected with HIV), the prevalence of anemia was high and more common in those HIV co-infected (76.9% in TB patients and 88.4% in co-infected patients,  $p=0.002$ ). Micronutrient deficiencies were common in all patients, with 59% deficient in vitamin A, 12% deficient in vitamin E, 80% deficient in zinc, and 88% deficient in selenium. Decreased concentrations of retinol, carotenoids, and selenium were associated with increasing degree of anemia. The authors suggest that selenium deficiency may contribute to anemia via increased oxidative stress.<sup>87</sup>

In contrast, iron overload occurs in approximately 10% of some rural African populations and is attributed to high dietary iron intake from consumption of traditional fermented beverages. Iron loading may enhance the growth of *Mycobacterium tuberculosis* by impairing macrophage suppression of invading microorganisms.

- In a study of 98 pulmonary TB patients and 98 control subjects in **Zimbabwe**, estimates were made of lifetime traditional beer consumption. Increased dietary iron was defined as an estimated lifetime consumption of >1000L of traditional beer. Iron indices were measured until nine months after the start of anti-TB drug therapy. At the beginning of therapy, the mean hemoglobin ( $9.4 \pm 2.1$  in TB,  $14.3 \pm 1.7$  in controls,  $p < 0.001$ ) was lower and the mean ferritin and transferrin saturation were higher in the TB patients. Overall with time, serum ferritin levels decreased significantly and hemoglobin concentrations increased significantly. Among the HIV-negative subjects, 20.2% of those without increased dietary iron had TB, while 44.8% of those with increased dietary iron had TB. Among the HIV-

positive subjects, 84.1% of those without increased dietary iron had TB while 71.4% of those with increased dietary iron had TB. After adjusting for age, HIV status, and liver function, increased dietary iron was associated with a 3.5 fold increased risk of developing TB and a 1.3 fold increase in risk of mortality. The authors conclude that elevated dietary iron may increase the risk of activating TB disease.<sup>89</sup> Other confounding variables, such as regular alcohol consumption, also need to be considered.

### Effect of micronutrient supplementation on TB outcomes

Data on the impact of micronutrient supplementation on TB outcomes are currently limited. Three randomized trials were found in the literature and warrant special attention due to the strength of their design:

- **Vitamin A and Zinc:** To investigate the effect of vitamin A and zinc supplementation on anti-TB treatment, Karyadi *et al.* conducted a double-blind placebo-controlled trial among newly diagnosed pulmonary TB patients in **Indonesia**. Subjects received either 1500 retinol equivalents (5000 IU) of vitamin A with 15mg zinc or placebo daily for six months. After two and six months, both groups had significant increases in hemoglobin and plasma retinol, but the increase in retinol was greater in the supplemented group. The proportions of patients with anemia or low plasma zinc or retinol were not different between groups. In both groups there was a significant increase in serum albumin and body weight, but the differences between groups were not significant. At two weeks and up until seven weeks, the number of patients with negative sputum smears in the micronutrient group was higher than the placebo group, as was the mean reduction in lesion area on the chest

x-ray. At six months, the Karnofsky score of well-being was higher in the micronutrient-supplemented group. The authors concluded that the supplementation improved the effectiveness of the anti-TB treatment in the first two months of therapy, with less improvement seen between two and six months of treatment. The major benefit is at the community level because the patient would become less infectious sooner, with less opportunity to infect others.<sup>16</sup>

- **Iron:** To investigate whether iron supplementation has a deleterious effect during active TB infection,<sup>90,91</sup> Devi *et al.* conducted a prospective double-blind study of the effect of iron therapy on moderately anemic (hemoglobin concentration 80-110g/L) adult male pulmonary TB patients in **India**. Patients were assigned to one of three groups for daily supplementation and followed for six months of TB treatment: (1) placebo, (2) 75mg elemental iron as ferrous fumarate, or (3) the same iron dose with added 25mg zinc, 2.5mg thiamine, 1.5mg riboflavin, 0.75 mg pyridoxine, 1.25mg cyanocobalamin, 20mg ascorbic acid, and 0.25mg folic acid. Significant increases in BMI, iron status, and other hematological indices occurred in all three groups. The highest increase in hemoglobin and iron status occurred at one and two months in both supplemented groups compared with the placebo group. This improved difference disappeared after six months of treatment, however. Radiological and clinical improvement was similar between groups. The authors concluded that in mild to moderately anemic TB patients, iron supplementation accelerated the normal hematopoiesis only in the initial phases of treatment, possibly because inflammation contributed towards anemia, and further improvement was dependent on the correction

of the inflammatory process. It should be noted that during the first two months of anti-TB treatment and supplementation, patients consumed a well balanced diet while hospitalized, with no information on the diet quality after return to home. Therefore the contribution of dietary intake to short- and long-term results could not be assessed.<sup>88</sup>

