

J IAPAC

**Journal of the
International Association
of Physicians in AIDS Care**

Vol. 1, No. 2

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A clinical review of micronutrients in HIV infection
*Neera Singhal, MBBS, MS, MHA, and
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Content

The *Journal of the International Association of Physicians in AIDS Care (JIAPAC)* seeks original research papers (see front), as well as "Letters to the Editor," "Short Communications," and "State-of-the-Art Reviews."

"Letters to the Editor" should be limited to 750 words. *JIAPAC* is under no obligation to print any letter or to provide an explanation for why any letter is not printed. The editors will consider the content of each letter in determining whether or not it will be peer-reviewed.

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Each abstract should be followed by three to ten words or terms chosen by the authors to assist in indexing the paper. Authors are advised to use terms from the *Index Medicus* medical subject headings list when possible.

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If randomized trials are discussed in a manuscript, then a completed CONSORT checklist must be submitted along with the manuscript. (See *JAMA* 1996; 227: 637-639.)

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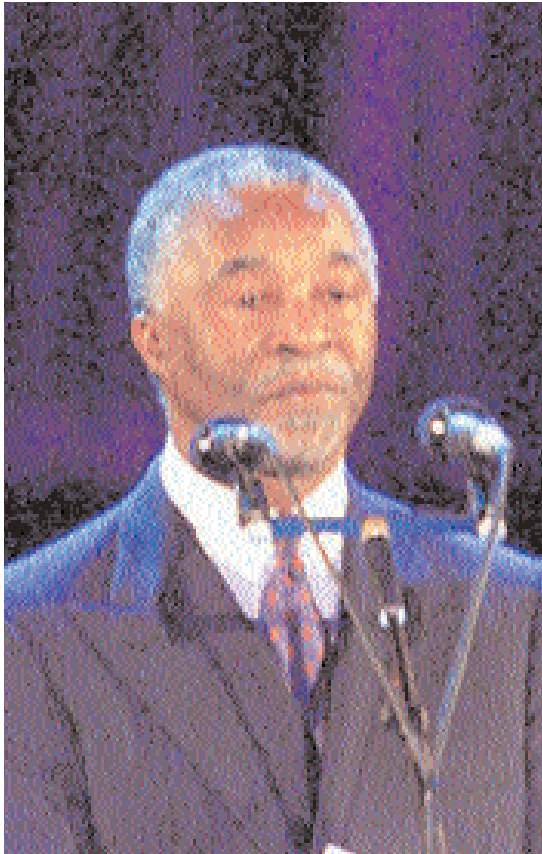
JIAPAC (ISSN 1081-454X), is published quarterly by IAPAC, 33 N. LaSalle Street, Suite 1700, Chicago, Illinois 60602-2601. Telephone: (312) 795-4930; FAX: (312) 795-4938. E-mail: jiapac@iapac.org. Web site: <http://www.iapac.org>. POSTMASTER: send address changes to IAPAC, 33 N. LaSalle Street, Suite 1700, Chicago, Illinois 60602-2601.

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Needs and prospects for HIV therapy in developing countries

D. William Cameron, MD, FRCPC

Editor-in-Chief, *JIAPAC*



*South African President Thabo Mbeki
cites multiple causes of AIDS.*

Two editorials in this issue of *JIAPAC* offer perspectives on HIV treatment in countries with great need, but constrained resources. The issues of whether and how best to introduce HIV treatments, widely available in developed nations with relatively little HIV, to developing nations with large burdens of AIDS, are dictated by the division of wealth and poverty. This is the same divide that makes the difference between living with HIV for one, or dying with AIDS for another. However, if only for enlightened self-interest, the industrialized world must participate in the welfare of impoverished developing countries.

The first editorial looks at the difficulties in using costly antiretroviral treatments that benefit a small number of people at the expense of the limited resources in the general healthcare system, and that may compromise investment in risk-reduction and HIV prevention. The second editorial identifies a perspective on the potential synergy of AIDS treatment on the public healthcare of HIV, by targeting resources to the highest-risk population of commercial sex workers.

A great deal of time and work has gone into a debate on whether HIV causes AIDS, a debate that was recently rekindled in South Africa by President Thabo Mbeki's decision to give voice to dissenters who believe that HIV does not cause AIDS. Not many of us in medical AIDS care would want to argue this point for long, when there is so much to be done for the needs of so many living with HIV and AIDS. However, we might be willing to discuss another point. While we do believe that *AIDS the disease* in a single person is due to HIV, we may also consider that *AIDS the epidemic* is due to many other factors besides the "one single virus."

There are large differences in the AIDS pandemic between different countries. These differences are a by-product of the same injustices that make some wealthy, and others poor. As President Mbeki has pointed out, factors such as poverty through displacement, crowding, militarism and war, family and social disruption, and malnutrition produce many epidemic diseases. Limited access to treatment is another factor that results from the lingering presence of disparities that exist at a global level, and within countries such as South Africa and Zimbabwe. But we must not underestimate the resilience of people to respond to the causes of AIDS. As political leadership in South Africa has produced a political miracle of democracy, so



AIDS orphans are everyone's children.

Photo courtesy of D. William Cameron

leadership in the war against AIDS must be recruited from those most in need.

We must respect that the response to AIDS differs according to each country's story, and each country's pressing needs. Although an ounce of prevention is worth a pound of cure, prevention efforts will not meet the needs of those living with HIV. The response to *AIDS the epidemic* lies with development that incorporates the full participation of each country. This means economic, political, and social development with wise and careful attention to distributive justice, not just vaccine development. For *AIDS the disease*, HIV drug treatment will not be usefully provided before development of the infrastructure of general healthcare. Rather than dwell on this "Catch-22," there is a solution to be found through vision and leadership. This is urgent, because treatment is like justice, where treatment delayed is treatment denied.

