

# Speaking truth to power in South Africa: Nutritional influences on HIV infection and tuberculosis

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## Public and policy confusion: nutrition and chronic infectious disease

The issues concerning nutritional influences on human immunity and the response to major epidemic infections such as those caused by HIV and *Mycobacterium tuberculosis* have been among the most controversial in South Africa in the last half-decade. These issues have given rise to serious differences in the approach to public policy in addressing the ravages of these diseases. There was a belief in certain quarters about a decade ago that poverty and under/malnutrition may themselves be the main aetiological agents of acquired human immunodeficiency syndrome (AIDS), with HIV infection being a non-contributory or trivial super-vening circumstance. Some still consider nutritional deficiencies to be a contributory, or even specific target of primary therapy of 'HIV infection and AIDS'. There is a plethora of products available over the counter that purportedly 'modulate' the immune system in a favourable manner to prevent or ameliorate HIV and/or active *M. tuberculosis* infections, ranging from 'active nutritional factors' present in certain foods to processed or crude 'complementary medicines'.

The science-based majority view, however, is that nutritional support of persons infected with either *M. tuberculosis* or HIV, or both, is a necessary and helpful part of a therapeutic approach that primarily concentrates on the eradication or, at least, control of the infected state in each affected person.

It is important to bear in mind, however, that prior to the advent of antibiotics, TB 'treatment' was characterized by intense concentration on strengthening the immune defences of infected subjects with diets, improved and altered environmental conditions and every other conceivably helpful measure. After the discovery of effective drugs, this aspect of TB therapy quickly became secondary and largely

uncontroversial. Because HIV infection currently cannot be cured, but only controlled with drugs being applied at particular serious stages of progressive disease (according to current guidelines, at least), the emphasis in the management of infected people during the phases prior to drug administration is still on general, non-pharmacological support, especially as for medically justifiable reasons it is highly desirable to postpone the introduction of specific antiretroviral therapy for as long as possible.

The Academy of Science of South Africa (ASSAf) accordingly set up a 15-member study panel<sup>†</sup> in 2005, to examine the most relevant and reliable evidence that had a bearing on the following issues, and to make recommendations that are the most appropriate and feasible based on the evidence. The areas to be covered were:

- Nutritional modulation of the normal human immune system (innate and adaptive, at different ages, in both sexes, over short or long periods), with respect both to general undernutrition (macronutrients) and to specific deficiencies of micronutrients.

<sup>†</sup>The study panel members were Barry Mendelow (panel chair, former head of Molecular Medicine and Haematology, University of the Witwatersrand), Peter Cegielski (Centers for Disease Control and Prevention, Atlanta, Georgia), M. Ali Dhansay (director of the Medical Research Council's Nutritional Intervention Research Unit), Wieland Gevers (professor emeritus of medical biochemistry, University of Cape Town), Clive Gray (head of the Department of HIV Immunology at the National Institute for Communicable Diseases, Johannesburg), Glenda Gray (Department of Paediatrics, and executive director, Perinatal HIV Research Unit, University of the Witwatersrand), Liesl Grobler (HIV/AIDS, TB and Malaria Clinical Trials Registry, University of Stellenbosch), Gregory Hussey (director of the Institute of Infectious Diseases and Molecular Medicine, University of Cape Town), David McMurray (chair of the Tuberculosis and Leprosy Panel of the US-Japan Cooperative Medical Sciences Program), Gernard Msamanga (Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania), Dan Ncayiyana (editor of the *South African Medical Journal*), Helen Rees (executive director of the Reproductive Health and HIV Research Unit, University of the Witwatersrand), Francois Venter (clinical director of the HIV Management Cluster, Reproductive Health and HIV Research Unit, University of the Witwatersrand), James Volmink (deputy dean (research) in the Faculty of Health Sciences, University of Stellenbosch), and Hester Vorster (director of the Africa Unit for Transdisciplinary Health Research, Faculty of Health Sciences, North-West University).

- Modulation of human nutritional status in states of infection, both acute and chronic, with special emphasis on active infection with *M. tuberculosis* and the human immunodeficiency virus (HIV).
- The effects of nutritional interventions on morbidity and mortality in adults and children infected with HIV or suffering from clinical tuberculosis, or both.

A preliminary survey of the review literature related to the topic has revealed a paucity of comprehensive, relevant and recent reviews in the mainstream literature of the relevant disciplines, and a relative absence of focus in the field. For example, amongst approximately 500 review articles in the last 10 years published respectively in the authoritative *Annual Reviews* of Nutrition, Immunology, Microbiology, Medicine, and Physiology, not a single article was devoted even indirectly to the topic in question. An early systematic review by the South African Cochrane Centre similarly identified alarmingly few reliable interventional studies against a background of a huge number of questionable literature sources.