- **Multiple micronutrients:** A randomized double-blind placebo-controlled trial was conducted among 530 patients newly diagnosed with pulmonary TB in **Tanzania** to determine if micronutrient supplementation reduced conversion time from sputum-positive to sputum-negative TB test results.<sup>92</sup> The patients were randomized to receive daily supplements of either: (1) placebo, (2) 45mg elemental zinc alone, (3) the same amount of zinc with multiple high doses of other micronutrients (5,000 IU vitamin A, 20mg each vitamin B<sub>1</sub>, and B<sub>2</sub>, 25mg vitamin B<sub>6</sub>, 50ug vitamin B<sub>12</sub>, 0.8mg folic acid, 40mg niacin, 200mg vitamin C, 60mg vitamin E, 200 IU vitamin D<sub>3</sub>, 0.2mg selenium, 5mg copper), or (4) the same micronutrients without zinc. Sputum cultures were obtained at two, four, and eight weeks of standard TB DOTS strategy therapy. The researchers did not find significant effects of micronutrient or zinc supplementation on their primary outcome, culture conversion, at any time point, although they report that patients receiving the zinc and multi-micronutrient supplements had a 2.4kg higher weight gain than those receiving placebo, multi-micronutrients, or zinc alone (95% CI 0.9, 3.8, p=0.002). The average weight gain overall was 6.88kg.<sup>92</sup> The group receiving zinc and multi-micronutrients also had reduced mortality (RR 0.29; 95% CI 0.10, 0.80). Interestingly, among the HIV-co-infected group, zinc or micronutrients alone or together were associated

with a 50-70% reduced risk of death, although this was not statistically significant. The main limitation of the study was that supplement compliance was not ascertained. The authors conclude that high dose supplementation of multiple

micronutrients may increase survival of HIV/TB co-infected patients during TB treatment, but that more research is needed in different settings among those with TB alone, and with differing nutrient doses depending on the location.

### Micronutrients and TB Summary

- The relationship between micronutrients and TB is complex.
- Active TB increases oxidative stress, creating higher demands for anti-oxidant nutrients.
- Depressed circulating levels of negative acute phase response nutrients may lead to overestimation of the role of micronutrients in TB disease.
- Limited studies suggest that for those with micronutrient deficiencies, daily micronutrient supplementation may have an added benefit during early months of anti-TB therapy—to improve nutritional status, improve clinical treatment, and reduce mortality.
- For TB as with other infections, intake of iron beyond correcting iron deficiency may have deleterious effects and should be avoided.
- Pyridoxine supplementation (vitamin B<sub>6</sub>) should be provided with INH therapy in areas where diets are low in this vitamin.
- Supplementation with vitamin D may also be necessary where sunlight and diets are insufficient, although further research on the impact of vitamin D supplementation during TB treatment is needed.
- Additional research is warranted on the impact of multiple-micronutrient supplements on TB-associated outcomes in settings where local, predominantly cereal-based diets are unlikely to provide adequate micronutrient content (due to low bioavailability and high fiber content).

## V. Experience and considerations for incorporating nutrition into TB programs

Accessing and successfully completing TB treatment is complex. It involves diagnosis of illness and treatment over an extended period of time (usually 6-8 months) in individuals who are often poor, food insecure and face barriers to accessing health care. A common cause of TB treatment failure is poor adherence to the lengthy treatment, resulting in TB drug resistance. Multi-drug resistant TB is a serious challenge and growing concern in Africa. Social support is helpful in successful adherence.<sup>93</sup> Ideally, a TB control program will include a set of policies to educate, to motivate, and to watch patients.<sup>94</sup>

Our review found that programmatic evidence of nutritional support for TB patients is too limited to make firm recommendations for specific programs. However there is reason to believe that nutritional support could be beneficial to disease management. Taking this reality into account and based on the evidence review, nutritional support within TB programs may include the following components:

- Nutritional assessment to determine nutritional status and necessary referrals or intervention
- Nutrition education and counseling on symptom-management and improved dietary intake during and after TB treatment and microbial cure
- Targeted micronutrient supplementation (e.g., vitamin B<sub>6</sub>)
- Food support for treatment of malnutrition in TB and TB/HIV co-infected patients
- Food support as a safety net program to increase treatment adherence

There is little documentation to date on the role of nutritional support within TB programs and thus it is uncertain whether any of these components are actually being implemented on the ground. Most of the experience has been with the provision of food support to TB patients, and these lessons are summarized below.

### Experience providing food assistance to TB patients

Several TB control programs have provided food to TB patients and health care providers as a means to improve performance of each.<sup>95</sup> Food assistance is a potentially influential, targeted means for increasing adherence to TB treatment, reducing the costs to patients of staying in treatment, and improving nutritional status. Food assistance may influence early case detection (encouraging patients to come for diagnosis and treatment sooner in the disease process), and promote the full course of treatment. Both of these are important to decrease TB transmission.<sup>95</sup> The economic costs to those in TB treatment programs include loss of employment, income and productivity, increased travel cost to reach the treatment centers, and other health-related costs.<sup>93</sup> Interventions that increase full treatment adherence are important not only for the patient, but for public health welfare.

### World Food Programme

The World Food Programme (WFP), the food aid arm of the United Nations, has drafted a report summarizing food assistance in the context of TB care. One goal of the WFP is to improve nutrition, quality of life, and self-help of individuals and communities. Their food assistance programs aim to enhance patient adherence to treatment under DOTS (resulting in improved detection and cure rates), while helping patients in food insecure households meet their nutrient needs during treatment. Food assistance increases health care center attendance thereby increasing case detection.<sup>93</sup> Feedback from WFP country offices indicates that food assistance motivates TB patients to remain on and complete treatment, improves their nutritional status, and encourages TB patients to participate in other health programs such as HIV/AIDS testing. Additional lessons are summarized in **Box 6**.