An essential priority is care and research in treatment and prevention through development, medically with vaccines and treatments, and economically by creating an infrastructure. Medical treatment and care for AIDS the disease within a viable infrastructure may be a catalyst, rather than a casualty in the fight against AIDS the epidemic. As the late Jonathan Mann said, "AIDS will not be controlled anywhere until it is controlled everywhere." This is everyone's concern, and requires both vision and leadership. Anyone may apply. ■

Justice and HIV care in Africa—Antiretrovirals in perspective

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Abstract

The immense burden of HIV disease in sub-Saharan Africa has focused international interest on HIV care, especially on the lack of access to antiretroviral therapy (ART).

Difficulties in implementing ART in Africa include drug costs, adequate long-term funding sources, assurance of drug quality, and rapid development of the human resources and healthcare infrastructure needed to deliver ART.

Important questions requiring study are the minimum level of laboratory monitoring and clinical support consistent with good treatment outcomes, the impact of antiretroviral drug resistance on treated individuals and communities, and the effect of ART on transmission at a community level.

There are some concerns and risks. First, a focus on treatment could compromise the commitment of individuals to risk-reduction, and of governments to prevention. Second, health equity could be reduced, by diverting scarce public funds from basic care for the poorest, to costly disease-suppressive care for a small and probably elite group.

In conclusion, while prevention must be the first priority, care is also essential. The vast prevailing economic inequity between the world's rich and poor is the fundamental determinant of inequities in health and healthcare, including care for HIV. The global community of healthcare workers must focus its substantial influence on changing political and economic policies that foster injustice and AIDS.

Key words: HIV, Africa, antiretroviral(s), HIV therapy, justice

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JIAPAC 2002;1(2):46-50. © 2002 IAPAC.

HIV in Africa—an unprecedented public health crisis

The immense burden of HIV infection in Africa demands better care for those already infected, as well as better prevention for those who are not infected. Having witnessed the benefits of antiretroviral therapy (ART) in industrialized countries, many individuals and organizations have begun to question why this treatment is not available to the millions of HIV-infected patients in Africa. Recent large reductions in the price of proprietary, and emerging generic antiretroviral drugs have raised hopes that wider use in Africa might be feasible.

The disparity in access to HIV treatment between the world's rich and poor is self-evidently unjust. This injustice provides a powerful argument for expanded provision of ART in Africa. However, this injustice is neither new, nor specific to HIV care. It has long characterized access to basic healthcare (the difference in annual per capita health spending between the world's richest and poorest countries now approaches 1000-fold), and to basic human needs such as food, clean water, shelter, and education in Africa. Moreover, this inequality is steadily worsening.¹

Drug costs and affordability

Costs of antiretroviral therapy have dropped over a very short period, from US\$10-12,000 per year, to as low as US\$320 per year for the lowest-cost combination antiretroviral regimen from a generic manufacturer.² These figures may now be approaching the cost of production. While these price reductions are remarkable and encouraging, the cost of ART remains far beyond the reach of the majority of Africans. Even at the lowest foreseeable prices, per patient cost of the drugs is many times greater than the per capita health spending of any poor country, and greater than per capita *income* in the poorest countries. In populations where more than one in four are HIV-infected, total national drug costs would be immense in relation to locally available resources.

Who will pay?

Support from aid agencies, nongovernmental organizations, or industry donors may play a useful role in pilot projects or in supporting specific aspects of an ART program. However, neither the carefully calculated generosity of the pharmaceutical industry, nor the usually short

attention span of Western donors is likely to prove a reliable foundation for a program of the necessary scale and duration. The United Nations has recently announced a program of increased support against the major disease killers in resource-poor countries, including HIV. Even if their funding target were to be reached and sustained, the proposed amount is not sufficient to meet both treatment, and other HIV-related needs such as basic health infrastructure and HIV vaccine development.³ There are also serious reservations about the proportion of aid funding for the poorest countries that would effectively be paid directly to the international pharmaceutical industry.⁴

Public funding of ART in low-income countries:

Primum non nocere*

Due to the high cost of ART and the limited resources available for health in Africa, paying for ART from the public healthcare budget would necessitate major cuts elsewhere in HIV prevention, primary care, or some other area of government services. By way of analogy, development advocate, David Morley, used to rail against developing countries spending a large proportion of their resources on national hospitals that effectively served only a small minority of the population. He pointed out that such hospitals were ultimately responsible for the deaths of large numbers of children whose lives could have been saved by the wiser and more equitable use of resources.⁵ In the case of ART, the poor majority would lose most from cutbacks in basic services, while members of a small, better off and well-connected urban elite would be most likely to benefit from an ART program. In many African countries today, diversion of large sums of public money to ART could very easily result in a net negative impact on population health, and an undesirable decrease in health equity.

How many people do we need to treat?

How do we choose who gets ART?

Given the obstacles confronting the provision of ART to millions, it is sometimes suggested that treating even a small number of people would help a little. But since one of the ethical imperatives to treatment is the large scale of illness and death caused by HIV, a realistic expectation of reaching some substantial proportion of HIV-infected individuals in the community is necessary in order to justify the introduction of ART. From a public health perspective, the scale of the intervention should be sufficient to result in a measurable population impact. If, as seems likely in the immediate future, treatment were available for only a minority, the processes of determining criteria for treatment and selecting treatment candidates would challenge the most cohesive and organized society.

**Editor's Note: First, do no harm.*

"New money"

It has been argued that ART would be supported from entirely new funding sources. "New money," like free lunch, has to be viewed with skepticism. Until there is a dramatic and sustained change in the level of commitment of donor countries, external funding for ART can only come at the expense of other programs such as vaccination initiatives. Over the past decade, the proportion of gross domestic product, directed by wealthy countries to foreign aid, has been declining steadily, rather than increasing.⁶

Determining priorities

African countries, in which HIV is now endemic, continue to face the daunting challenge of distributing limited resources among the many competing needs within their health sectors. They must ask how many lives could be saved by investing US\$320, multiplied by some thousands of patients treated with ART, in immunization, malaria control, the tuberculosis (TB) program, HIV prevention, or primary education.