## A study of a special kind

The ASSAf consensus study has set out to achieve distinctive features of the kind of reports the Academy seeks to produce, and the unique benefits they should provide (see Box on next page). The study has been carried out independently by a selected group of eminent scholars bringing a variety of disciplinary insights and conceptual strengths to the topics to be examined. Both tuberculosis and HIV infections were studied, separately, and as conditions that frequently coexist, against a background of a general, evidence-based understanding of the functional inter-relationships between infection and nutrition. Specific attention has been given to the functioning of the immune system in relation to nutritional factors. Specificity related to genetic and individually applicable developmental factors has been thoroughly explored and interpreted in relation to generally applicable human responses. The study aimed to be firmly rooted in the national context, and the report on the study, while strong in reviewing and evaluating all the available, reliable scientific evidence, needed to be written in very clear, non-technical language so that it would be understandable to a broad range of users.

## A complex and demanding process

The study panel found it practical to request members (or, on occasion, outside experts) to provide initial drafts of parts of

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### A background to the national academies of science

National academies of science have in recent times begun to turn their collective intellectual muscle to the task of generating evidence-based advice on important and unresolved problems. This is because they are independent and highly multidisciplinary, can mobilize the best-available expertise in a low-cost but professional manner, and are well-connected to the science academies of other countries.

South Africa's own national academy of science (ASSAf) was established as late as 1996, and accorded statutory recognition by parliament in 2001. Its late start allowed it to leapfrog two key issues that still plague many other science academies—it is inclusive in that it considers 'science' as any discipline using continuously evolving, evidence-tested enquiry, true of the social and human sciences as much as of physics and chemistry,<sup>1</sup> and it uses its honorific nature as a vehicle for serving the nation more actively and directly (ASSAf's key objective is 'Science for Society', see [www.assaf.org.za](http://www.assaf.org.za)). ASSAf was also fortunate in being selected in 2005 to be a recipient of major funding from the US National Academies as part of the African Science Academy Development Initiative, specifically to focus on the generation of evidence-based advice on problematic national policy issues.<sup>2</sup> This can be done by setting up expert panels, holding open national forums or any other suitable method.<sup>3</sup>

the report that were related to specific topics. These drafts were first circulated and then discussed at panel meetings, and stock was taken of problems such as critical omissions, controversies, overlaps and contradictions. Further drafting then took place, often by several panelists other than the original author. In one instance, the study panel decided to arrange a public workshop to review and discuss highly topical recent advances in the inter-disciplinary field of HIV immunology in the gut, inflammatory bowel disease and the burgeoning area of intestinal microbiota; the insights obtained from this exercise were incorporated into various sections of the consolidated draft report. A short paper on the possible programming of the human immune system as a result of fetal insults of various kinds, including maternal under- and malnutrition, was commissioned from specialists in the U.K. A special policy workshop was attended by a subset of panelists convened for this purpose. The study panel met face-to-face as a whole on six occasions from mid-2005 until mid-2007.

The pre-final report agreed upon by all panel members was subjected to international peer review before it was approved by the Academy Council and publicly released on 22 August 2007. The full report can be read at [www.assaf.org.za](http://www.assaf.org.za).

### ASSAf's report on HIV/AIDS, TB and nutrition: summarized findings and recommendations

The report provides a set of recommendations for policy and practice, as well as recommendations for further research that is needed to address the many as yet unanswered questions identified during the study.

The panel has concluded that no component of food has yet been identified in any credible scientific study as being an effective substitute for appropriate antiretroviral agents when indicated for the treatment of HIV infection, or the appropriate specific antimicrobial agents when indicated for the treatment of active tuberculosis. Specifically, correction of existing nutritional deficiencies, or supplying additional nutrients with demonstrable beneficial effects on disease processes, may plausibly provide material support to antimicrobial therapy, but solid evidence on this is surprisingly sparse. The report notes that the 'debate has been so bitter, because the actual knowledge base has been so small'.

### Only a small number of sound interventional studies have been done

There is a serious shortage of soundly designed, locally relevant and contextually appropriate studies that could effectively inform policies designed to optimize nutritional support for infected people, before or after specific therapy is started, in a population where macronutrient deficiencies (overt hunger) and/or micronutrient deficiencies ('hidden hunger') are particularly common.

There are no sets of agreed, cost-effective methods for detecting micronutrient deficiencies that are functionally significant, or for assessing immune functions in relation to nutritional status in both individuals and populations, in a situation where many unsubstantiated claims for supplements of various kinds are being made. The panel recommends that a cooperative programme of studies be commissioned to achieve a national working consensus in both of these areas.

### A new focus on HIV and the gut

Recent studies on the basic science of HIV infection have revealed that many of the processes determining the main features of the disease occur in the gastrointestinal tract, and may be prime drivers of persistence and progression to AIDS.<sup>4</sup> This insight suggests new approaches to the search for better therapeutic strategies, which the panel believes should be taken up in the South African basic and clinical research system as a matter of urgency. The programme of research recommended by the panel reflects the research creativity which can be generated in a review panel of this kind; they recommend bringing together gastroenterologists, immunologists and nutritionists/dietitians in joint studies, and sharpening up and expanding diagnostic tests of intestinal function. These should develop the capacity to characterize the microbiota present in both the small and the large intestines of individuals and populations, quantitatively and qualitatively, and to determine temporal responses during follow-up and treatment scheduling, in order to understand the systematic relationships between diets of various kinds and the intestinal microbiota, as well as gut function and inflammation. It is essential to establish why there may be malabsorption of specific nutrients in asymptomatic HIV-infected individuals, whether this is selective, and whether compensatory change in the bowel microarchitecture/biochemical physiology take place, and with what significance for morbidity and mortality.