**Box 6. Experience from three WFP food-assisted TB programs<sup>93</sup>**

	<b>Lesotho</b>	<b>Sudan</b>	<b>Burkina Faso</b>
<b>Setting</b>	Low TB treatment completion rate and high HIV prevalence	Conflict setting	Low TB detection rate and moderate HIV prevalence rate
<b>Partners</b>	Lesotho Ministry of Health and Social Welfare	National TB Program TB Control Initiative “Horn of Africa”	National TB Program Global Fund to fight HIV/AIDS, TB, and Malaria
<b>Eligibility criteria</b>	Food insecurity Positive TB test (sputum or chest x-ray) Enrollment in DOTS strategy TB treatment program	Vulnerability, Conflict in the area	None
<b>Local assessment</b>	HIV is fueling TB epidemic, Male to female TB cases: 2:1	Displaced people with poor hygiene and malnutrition. Most patients with TB are food insecure and with poor nutritional status.	Objective of food support is to increase attendance at testing and treatment centers, reduce default rate.
<b>Ration type</b>	Outpatient, monthly, distributed through health centers Family and patient portions	Patient portions only	Food provided to all TB patients and volunteers managing food distribution in health centers. Patient ration provided monthly.
<b>Ration content</b>	Family: 400g maize meal, 60g pulses, 20g oil per person per day Patient: 200g corn soya blend (CSB) per day	Patient: 50g CSB, 450g cereals, 50g pulses, 30g oil, 10g salt, 25g sugar per day (2,226 kcal/day)	Patient: 1.5kg CSB, 12kg cereals, 1.8kg pulses, 0.75kg oil, 0.15kg salt, 0.6kg sugar per person per month
<b>Reach</b>	2,529 patients/month and 18,953 indirect beneficiaries/month	13,452 patients from January–August 2005	5,875 estimated beneficiaries for 2006
<b>Patient comments</b>	CSB helped them to gain weight quickly. Food assistance increased adherence to treatment.	Improved well being. Food assistance increased adherence to treatment.	Observation of increased attendance at health centers and decrease in number of defaulters.
<b>Problems encountered</b>	Health workers: hard to give away food but not receive incentive themselves. Difficult to integrate TB into HIV/AIDS treatment program. Difficulty with timely coordination between medication and food distribution.	Health workers: hard to target beneficiaries since patients tend to deny illness and avoid treatment due to fear and stigma.	Assessment not yet carried out.

### Cost of providing food support

Food supplementation may be considered an intervention targeted at overcoming barriers associated with continuing TB treatment and also one that ensures that health services are tailored to the patient's needs. If a significant number of persons do not complete treatment, then the health care system may be considered to have failed.<sup>94</sup>

Data on the estimated numbers of patients with active TB that would benefit from nutritional support and the cost-effectiveness of food support for TB patients are as yet unavailable. WFP estimated that 3.8 million people affected by HIV were in need of nutritional support in 2006, and that nearly double that number will be in need by the year 2008. An estimated nine million Africans are co-infected with HIV and TB. These individuals are the most nutritionally vulnerable and many are likely to be in need of nutritional support. WFP and UNAIDS estimate that approximately \$0.66 daily is required to support an AIDS patient and his/her family, and most likely the cost would be the same for a patient with TB. Depending on the length of nutritional support during medical treatment, the theoretical cost of food support per patient would vary from approximately \$40 for two months to \$119 for six months. The estimated medical costs to treat a person with active TB successfully vary considerably from country to country, from \$140 in Uganda to more than \$350 per patient in Mozambique and Nigeria. Therefore, the cost of food support during treatment would require considerable additional resources.<sup>10</sup>

### Stop TB/World Bank

A group from Stop TB/World Bank and Management Sciences for Health/Rational Pharmaceutical Management Plus/USAID completed a case study to examine the food assistance program in **Cambodia**, an area with high burdens of both TB and malnutrition. Although the direct impact of food assistance on TB case detection or treat-

ment success within the DOTS strategy program could not be determined, overall both patients and providers believed that the program benefits offset the costs of treatment, motivated patients to seek treatment earlier, improved adherence to treatment and nutritional status, and reduced stress. Cured patients and their family members communicated the benefits of the program and promoted TB treatment within their communities. Patients reported that the monthly food ration lasted for two to nine days, depending on the household size and income. The group concluded that integrating the food program into the DOTS strategy TB treatment program fits well within the Millennium Development Goals of poverty reduction, while promoting collaboration and demonstrating sustainability and impact.<sup>95</sup>

### C-SAFE

The Consortium for the Southern Africa Food Security Emergency (C-SAFE) provides food assistance to patients with HIV/AIDS, including those co-infected with TB. They conducted a literature review on the impact of targeted food assistance in people living with HIV/AIDS and field research in **Malawi, Zambia, and Zimbabwe**, but concluded that it is quite difficult to measure the impact of food aid within these programs due to very limited documentation. The most commonly reported measure of success across programs was increased treatment uptake and adherence. Based on anecdotal stories and testimonials, the authors report that individuals and families believed that the food aid increased the daily food intake of all household members, increased the money available for other needs, and improved household food security. These benefits were believed to result in improved weight and health, increased energy level, medical treatment adherence, school attendance, immunity, quality of life, productive ability, and survival—although objective measures of these outcomes were limited.<sup>96</sup>