Consider a hypothetical, but all-too-typical, African family in a setting where ART was widely introduced in the absence of broader economic and social changes. A father with symptomatic HIV infection receives treatment that costs at least US\$320 annually. His wife has TB for which adequate diagnosis and treatment are not available in their community. His two youngest children are malnourished and suffer from recurrent malaria. One child has died of pneumonia, for which basic care was unavailable, and the family cannot afford primary school fees. Even when he is well, the father's annual income is less than US\$320. The annual cost of disease-suppressive treatment for one person could have met most or all of the whole family's basic nutritional and educational needs, and paid for life-saving TB and pneumonia treatment. The father might even consider trading his medication to feed his family. What are the health spending priorities in this family, this community, this country?

Prevention of vertical transmission

Prevention of mother-to-child transmission (MTCT) would be a more efficient, and immediately feasible use of antiretroviral drugs than therapy. The amount of drug required is orders of magnitude smaller, and the benefit of preventing infection is qualitatively different from that of suppressing it.

Even so, there are a number of reasons MCTC prevention in resource-poor countries remains almost entirely limited to small pilot projects. The ultimate preventive benefit of the low-cost regimens after follow-up through the period of breast-feeding, has been modest. There was 15 percent transmission at follow-up to 18

months after delivery in the Ugandan nevirapine study.⁷ Prerequisites for implementation of MTCT prevention, which are currently lacking in many African settings, are a greatly strengthened obstetrical care system; acceptance of testing by women, their partners, and communities; widely available, accurate serologic testing; adequate qualified staff for counselling and testing; and assured procurement and distribution of antiretroviral drugs. The children whose lives are saved by this intervention are almost all at markedly increased risk of the nutritional, educational, and survival hazards of being orphaned in Africa, so that MTCT prevention programs need to be accompanied by enhanced supports for them. Finally, the difficulties of stopping the mother's therapy as soon as the child is born, and of treating only one member of the family, may also prove a challenge for MTCT programs in some communities.

Program requirements and non-drug costs

Aside from the purchase cost of antiretroviral drugs, there are also daunting problems posed by procurement, distribution, and management. A relevant parallel for many African countries is the national tuberculosis program. Tuberculosis treatment is completed in six months, the drugs cost less than US\$10 per course, and the annual number of patients in Zimbabwe is 50,000. In contrast, ART requires indefinite treatment, the drugs cost at least US\$320 per year, and a conservative estimate of ART candidates is 250,000 among 1.5 million HIV-infected people. Yet many countries in Africa, including Zimbabwe, are struggling to meet the human and material resource needs and organizational requirements of their TB programs. In other areas of many African healthcare systems, basic and inexpensive drugs are often "out of stock" due to shortage of management capacity, limited funds, and occasionally, theft or fraud. The risk of theft or fraud would be multiplied many times by the introduction of antiretroviral agents with their very high monetary value, into the drug distribution systems of very poor countries.

Treatment without current standard monitoring and other program elements

The striking benefits observed with ART in Western countries were obtained in treatment programs incorporating frequent viral load and CD4 cell count monitoring which has been considered an essential element of therapy.⁸ The cost and logistic requirements of these investigations comprise a major obstacle to the implementation of ART in sub-Saharan Africa. It has been proposed that most of the benefits of ART might be realized without them. This is an exciting, but unproven hypothesis. Studies to evaluate the efficacy of this strategy, and to determine the practical details of implementation will be necessary before large-scale programs can be based on it.

In TB treatment programs, practical and operational details, and program quality make the difference between success of greater than 95 percent in the best programs, versus cure rates as low as 11 percent.⁹ Similarly, in treatment of HIV infection, how treatment is delivered makes all the difference. Specially qualified doctors and nurses with multidisciplinary teams support adherence, manage adverse effects, address complex drug interactions, and provide other types of medical and psychosocial support in many "Western" HIV clinics. How much of this can we do without? At present, there is very little evidence to indicate how ART might be provided on a large scale in Africa, or to predict the likely magnitude or sustainability of benefits achievable under "field conditions" there.

Drug quality

Another lesson from the TB experience is the need for routine assessment of drug quality and bioavailability, especially when new suppliers are used.¹⁰⁻¹² The quality of drugs available in many low-income countries has been found to be highly inconsistent, particularly in the case of more complex products such as fixed-dose combination tablets for TB.¹³

The manufacture of some antiretroviral drugs is complex, and for some agents, the formulation is critical to adequate absorption. With current ART, there is very little "margin for error," so that relatively small reductions in bioavailability could lead to treatment failure and drug resistance. Bioequivalence studies on the generic products, proposed for use in ART programs, are not yet widely available.

Drug resistance

We are still at an early stage in our understanding of antiretroviral resistance in terms of how to measure it, its transmission, and particularly, its long-term population impact. In the United Kingdom, where most treatment has been delivered with frequent laboratory monitoring and expert supervision, 27 percent of newly diagnosed cases of HIV have laboratory evidence of key mutations associated with drug resistance, after about five years of population exposure to combination ART.¹⁴ Clinics in industrialized countries encounter increasing numbers of patients who are difficult to treat because of drug resistance. In low-income countries, resistance could lead to individual treatment failure, compromise a patient's future treatment options, limit the efficacy of community treatment programs, and even compromise the most cost-effective use of antiretroviral drugs such as prevention of mother-to-child transmission. The disastrous impact of multiple drug resistance in TB should prompt serious concerns about the potential for development of resistance in any ART program.

The impact of ART on attitudes of patients, healthcare workers, governments, and the public

It has been argued that the promise or hope of ART is needed to "Break the Silence" that stifles community response to HIV in southern Africa. While this is an attractive hypothesis, it is supported by few precedents. The major successes in HIV prevention, in Western gay men,¹⁵ Thai commercial sex workers and their clients,^{16,17} young women in Uganda,¹⁸ and others were achieved in the absence of access to ART. On the other hand, there are reports from Western countries,^{19,20} and anecdotal indications from Africa, suggesting that the perceived availability of effective treatment can *reduce* uptake of the prevention messages so vital to any effective response to the HIV epidemic. There is widespread concern that a focus on treatment may distract governments from the necessary commitment to HIV prevention—the natural tendency for clinical care to trump public health when spending decisions are made, is all the more likely to manifest in the context of an issue as emotive as ART.