Other requirements are to characterize the short- and long-term effects of selected probiotics and prebiotics, of various kinds and at various dose levels, on gut microbiota in various kinds of subjects, including those with and without HIV infection. Controlled clinical trials will be needed of the possible therapeutic value of selected probiotics and/or prebiotics on HIV-infected subjects at varying stages of the disease and with varying intestinal symptoms and complications. In addition, the possible therapeutic value of specific anti-inflammatory agents (such as 5-aminosalicylic acid) and/or specialized diets that have proved to be effective in chronic inflammatory bowel disease will have to be tested in HIV-infected subjects. The reliability and informativeness of direct or proxy tests of immune functioning in the intestinal mucosa will have to be improved, and the relationships documented between intestinal symptoms and signs, on the one hand, and the progression of HIV infection to its final end-

stages, on the other. Finally, the role of already well-accepted opportunistic intestinal pathogens will have to be much better understood in the context of newer conceptual frameworks of local immune defences and accompanying systemic changes.

#### Other relevant research that is needed

There is an urgent need to establish the precise physiology and (possibly competitive) pharmacokinetics of food-derived versus formulated vitamin and/or mineral intakes/supplements, the latter singly or as multi-component preparations: Are the consequences of self-administration of (commonly available) multivitamin preparations properly understood in terms of interactions between constituent compounds and body constituents? Are the individual bioavailability patterns affected by bulk ingestion? Do different preparations differ in their effects/efficacy? Are measurable parameters of immune function altered when multivitamin preparations are taken by uninfected persons? What about HIV-infected persons?

A better understanding is also needed of the significance of lifelong programming of the human immune system arising from fetal 'insults'.<sup>5</sup> The evidence for a systematic, programmed 'stunting' of the immune system of malnourished people through this mechanism is not yet firm enough to become an accepted part of thinking in the field. Nevertheless, it is clear that proper studies of South African communities need to be performed to help assess the importance of this possibly quite general phenomenon within the general context of the high prevalence in South Africa of 'hidden hunger' (micronutrient deficiencies) as opposed to protein/energy starvation.

Recent developments in the understanding of some micronutrients such as vitamins A and D are so important that they merit thorough study and further interventional trials. Both appear to be precursors of highly active metabolites that are crucially involved in specific immune mechanisms, respectively in mucosal immunity and in intracellular microbial destruction.<sup>6,7</sup>

The fact that active vitamin A repletion has proved helpful in many childhood

diseases, including HIV infection, and (potentially) unhelpful in preventing mother-to-child transmission of the same virus, points to the need more fully to understand the exact situation with respect to this vitamin-'prohormone' in the bodies of subjects included in clinical trials, on the one hand, or in clinic-going populations, on the other. We need to know whether many South Africans are unable to synthesize enough of their own vitamin D, with possible lowering of serum 1,25-cholecalciferol levels and increased susceptibility to tuberculosis. Do dietary intakes have a bearing on this? Randomized controlled clinical trials of vitamin D supplementation are obviously necessary in active tuberculosis, making sure the design includes the detection of subjects with sub-clinical hypovitaminosis, and, if there are such subjects, determining if possible the reasons for this status. Intersections with calcium intake and status will need to be established.

Other specific nutrients notably requiring detailed investigation using modern methods are folate, zinc and selenium.

#### Genetic differences in the susceptibility to HIV and TB infection of different members of the population

A pitfall of many clinical trials is the acceptance of a 'blank slate' model of the population under study. A spectrum of infection prevalences and progression rates has emerged in the case of both HIV and *M. tuberculosis* infections. Within any population, and between different populations, there are individuals with increased susceptibility and others with increased resistance, who may in either group progress to AIDS or develop TB slowly or quickly.<sup>8,9</sup> Generally, however, increased susceptibility to becoming infected with HIV has accompanied the trait of more rapid progression to AIDS. Many gene loci have been found that variously affect virus entry and intracellular replication, host innate immunity and especially adaptive immune processes, and affect the clinical course of the infection accordingly. Similar findings have been made in the case of tuberculosis. These genetically determined variations in host susceptibility are important because they will constitute 'background

noise' in any clinical trial or other investigation of clinical HIV progression. Fortunately, the laboratory means to establish the nature of other possible resistance or susceptibility genes in human subjects are being created through active research and will impact positively on this problem.

#### Cutting-edge research in nutrition is a national priority

The elevation of the research agenda to the national level in the field of nutrition and immunity means that this focus must be given special attention in the current (strategic) enhanced resourcing of science and technology in South Africa. There can be no doubt that the national interest requires a deliberate and coordinated focus on epidemic infectious diseases and their nutritional components. This means that the programmes for new research chairs, centres of excellence, special training programmes (as found in astrophysics and information technology), and international collaborations should include in their calls for proposals a priority for this critically important field.

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