## C-SAFE guidelines for the use of food aid for TB patients:

- Work closely with all levels of the National TB Control Program to strengthen both referral mechanisms/case-finding and monitoring and evaluation.
- Ensure that patients receiving food are adhering to treatment plans. Checking of DOTS cards and spot-checking of clinic records should be included in the beneficiary verification protocol.
- Provide food aid to eligible TB patients who are adhering to treatment for the entire length of the treatment.
- Ensure provision of nutrient-dense, fortified commodities in food ration for at least the first two months of TB treatment (or entire treatment period if possible).
- Discharge beneficiaries who fail to adhere to treatment plans.
- Ensure that providers are well-informed about TB and are able to provide beneficiaries with simple advice, information, and encouragement.
- Use every possible opportunity to disseminate information on TB to communities to encourage early case identification, treatment adherence, and HIV testing.
- Deliberately link TB patients to long-term food security initiatives once they regain sufficient strength.
- Discharge TB patients from food assistance upon completion of treatment, unless they remain chronically ill (in which case they should be transferred to another category).
- Develop a recording system that identifies TB patients separately from other chronically ill beneficiaries in order to track the success of this initiative.
- Refer individuals to a different beneficiary category on a case-by-base basis as required.

Source: C-Safe Learning Center. Targeted food assistance in the context of HIV

### Technical considerations for providing food assistance in TB programs

To deliver an intervention that is effective in treating and controlling a life threatening disease such as TB, health care practitioners must work within the health care system that delivers care appropriate to people's needs.<sup>94</sup> Although most evidence of the impact of food support on TB patients' nutritional status, quality of life, and adherence to and outcome of treatment is anecdotal, there is strong reason to believe that such support will provide direct benefits to adults and children infected with TB as well as their families, during and following anti-TB therapy (See section III).

With this in mind, it is possible to outline specific technical considerations for planning such support, including defining the objectives, assessing nutritional need (status, food insecurity), delivery channels, and other logistical considerations. For example:

- **Questions to ask before getting started:** Is food insecurity an issue for the target population? Is TB treatment adherence a challenge? Is TB program management strong? Who will be responsible for the design and management of the food program? Are there mechanisms for procuring food and monitoring its distribution? Is there sufficient staff and time to do proper

nutritional assessments, to distribute food, and to monitor program impact? Is there adequate and proper equipment for measuring anthropometry? What training will be needed?

- **Objectives:** The objectives of food and nutritional support should be clearly articulated. Possible objectives include increased adherence to and completion of anti-TB therapy, improved nutritional status, or reduced proportion of TB patients who have BMI <18.5 at treatment completion.
- **Assessing nutritional need:** Food support may be based on individual vulnerability to food insecurity or clinical evidence of malnutrition, or it may be based on household or community vulnerability to food insecurity. In either case, baseline assessments of BMI (weight, height) or MUAC are recommended. If skin-fold thickness or bioelectric impedance analysis (BIA) is feasible then these measurements should be taken as well to assess body composition and degree of wasting. Understanding something about the local diet is necessary in order to give timely and appropriate nutritional advice for patients presenting with appetite loss, nausea, or other symptoms related to infection and/or treatment. Need for micronutrient supplements can be ascertained based on knowledge of the local diet or on individual dietary risk assessment.
- **Delivery channels:** Programs need to decide where food will be delivered and if food support will be “directly observed” (on-site, cooked) or provided for home consumption (usually raw ingredients). Programs also need to determine whether rations will be made available to TB patients only, which is easier to do with on-site feeding, or made available to other household members,

which is sometimes necessary for take-home rations and where food insecurity affects the entire household.

- **Duration of support:** Most programs provide food support for the duration of anti-TB treatment since assuring treatment adherence and completion is a primary objective.<sup>93</sup> However, in some instances programs may wish to extend food support to assure adequate nutritional recovery following treatment completion.
- **Food ration:** The composition of a food assistance package will likely vary from country to country as there are no particular foods that are specifically recommended in the management of TB. Two models have been used: food by prescription (i.e., food is prescribed like a medicine for an individual) and food rations for the household. The most important considerations are that food should be palatable, nutrient dense, culturally appropriate, affordable, and available. There are, however, special considerations for therapeutic feeding that should be adhered to if that is the primary objective of food support. Most WFP-assisted programs provide household rations that include maize, pulses, vegetable oil, and corn-soya blend. Some sites include additional items such as sugar, salt, rice, lentils, and fish. The overall food security situation will help determine whether the ration should be based on the individual or household. Frequently the patient who is receiving the individual ration will share it with other family members, resulting in an inadequate amount of nutritional support for the patient. Household rations, therefore, may help maintain the productivity and income generating ability of other household members, indirectly benefiting the patient as well.<sup>93</sup>



- **Monitoring and evaluation:** The indicators used to monitor and evaluate the effectiveness of the food assistance program are usually TB specific: cure rate, death rate, and default rate.<sup>96,93</sup> Additional social markers of quality of life, well-being, and health center attendance before and after the program is initiated may help evaluate its impact as well. Repeated weight, skin-fold thicknesses, and BMI measurements should also be considered for routine monitoring and recording.<sup>96</sup> Since nutritional status is related to TB treatment as well as to food intake, it may be difficult to distinguish whether improvement in nutritional status is due to control of the disease or to improved food intake supplied by the food assistance program. (Additional information on indicators is provided in the next section.)
- **Procurement and distribution:** Procurement and distribution of food rations are major challenges for food support programs. Program managers should determine where they can obtain a reliable source of food and which delivery option(s) they will implement. These may include: (1) food and medicine delivered to patient at the same time, with directly observed therapy; (2) food delivered on a fixed day, different from medicine delivery; or (3) food delivered weekly or every two weeks for on-site or take-home feeding. At some facilities staff make up individual food packets; at others, the patients apportion and distribute the food among themselves according to ration guidelines. The food can be delivered to the patient from health care facilities, from a local store, or other delivery points. Flexibility in food delivery to patients helps providers adapt to local conditions.<sup>95</sup> Reporting systems, training, and supervision are essential to limit misuse and to track the number of participants served. Issuance and use of food prescriptions or ration cards should be required before food is distributed to individuals.<sup>95,96</sup>
- **Other management issues:** A successful food assistance program can serve large numbers of TB patients, and is feasible and sustainable within a strong TB control program, as long as attention is paid to transparent management systems, communication, and problem solving capacity across all stakeholders including ministries of health, funders, communities, and patients.<sup>93</sup> Cost-effectiveness will need to be measured.