Ultimately, acceptance of the premise that prevention is dependent on access to ART, implies an alarmingly defeatist attitude in respect to the prevention measures which are both essential and possible. Experience in many populations, including some in Africa, firmly contradicts the assertion that "we still have no good evidence that primary prevention works."²¹

Prevention is still the first priority. While there are 1.5 million Zimbabweans living with HIV infection, there are 6 million under the age of 15, of whom UNAIDS predicts that fewer than 30 percent will survive free of HIV infection, unless we dramatically improve our commitment to effective prevention measures.

Reducing transmission with ART?

It has been hypothesized, extrapolating from observational studies,²² that ART might reduce HIV transmission by lowering viral loads.²³ However, the proposed use of ART in Africa would involve initiation of treatment at a relatively late, symptomatic stage of infection so that treatment would be likely to affect only a small part of an individual's total lifetime transmission potential. A further concern is that modest negative changes in risk behaviour would overwhelm any positive effects from viral load reduction.²⁴

Care is essential

We must provide care for people with HIV infection for basic humanitarian reasons, and because fundamental principles of healthcare ethics demand no less. Moreover, while much is made of a conflict between care and prevention, the two are inextricably intertwined. Refusal of care would reinforce the stigma of HIV, adding greatly to the obstacles facing prevention.

Action

These cautions in regard to ART do not constitute a reason for inaction, but a call to action on a broader front. With the increased profile currently given to HIV by the press, the United Nations, and others, we have an opportunity that we cannot afford to miss, to reassess and reinvigorate global, national, and community responses to the HIV epidemic. Such a comprehensive response must include strong political leadership, open public discussion, commitment on a large scale to prevention of sexual transmission, systematic strengthening of prevention and treatment of sexually transmitted disease, and development of comprehensive programs for prevention of mother-to-child transmission. Other immediate priorities are enhanced basic medical and symptomatic care of people with advanced disease, and management of opportunistic infections, especially TB. A number of critical questions require rigorous scientific investigation that must involve creative collaboration between communities, healthcare workers, and scientists of North and South.

HIV and its treatment confront us with the human impact of the intolerable current levels of global disparity. We need to ensure that efforts to obtain drugs for one disease, however important it may be, do not detract from awareness of the enormous inequality that underlies Africa's health crisis. No drugs, however good or cheap, will cure the virus of inequity infecting the industrialized world's relations with Africa. Progress in remedying the structural causes of disparity, such as the insupportable debt burden and discriminatory trade rules, is essential to real, sustainable advances in health, including access to treatment for HIV.

This is a new field of advocacy and action for health workers, but it is where we belong. In addressing the twin problems of disease and inequality, members of the global community of healthcare workers are natural leaders, with the knowledge, credibility, and resources to influence public opinion and political decisions at an international level. ■

Acknowledgements:

I owe a debt of gratitude to Walter Kipp, MD, MPH, PhD, and Adam Houston who provided valuable insight, suggestions and criticism, and to Janet McDonald who carefully prepared the manuscript.

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Additional relevant resource:

A consensus statement by organizations delivering AIDS projects for the Canadian International Development Agency (CIDA). The opportunities and challenges of introducing anti-retroviral therapy (ART) in resource-poor settings. Online at http://www.cpha.ca/english/intprog/ART/ART_Consensus.pdf. Accessed March 8, 2002.

Targeted HIV treatment to sex workers to promote HIV prevention

A proposal for an HIV treatment public health initiative in countries without general access to anti-HIV drugs: Can we reduce HIV transmission by providing healthcare and HIV therapy to commercial sex workers? (Revised reprint from *IAPAC Monthly*, November 1998)

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The pandemic of HIV/AIDS and secondary tuberculosis has maintained its timetable. There have been some 60 million people infected with HIV, tens of millions dead, and tens of thousands of daily new infections that continue to fuel the pandemic. This represents about 1 percent of the world's population. Despite the World Health Organization's goal in the 1960's of "health for all by the year 2000," most infected people do not have a reasonable prospect of healthcare now or in any foreseeable future. The WHO's goal for HIV in developing countries is "five million treated by 2005." Who will pay? Where and how can we start?

One possible response is to design and implement an anti-HIV therapy program, and evaluate it for more than treatment alone in a developing country. The cost could be justified as a public health investment with measurable public health and economic benefits through the reduction of HIV infections. Simply put, the challenge is to find a way to benefit the entire population by HIV treatment limited to only a few. The first task is to believe that this is possible. The second task is to find a setting in which it is plausible. The third task is to cultivate the political will to implement and evaluate it. The context, design, conduct, and analysis of this study are tactical and technical tasks. The most difficult task may be to believe this is possible, because if we do not, we will never make the commitment to pursue it.

There are ecological differences in many localized HIV epidemics that are based on geography and demographics. AIDS is driven by a variety of factors like poverty, malnutrition, crowding, migration, social disruption of wars, and economic developments that create domestic poverty, as well as exportable wealth in many developing countries.

Many HIV epidemics have emerged from an older economy of bartering sex for food, shelter, security, money, drugs, and other basic, acquired or imposed needs. We cannot change the economic realities of life in such settings. Sexual prostitution on a sustained

industrial scale will continue to ignite and fuel HIV epidemics. With limited prospects for allocation of precious and scarce healthcare resources, how can we make a difference in the face of an avalanche of disease and death? We must carefully pick the battles that we can win. We must not simply fight for what is right in a losing battle that leaves us dead right. We live in a time of economic realities. It is necessary to demonstrate both the health and economic benefits of our healthcare strategies to justify the required investment into healthcare.

In the conduct of health research, we study nature in an effort to understand disease, but we also want to change the world for the better. We gain information, knowledge, and some understanding from our conceptual models of the driving forces in HIV epidemics in the cities of the developing world. However, we must now show some collective wisdom, since we have not yet changed anything globally, despite our vast resources.

As an example, a child at school has impetigo, a visible, messy, and contagious skin disease. The child's family cannot afford medical treatment. Social justice prohibits the child's exile to another class. So we take up a collection, and with respect for his or her dignity, we are able to treat the child. This respectful gift of treatment benefits all the other children in the classroom, and their families. It prevents the transmission of impetigo, and eliminates the subsequent cost of additional treatment of others.