### Assessing the impact of food support

Practical tools to assess the impact of food assistance are not commonly available and experience with impact evaluation is still lacking in most food-assisted programs.<sup>96</sup> However, below are some suggested indicators for measuring the impact of food assistance based on experience and expert opinion:

- **Nutrition:** Traditional quantitative measurements to assess nutritional status at the beginning and during the program include anthropometric measurements such as height, weight, BMI and MUAC. Little is known about the sensitivity and specificity of these measures to monitor changes in nutritional status in TB (and TB/HIV co-infected) patients receiving food support during treatment, and more study is needed to determine their utility. Therefore, anthropometric assessment may be most helpful in measuring program impact when used in conjunction with other measures.<sup>96</sup>
- **Strength and stamina:** Handgrip strength (using a handgrip dynamometer) could be used to measure change in strength but, like anthropometry, has not been tested in TB patients. Handgrip strength correlates to BMI and MUAC and is a relatively new tool for use as a proxy measurement of nutritional status.<sup>96</sup>
- **Treatment uptake and efficacy:** This is the number of patients coming for

diagnosis and successfully completing treatment. The TB cure rate, death rate, and default rate should also be reported. Uptake of other services, such as HIV testing, can also be measured.

- **Quality of life:** Food support may have a positive impact on quality of life, but there are no published studies that directly examine the impact of food supplementation on quality of life in TB.<sup>96</sup> Quality of life can be measured with several different tools, such as the Karnofsky score. The impact of food support can also be assessed in relation to social and psychological considerations.
- **Household food security:** Even though a food assistance program may target an individual, it also directly impacts all household members. Many programs provide household rations. Impact at the household level, however, is not necessarily the same as impact on the targeted household member, and may warrant specific monitoring and evaluation. Indicators of household food security include dietary diversity, number of meals consumed daily, diet changes, frequency of hunger and lack of food in the household, consumption of “luxury” foods, expenditures on food, and asset retention.

### Research priorities

Although the inter-relationship between nutritional status and TB disease is well documented, many areas require further investigation to improve understanding and management of malnutrition in TB. Specific priorities that have emerged from this review include studies of:

- The effect of generalized malnutrition and micronutrient deficiency on TB treatment outcomes.
- The most effective formulation (nutritional profile) and duration of food support—taking into consideration local diets and food availability—for treating malnutrition and improving: (1) overall nutritional status (muscle mass in TB patients, including adults and children) during and after TB treatment; (2) TB treatment outcome; and (3) survival.
- The most effective formulation, duration, and impact of micronutrient supplements, in addition to anti-TB treatment, to improve: (1) nutritional status; (2) TB treatment outcome; and (3) survival in persons with TB (including those with TB/HIV co-infection).
- The effect of nutrition education focusing on nutrient-rich food cultivation and consumption, on the nutritional status of TB patients, their recovery, and on their families.
- Non-nutritional benefits of nutritional support in TB and TB/HIV co-infected patients and programs on increased TB case detection, treatment adherence, and outcome of treatment (e.g., in relation to re-emergence of TB disease and incidence of other infections, particularly in children).
- Other non-nutritional benefits of nutritional support in TB and TB/HIV co-infection including on quality of life, physical activity and endurance, and improved socioeconomic benefit with sooner ability to return to work.
- Screening for vitamin D deficiency in newly diagnosed TB patients to determine prevalence of the condition and relationship with TB.
- Trials of vitamin D supplementation to determine the link between vitamin D<sub>3</sub> deficiency and susceptibility to active TB disease.
- Successful models for integrating nutritional support in TB and TB/HIV programs, including collaboration between programs to achieve shared goals of successful treatment.
- Best practices for nutrition assessment, referral, and protocols for treating malnutrition in adults and children in TB and TB/HIV programs.
- The cost-effectiveness of food and nutritional support within TB and TB/HIV programs.

## Conclusion

Based on the information summarized in this report, it is clear that TB affects nutritional status. Many patients with active TB experience severe weight loss and some show signs of vitamin and mineral deficiencies. Persons with TB/HIV co-infection are even worse off nutritionally. However, the evidence surrounding best practices for nutritional management is very limited.

Some TB control programs have provided food to both TB patients and health care providers as a means to improve performance of each. Food assistance is a potentially influential means for increasing adherence to TB treatment, reducing the costs to patients of staying in treatment, and for improving nutritional status. Although most evidence of the impact of food support on TB patients' nutritional status, quality of life, treatment adherence, and outcome is anecdotal, there is reason to believe that such support will provide direct benefits to adults and children infected with TB both during and following drug therapy. However, the

cost to programs of providing food support may be considerable. Other low-cost interventions such as periodic nutritional assessment and counseling on diet, and nutritional management of symptoms and drug-side effects, may help TB patients to maintain or increase their food intake and adhere to TB medications. But again, program and/or research evidence is limited.