The treatment of HIV infection has become more acceptable, tolerable, practical, effective and durable, if not more affordable. We have learned that other sexually transmitted diseases increase the shedding of HIV in sexual genital secretions and increase the contagion of HIV, just as the treatment of other sexually transmitted diseases can reduce the shedding of HIV and reduce the sexual contagion of HIV. We have learned that shedding of HIV in sexual secretions is related to the severity of HIV-related immune disease and the degree of

plasma viremia. We have learned that clinically effective treatment of HIV infection can reduce the shedding of HIV in sexual secretions. It is now time to turn from biologic study, and evaluate the potential impact of anti-HIV therapy on AIDS, and on the ecology of the HIV epidemic where the desired results are most likely and may be possible to measure.

We have studies to show that zidovudine monotherapy, even provided late in pregnancy, may reduce HIV transmission by two-thirds from mother to newborn during childbirth. This demonstrates the well-known human principle that the key to infant health is maternal health. We have one study to suggest that zidovudine monotherapy for men with HIV may reduce sexual transmission by half to female sexual partners. We now have therapy far more active than zidovudine, but we have not used it for such a likely effect.

In some settings, the natural economy of industrial scale urban prostitution results in HIV infection that is acquired and re-transmitted between a relatively small population of commercial sex workers and a larger number of their clientele. This produces a brisk, but initially confined or localized HIV epidemic. Through networks of changing sexual partners, the epidemic enters and grows, through the long latency and persistent contagion of HIV, in lower-risk but larger populations with less-frequent and less-likely exposure. Directly or indirectly, this affects everyone eventually. For the highest-risk, but smaller population which represents the leading edge or "core group" of the HIV epidemic, health promotion and safer sex practices are overshadowed by immediate survival needs that dictate the economics of prostitution. The customer is always right.

In such situations, healthcare, as well as human and civil rights of the very poor, is often disregarded. However, it is possible to provide healthcare to commercial sex workers based on their needs, and benefit the larger society of which they are a part. We need to convince the public payers of healthcare to treat commercial sex workers like human beings.

We have learned empirically that classic sexually transmitted diseases, such as syphilis and chancroid, have this same "core group" or reservoir epidemiology. These diseases can be controlled by the provision of healthcare targeted to persons who are at highest-risk, and who may be high-frequency transmitters. We have also learned that by treating other sexually transmitted diseases, we can reduce sexual HIV transmission. In a core group setting, the measured attributable risk for HIV to genital ulcer disease was over 50 percent. We have demonstrated that providing effective treatment of other sexually transmitted diseases can reduce the rate

of new HIV infections in a target population by 50 percent. Healthcare and public health priorities are often in competition for limited funds, but with this approach, there is potential health and economic synergy.

No one reasonably doubts that curative treatment of an infectious disease reduces the contagion, or that specific medical healthcare provided to those at the heart of an epidemic reduces secondary transmission and further dissemination. This is true for tuberculosis control, a far more contagious, but more treatable infectious disease, that has been the leading single cause of death in the world, and perhaps a single leading cause of death in people with AIDS. Yet we lack the political will, if not the organization and resources, to control this curable and preventable disease. The world is such a badly run place that at times one hardly knows where to complain. If we cannot manage tuberculosis in the face of all the distributive injustices of life, how can we hope to manage HIV? We must be strategic and humble at the same time. We must do what we can and, like the environmental movement, "think globally, and act locally."

So where might HIV therapy be both practical as healthcare and as HIV prevention? We need to look in places where healthcare resources are scarce, where HIV prevention has priority, and where we can identify the ecological core of HIV epidemics. These are settings in which there is the localized practice of large-scale prostitution, as well as the need and acceptance of healthcare. To say that healthcare for the poor in their daily struggle for survival is a lower priority than for those who are not poor, is unfounded and paternalistic. We can reach commercial sex workers and their clients if we meet their need for healthcare and treatment of other sexually transmitted diseases. We can use this opportunity to measure new HIV infections after exposure, both before and after an intervention with anti-HIV therapy in these groups. At the same time as we promote general health and safer sex in generalized and educational campaigns, there is the opportunity to provide general, sexual, and reproductive healthcare education that includes effective HIV therapies to those who need it. There is also the opportunity to measure the likely resulting beneficial reduction in HIV transmission in the larger population, including sex trade workers and their clients.

In this way, even in the poorest cities of developing countries, relatively small and affordable HIV treatment programs may be shown to have broad and general public health benefit, and calculable health economic impact. Treatment of a few, according to their needs rather than their means, may help many by effective HIV prevention. If an ounce of prevention is worth a pound of cure, then here and now with no cure, an ounce of treatment may produce a pound of prevention. ■

Diagnosis and management of infectious esophagitis associated with human immunodeficiency virus infection

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Abstract

Esophageal disease is a common complication and cause of morbidity in patients with human immunodeficiency virus (HIV) infection. Opportunistic infections are the leading cause of esophageal complaints and may be a predictor of poor long-term prognosis, presumably as a reflection of severe underlying HIV immunodeficiency. The esophagus may be the site of the first acquired immunodeficiency syndrome (AIDS)-defining opportunistic illness in a large number of patients. Barium esophagography and upper gastrointestinal endoscopy are diagnostic modalities, commonly used to evaluate esophageal complaints in patients with AIDS. Treatment for most etiologies of esophagitis generally has a high degree of success, with a resultant improvement in quality of life. In addition to optimizing antiretroviral therapy, a thorough diagnostic assessment of every HIV-infected patient with esophageal complaints is warranted, followed by timely and appropriate treatment.

Key words: AIDS, esophagitis, *Candida*, cytomegalovirus, herpes simplex virus

Introduction

Esophageal symptoms occur in 40 percent to 50 percent of patients with AIDS at some point in the course of their disease, and may have a significant impact on their nutritional status and morbidity.¹ Infections are the most common cause of esophageal disease, and the incidence of opportunistic disorders increases as immunodeficiency worsens. In the present era of highly active antiretroviral therapy (HAART), the clinical spectrum of esophageal disease is changing and the incidence of many opportunistic diseases appears to be decreasing. Although no controlled trials are available, extensive clinical studies

have shown that effective HAART (with consequent CD4 cell count recovery greater than 200/mm³) does result in prolonged remission of symptoms without a need for long-term secondary prophylaxis. Because almost all esophageal infections in HIV-infected patients are treatable, a thorough evaluation is recommended. However, diagnostic modalities, such as barium esophagography and endoscopy, may not be widely available in developing countries where this complication of HIV disease is most prevalent, and where management and treatment may frequently be syndromic or empiric. Treatment is usually rewarding, although the long-term prognosis is primarily dependent on the severity of HIV infection and the accompanying degree of immunodeficiency.

This article reviews the various infectious etiologies of esophagitis in HIV-infected patients, their clinical manifestations, diagnostic modalities involved, and provides an algorithmic approach for empiric and specific therapy, as well as prophylaxis.

Etiology

Opportunistic infections represent the most common etiology of symptomatic esophageal disease in HIV-infected individuals. Candidiasis is the most common infectious cause of esophagitis, occurring in 50 percent to 79 percent of symptomatic patients.^{1,2} Besides *Candida albicans*, several other species, including *C. tropicalis*, *C. krusei*, *C. dublinensis*,³ *C. parapsilosis*, and *C. glabrata*, have been associated with oral and esophageal disease in HIV-infected individuals. Esophageal candidiasis often occurs concurrently with other infectious esophageal disorders. In a review of 57 patients with AIDS and *Candida* esophagitis, 22 patients had coexistent cytomegalovirus (CMV) while 2 patients had *Candida* with CMV and herpes simplex virus (HSV).¹ Fungi other than *Candida* involve the esophagus rarely, and include *Histoplasma capsulatum*,⁴ *Exophiala jeanselmei*,⁵ and *Penicillium chrysogenum*.⁶

The most common viral pathogen that causes esophageal disease in patients with AIDS is cytomegalovirus, seen in 10 percent to 40 percent of endoscopic biopsies of

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JIA PAC 2002;1(2):53-62. © 2002 IAPAC.

esophageal lesions.⁷ CMV and *Candida* may coexist in up to 20 percent of the patients. Although a frequent cause of esophagitis in immunosuppressed transplant patients and commonly causing oral disease, herpes simplex virus type I (HSV I) appears to be an uncommon primary esophageal pathogen. In a prospective study of 100 HIV-infected patients with ulcerative esophagitis, HSV I esophagitis was only identified in 5 percent, in contrast to a 50 percent prevalence of CMV disease.⁸ Less commonly occurring viral pathogens include Epstein-Barr virus,⁹ papovavirus,¹⁰ and human herpes virus 6.¹¹ To date, varicella zoster virus (VZV) esophagitis has only been reported in patients without AIDS, although patients with AIDS do develop recurrent VZV infection and are certainly at risk for esophageal manifestations.¹²

Bacterial and mycobacterial (*Mycobacterium tuberculosis*, MTB¹³ and *Mycobacterium avium* complex, MAC¹⁴) esophageal involvement are uncommon in HIV-infected patients. MTB can complicate HIV disease at all stages of immunodeficiency, while MAC infection is generally limited to those with CD4 cell counts below 100/mm³. Esophageal involvement by *Nocardia*¹⁵ and *Bartonella henselae*¹⁶ (bacillary angiomatosis) has also been reported. Actinomyces can cause superinfection of esophageal ulcers or primary esophageal infection.¹⁷ Extremely rare protozoal causes of esophagitis include *Cryptosporidium parvum*,¹⁸ *Pneumocystis carinii*,¹⁹ and *Leishmania*.²⁰

Idiopathic esophageal ulceration (IEU) is a significant problem in HIV-infected patients. These ulcers are almost as frequent as CMV esophagitis, comprising about 40

percent of ulcers in these patients.² The pathogenic role of HIV in IEU is unclear. Studies have shown that, although HIV viral particles and genome can be shown in the esophagus of these patients, HIV is unlikely to be playing a causal role in every esophageal ulcer. The presence of HIV in esophagitis or esophageal ulcers is incidental to the underlying opportunistic pathogens causing the esophagitis or ulcers.²¹

Lymphoma and Kaposi's sarcoma are the most common HIV-related neoplastic lesions found in the esophagus. Most patients with AIDS take a variety of common medications, any one of which can cause esophagitis. Among the antiretroviral medications, zidovudine (AZT)²² and zalcitabine (ddC)²³ have been reported to cause esophageal ulceration. Patients should be advised to take oral medications in the upright position with water to ensure complete ingestion.

Finally, gastroesophageal reflux disease (GERD) is uncommon in HIV-infected patients. The reason for this low prevalence is not fully known. It may partly be related to hypochlorhydria, which has been described as occurring in about 25 percent of patients with late-stage disease.²⁴ However, several later reports have found acid production to be normal in HIV-infected patients.^{25,26}

Clinical presentation

The most common esophageal symptoms described by patients with HIV infection are dysphagia (sensation of food "sticking" in the retrosternal area), and/or odynophagia (painful swallowing). The absence of these symptoms

Table 1. Presenting signs and symptoms of HIV-infected patients with esophageal infection

<i>Signs and symptoms</i>	<i>Candida</i>	<i>CMV</i>	<i>HSV</i>	<i>MTB</i>	<i>HIV/IEU</i>
Dysphagia	Very common	Common	Common	Common	Occasional
Odynophagia	Common	Almost always present	Very common	Occasional	Very common
Oral ulcers	Rare	Occasional	Common	Occasional	Occasional
Thrush	Very common	Occasional	Occasional	Occasional	Occasional
Nausea/vomiting	Rare to Occasional	Common to Very common	Occasional to Common	Rare	Rare
Bleeding	Rare	Occasional to Common	Occasional	Rare	Occasional
Abdominal pain	Occasional	Common	Rare	Rare	Occasional
Weight loss	Occasional	Common	Occasional	Common	Common
Fever	Rare	Common	Common	Common	Occasional
Cough	Rare	Rare	Rare	Common	Rare
Diarrhea	Rare	Common	Rare	Rare	Occasional
Rash	Rare	Not reported	Not reported	Not reported	Common
Asymptomatic	Common	Rare	Rare	Rare	Rare

Note: CMV=cytomegalovirus; HSV=herpes simplex virus; MTB=*mycobacterium tuberculosis*; HIV/IEU=HIV-associated idiopathic esophageal ulceration

should not be used as evidence against esophageal infection.¹² Uncommonly, esophageal involvement may present with singultus (hiccups), chest pain, and gastrointestinal bleeding.²¹ Table 1 shows the presenting signs and symptoms of HIV-infected patients with different esophageal infections.