Many areas require further investigation to improve our understanding and management of malnutrition in TB and TB/HIV co-infection. Of particular priority are studies of the most effective approaches for treating malnutrition and improving overall nutritional status and muscle mass in TB and TB/HIV co-infected adults and children during and after TB treatment—taking into consideration local diets and food availability. Successful and varied models for integrating nutritional support into TB and TB/HIV programs and data on the cost-effectiveness of integrated nutritional support are also needed.

**ANNEX 1: Body Mass Index in HIV-positive and HIV-negative patients with newly diagnosed tuberculosis**

<b>BMI kg/m<sup>2</sup> Mean ± SD</b>						
<b>Reference, location</b>	<b>Men</b>			<b>Women</b>		
	<b>HIV+ (n)</b>	<b>HIV- (n)</b>	<b>p value</b>	<b>HIV+ (n)</b>	<b>HIV- (n)</b>	<b>p value</b>
Van Lettow <sup>51</sup> <b>Malawi</b>	18.3 ± 2.3 (100)	18.6 ± 2.4 (49)	NS	18.4 ± 2.9 (136)	18.7 ± 2.7 (34)	NS
Van Lettow <sup>97</sup> <b>Malawi</b>	18.5 ± 2.6 (156)	18.7 ± 3.1 (71)	NS	18.3 ± 2.8 (214)	18.6 ± 2.7 (59)	NS
Villamor <sup>67</sup> <b>Tanzania</b>	19.0 ± 2.4 (376)	18.9 ± 2.2 (1169)	NS	19.3 ± 3.7 (344)	19.3 ± 3.0 (342)	NS
Niyongabo <sup>71</sup> <b>Burundi</b>	15.6 ± 3.4 (50) M:F 1.63	18.5 ± 2.5 (15) M:F 0.88	0.03			
Kennedy <sup>64</sup> <b>Tanzania</b>	16.6 ± 1.7 (32)	17.6 ± 1.8 (67)	<0.01	18.2 ± 2.8 (21)	17.6 ± 1.9 (28)	NS
Mugusi <sup>69</sup> <b>Tanzania</b>	17.8 ± 2.6 (61) M:F 0.86	18.6 ± 3.2 (39) M:F 1.35	NS			
Mabedo <sup>68</sup> <b>Ethiopia</b>	16.5 ± 2.5 (25) M:F 2.1	6.6 ± 2.4 (100) M:F 2.5				
Kassu <sup>59</sup> <b>Ethiopia</b>	5.5 ± 2.5 (74) M:F 0.54	18.0 ± 2.5 (81) M:F 0.72	NS			
Paton <sup>56</sup> <b>Singapore</b>	17.3 ± 2.4 (8)	17.1 ± 1.3 (10)	NS			

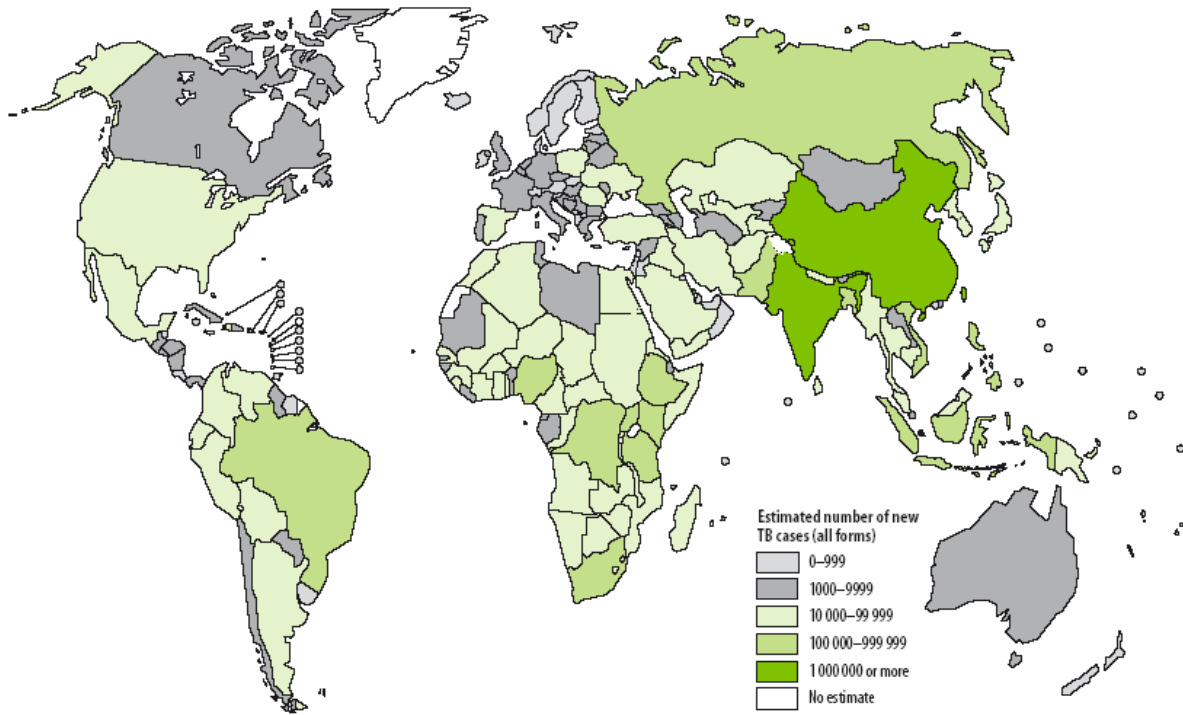
**ANNEX 2: Summary of studies investigating micronutrient status of patients with pulmonary tuberculosis**