The chief presenting characteristics of esophageal candidiasis are dysphagia and odynophagia, with heartburn or retrosternal pain less commonly reported. However, the infection can be completely asymptomatic. In a prospective study by Porro et al, 10 out of 25 patients (40 percent) with AIDS and *Candida* esophagitis were found to be asymptomatic. When persistent nausea and vomiting, abdominal pain, gastrointestinal bleeding, fever, cough, or diarrhea are present, *Candida* is unlikely to be the only infecting organism²⁷ (see Table 1). Physical examination may reveal lesions of thrush (oropharyngeal candidiasis), which according to one large series, has a positive predictive value of 90 percent for esophageal candidiasis. However, thrush may be absent in one-third of patients with endoscopically documented candidiasis. Oropharyngeal candidiasis is consequently considered to be a moderately useful diagnostic marker for *Candida* esophagitis.²⁸ Although the infection may occur at any stage of HIV infection, it is usually seen in patients with a CD4 count less than 200/mm³, with approximately 90 percent of patients having a CD4 count less than 100/mm³. Esophageal candidiasis has been reported during primary HIV infection (HIV seroconversion syndrome).²⁹⁻³¹ It is associated with a transient but severe decrease in the percentage and absolute number of CD4⁺ cells, and with an increase in the absolute number of CD8⁺ cells. Spontaneous resolution of the esophagitis has also been reported in patients seroconverting for HIV antibodies.³²

CMV esophagitis differs in its clinical presentation from other infections. Along with idiopathic esophageal ulceration, it is the most common cause of esophageal ulcerations in HIV-infected patients. Odynophagia is the principal manifestation, while dysphagia is distinctly uncommon, in contrast to *Candida* esophagitis. Nausea, vomiting, fever, epigastric pain, diarrhea, and weight loss have commonly been reported, reflecting the systemic nature of CMV infection.^{33,34} The incidence of CMV disease increases with CD4 cell count less than 100/mm³. Concurrent oropharyngeal ulcerations are uncommon, but thrush is often present. CMV may coexist with *Candida* and/or HSV infections, but the mere presence of CMV cannot be equated with clinical CMV esophagitis, although it may be a predictor of serious extraesophageal infection. In one study, it has been demonstrated that patients with esophagitis and evidence of concomitant *Candida* and CMV infections (by culture or histology), improved with antifungal

therapy alone, regardless of treatment with antiviral agents.³⁵

HSV esophagitis usually presents with an acute onset of severely painful and difficult swallowing. Nausea, vomiting, hematemesis, and fever may be present, although systemic and intra-abdominal symptoms are uncommon. Oral, labial, or cutaneous HSV is evident in only 19 percent to 38 percent of patients.³⁶ The absence of mucocutaneous herpes does not in any way rule out the diagnosis of herpetic esophagitis. As with CMV, HSV esophagitis becomes increasingly common with CD4 cell count less than 100/mm³, and the incidence rises sharply with counts less than 50/mm³. Complications of herpetic esophagitis, including fatal hemorrhage,³⁷ esophageal perforation with tracheoesophageal fistula formation,³⁸ and diffuse visceral dissemination,³⁹ have been reported.

Idiopathic esophageal ulceration generally occurs with severe immunodeficiency, with the median CD4 count less than 50/mm³ in most patients.^{3,40} As with other causes of ulcerative esophagitis, severe odynophagia is the predominant symptom, often accompanied by chest pain, dehydration, and weight loss. Painful, self-limited IEUs have been reported during acute HIV seroconversion syndrome.⁴¹ A macular erythematous lesion is frequently seen in this setting. The diagnosis of IEU should essentially be one of exclusion, and is made after more common infectious etiologies have been ruled out.

Mycobacterium tuberculosis usually causes esophageal symptoms due to erosion of a contiguous mediastinal lymph node into the esophagus.⁴² Reported complications have been fistulae between the esophagus and the tracheobronchial tree,¹³ and esophageal perforation.⁴³ Although *Mycobacterium avium* complex is often widely disseminated in patients with AIDS and also colonizes the gastrointestinal tract, clinical esophageal disease caused by mucosal invasion is unusual. Clinical features of MAC esophagitis can include fever, weight loss, dysphagia and/or odynophagia. Esophageal ulcerations and esophagomediastinal and bronchial fistulae have been described with MAC esophagitis.^{12,14}

Diagnosis

Radiographic evaluation: Radiographic studies are relatively insensitive in establishing an etiologic diagnosis of esophageal infection. Although some features may be unique to these infectious processes, barium esophagography is too often non-specific, necessitating endoscopic evaluation in symptomatic patients. *Candida* esophagitis usually presents with focal or confluent plaques or a diffuse "shaggy" appearance. Esophagograms may appear normal or, alternatively, have non-specific abnormalities such as stricture, ulceration, polyps, or

Table 2. Endoscopic findings of common esophageal infections in HIV-infected patients

<i>Finding</i>	<i>Candida</i>	<i>CMV</i>	<i>HSV</i>	<i>Mycobacteria</i>	<i>IEU</i>
Ulceration	Rare	Almost always present	Common to Almost always present	Common	Almost always present
Plaque	Almost always present	Rare	Rare	Rare	Not reported
Fistula	Rare*	Occasional	Rare to Occasional	Common	Rare
Stricture	Rare*	Occasional	Occasional	Occasional	Rare
Polypoid nodule/mass	Rare to Occasional	Rare	Rare to Occasional	Occasional	Rare