<b>Nutrient</b>	<b>Subjects/study type</b>	<b>Findings</b>	<b>Reference</b>
Vitamin B <sub>6</sub> (pyridoxine) South Africa	20 TB patients Longitudinal (one week before and after initiation of TB treatment)	90% with low B <sub>6</sub> at initiation of therapy, 100% patients ↓ B <sub>6</sub> concentration significantly at one week	Visser, 200470
Vitamin A Rwanda	94 TB/HIV+ patients Cross sectional	29% vitamin A deficient Limitation: no healthy control group, no acute phase response control	Rwangabwoba, 199898
Vitamin A India	47 TB patients 46 healthy household controls 30 health “normal” controls Longitudinal	81% of TB patients with marginal vitamin A status at baseline ↓ Mean vitamin A in TB patients versus household or normal controls ↑ Mean vitamin A in TB patients at six months Limitation: no acute phase response control	Ramachandran, 200480
Vitamin A, hemoglobin, albumin Tanzania	Pulmonary TB patients (39 HIV-, 61 HIV+) 144 blood donor TB-controls (99 HIV-, 45 HIV+) Longitudinal (two months)	↓ Mean vitamin A, hemoglobin, albumin in all TB patients compared with controls; lowest in TB/HIV patients ↑ Vitamin A deficiency in TB/HIV patients ↑ Mean vitamin A, hemoglobin, albumin in TB/HIV- at two mo, no change in TB/HIV+ patients Limitation: no acute phase response control	Mugusi, 200369
Vitamin A, Vitamin C, Vitamin E, hematocrit, albumin Ethiopia	Pulmonary TB patients (100 HIV-, 25 HIV+) 45 Ethiopian healthy controls Cross-sectional	↓ Mean vitamin A, C and E, hematocrit, albumin in TB patients versus controls	Mabedo, 200368
Vitamin A, E, ferritin, hemoglobin, zinc, selenium Malawi	370 TB/HIV+ patients 130 TB/HIV- patients	↓ Mean hemoglobin in TB/HIV+ patients, ↑ Prevalence of anemia compared to TB/HIV- patients, ↑ Mean ferritin in TB/HIV+ patients compared to TB/HIV- patients, 59% of all deficient in vitamin A 12% of all deficient in vitamin E 80% of all deficient in zinc 88% of all deficient in selenium	Van Lettow, 200587

Vitamin A, hemoglobin, zinc, albumin Indonesia	41 TB patients 41 healthy controls Cross-sectional	↓ Mean vitamin A, hemoglobin, zinc, albumin in TB patients versus controls ↑ Prevalence of anemia, vitamin A and zinc deficiency in TB patients	Karyadi, 200015
Vitamin C, Vitamin E India	30 TB patients 30 healthy controls; Cross-sectional	↓ Mean vitamin C and E in TB patients versus controls	Vijayamalini, 200477
Vitamin C Russia	159 TB patients, 20 healthy controls all participants smoked; Cross-sectional	↓ Mean vitamin C in TB patients versus controls	Bakaev, 200482
Iron Zimbabwe	98 TB patients (69 HIV+, 19 HIV-) 98 (15 HIV+, 83 HIV-) controls, matched for age and sex Longitudinal (seven to nine months)	↑ Mean ferritin and transferrin saturation in TB patients compared with controls ↓ Mean hemoglobin in TB patients, lowest in TB/HIV+ patients ↑ Mean hemoglobin in all patients	Gangaidzo, 200189
Copper, zinc, selenium, iron Ethiopia	155 TB patients (74 HIV+, 81 HIV-) 31 healthy controls Longitudinal	↑ Mean copper in all TB patients compared with controls ↓ Mean zinc in TB/HIV+ patients compared to TB/HIV- and controls ↓ Mean selenium in TB/HIV+ patients compared to TB/HIV- and controls ↓ Mean iron in TB/HIV+ patients compared to controls After two mo of therapy, ↓ Mean copper, no change in selenium and iron, ↑ Mean zinc in TB/HIV- but no change in HIV+	Kassu, 200559
Vitamin D England	126 TB patients 116 healthy controls	26% prevalence vitamin D deficiency Vitamin D deficiency associated with active TB (OR 2.9; 95% CI 1.3-6.5)	Wilkinson , 200014
Vitamin D England	210 TB patients foreign born	76% prevalence vitamin D deficiency	Ustianowski, 200485

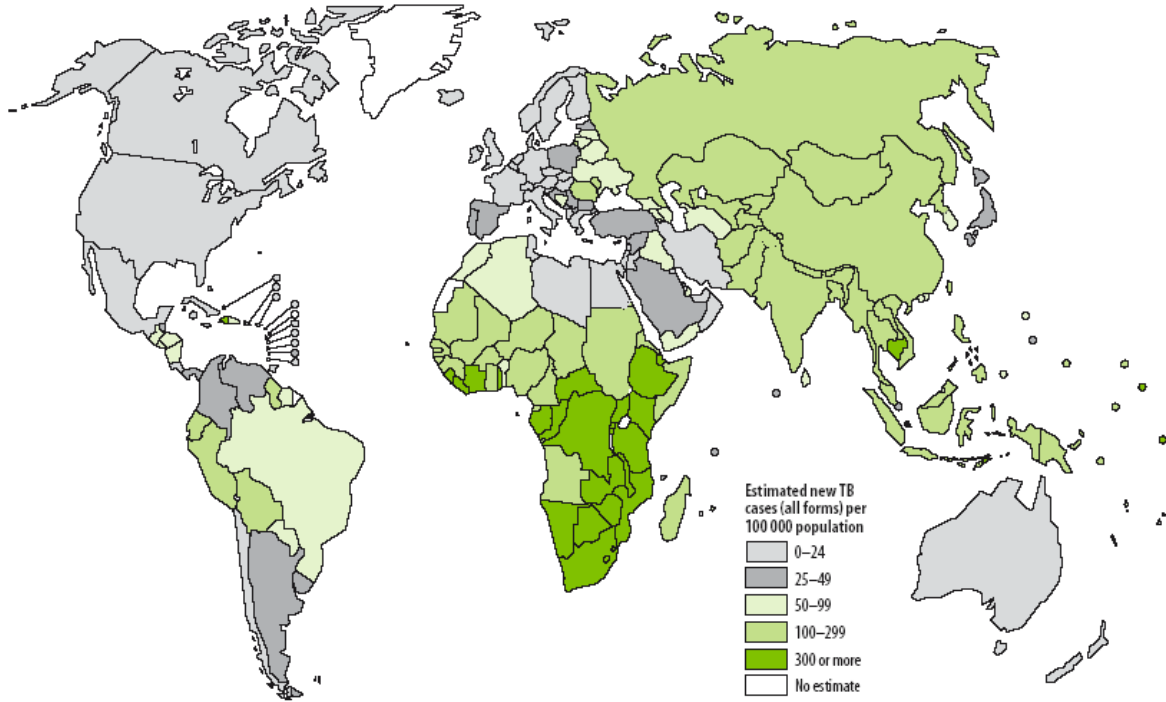
**FIGURE 1**

Estimated numbers of new TB cases, 2005



**FIGURE 2**

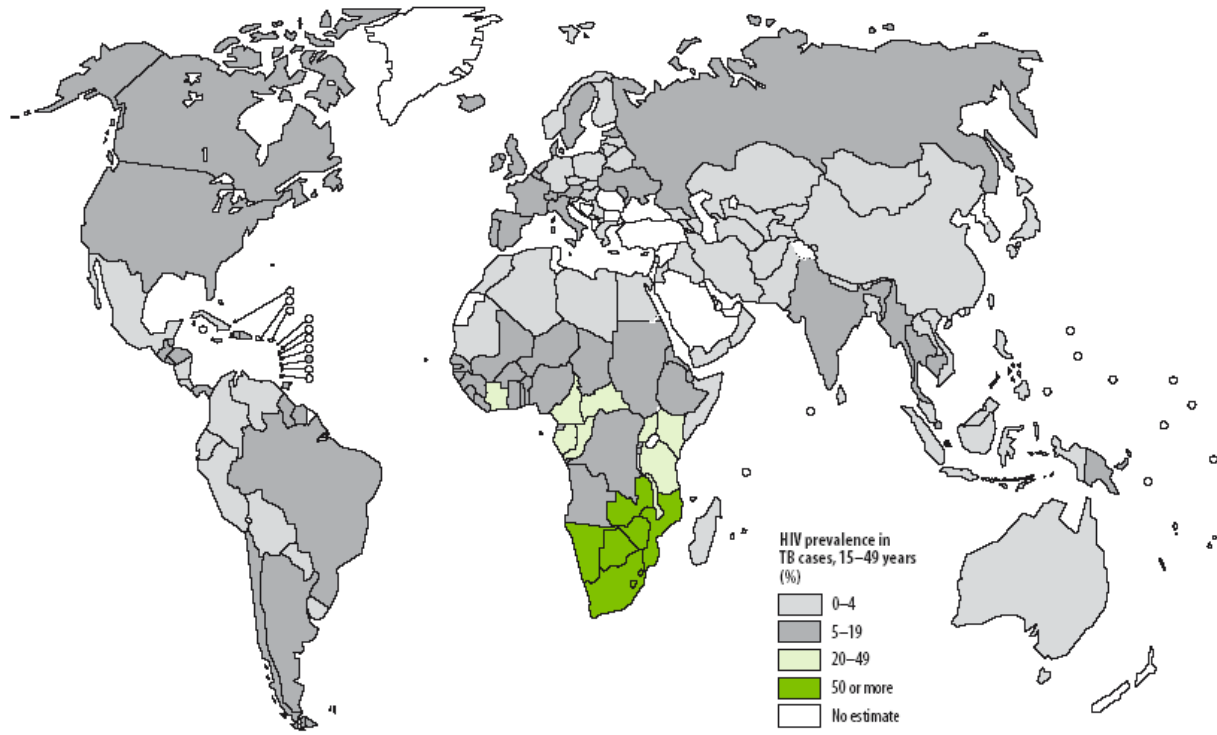
Estimated TB incidence rates, 2005





**FIGURE 3**

Estimated HIV prevalence in new adult TB cases, 2005



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