Note: CMV=cytomegalovirus; HSV=herpes simplex virus; IEU=idiopathic esophageal ulceration;
* usually represents *Candida* colonization of these anatomic abnormalities caused by other underlying disorders

fistula formation.⁴⁴ HSV esophagitis is usually associated with multiple, stellate ulcerations in mid-esophagus (less than 1.5 cm in diameter), whereas CMV esophageal ulcers are characteristically quite large and may be single or multiple.¹⁹ Ulcers within plaques should suggest herpetic infection or concomitant herpes and *Candida* esophagitis.⁴⁵ As with CMV, IEU can result in one or multiple, well-circumscribed ulcers of variable depth.⁴² Esophagitis secondary to *Mycobacterium tuberculosis* may be suggested by the presence of fistulas to the mediastinum with or without esophageal ulcerations.¹³ Fistulization is not unique to *Mycobacterium tuberculosis*, and may result from MAC, CMV, or rarely *Candida* infection.²

Endoscopic evaluation and microbiologic diagnosis: Endoscopy is the most valuable technique in the evaluation of esophageal symptoms in HIV-infected patients. Table 2 summarizes the endoscopic findings seen in various esophageal infections. Multiple biopsies of any lesion (of both the base and margins in case of an ulcer) should be obtained. Various studies have suggested that at least ten biopsy specimens of an esophageal ulcer should be obtained in order to exclude a viral etiology in HIV-infected patients.^{8,42} The exact number of biopsies required from an esophageal ulcer is not well-established. The standard practice is to obtain at least six biopsy specimens, although the sensitivity of diagnostic biopsy is dependent on the number of biopsies.

The endoscopic appearance of candidiasis resembles cheesy friable plaques that may involve the entire esophagus, occasionally causing luminal obstruction. It rarely causes ulcers. Biopsy of an ulcer in the patient with *Candida* esophagitis is necessary to identify coexisting pathogens like CMV, or to suggest an idiopathic cause.⁴² A definitive diagnosis is established by esophageal brushings with subsequent fungal staining or by mucosal biopsy. Budding yeast cells, and pseudohyphae are best seen by silver stain, periodic acid-shiff (PAS) stain, or gram stain and are diagnostic of *Candida* infection.¹² Balloon cytology is another useful tool for

the evaluation of *Candida* esophagitis.⁴⁶ The use of this technique is becoming increasingly widespread due to potential diagnostic and therapeutic implications to either identify or exclude coexistent processes. It should be remembered that detection of *Candida* does not exclude concurrent infectious etiologies, which should specifically be looked for in patients.

CMV esophagitis most commonly results in one or more, large (greater than 10 cm²), shallow or deep, "punched-out" ulcers, located in the middle to distal half of the esophagus.⁴² In contrast to HSV infection, complete esophageal denudation is unusual. Histopathologic examination is the most reliable diagnostic method. Characteristic histologic features include large cells in the subepithelial layer with intranuclear inclusions, a peri-nuclear halo, and cytoplasmic inclusions.¹² Viral culture of biopsy material is not useful in diagnosis since cultures are frequently positive when there is no histologic evidence of CMV and vice versa. This is likely due to contamination of esophageal specimens by virus harbored in blood or saliva. Immunohistochemical staining (for early, intermediate, and late antigens), and direct fluorescent staining techniques are highly specific for the diagnosis of CMV and HSV infections. According to a study by Goodgame et al, CMV was identified by immunoperoxidase stain in only 50 percent of lesions with cytomegalic cells.⁴⁷

HSV lesions appear endoscopically as multiple, small, superficial ulcers in the distal third of the esophagus, which may have raised margins around a central crater ("volcano ulcers").^{42,45} Alternatively, a diffuse and erosive esophagitis may be seen. Although the presence of small vesicles is commonly seen in immunocompetent hosts, this finding is unusual in HIV-infected patients.⁵ HSV is usually readily identified on biopsy, cytology, or culture. Overall, viral culture is more sensitive than microscopic examination for the diagnosis of HSV infection.³⁶ Diagnostic histologic features include multinucleated giant cells and intranuclear Cowdrey type A inclusion bodies, but cytoplasmic inclusions are

Table 3. Treatment regimens for common esophageal infections in HIV-infected patients

<i>Etiology</i>	<i>Usual therapy (Adult dose)</i>	<i>Alternative drugs</i>
<i>Candida</i>	Fluconazole, 100-200 mg/day PO for 14-21 days	Itraconazole, 200 mg/day PO for 7-14 days Ketoconazole, 200-400 mg/day PO for 7-14 days Amphotericin B, 0.5 mg/kg/day IV for 7 days
CMV	Ganciclovir, 5mg/kg BID IV for 2-4 weeks	Foscarnet, 90 mg/kg BID IV for 2-4 weeks
HSV	Acyclovir, 5 mg/kg q8h IV followed by 400 mg 5 times a day PO for a total of 14 days	Valacyclovir, 1g TID PO for 14 days Famciclovir, 500 mg TID PO for 14 days Foscarnet, 60-90 mg/kg BID IV for 14 days (used if acyclovir resistant)
IEU	Prednisone, 40 mg/day PO for 14 days, then taper (decrease 10 mg/week) for a total of 4 weeks	Thalidomide, 200 mg/day PO for 4 weeks

Note. CMV=cytomegalovirus; HSV=herpes simplex virus; IEU=idiopathic esophageal ulceration; PO=per oral (orally); IV=intravenously; BID=twice a day; TID=three times a day

typically absent.¹² As with CMV, immunohistochemical staining may increase diagnostic specificity.

Idiopathic esophageal ulceration appears endoscopically as one or multiple well-circumscribed ulcers of variable depth, with normal intervening mucosa.⁴⁰ A diffuse superficial esophagitis has not been described. Histopathologically, the ulcer tissue resembles that of CMV and HSV except viral cytopathic effect is absent. IEU and CMV esophagitis are indistinguishable clinically, radiographically, and endoscopically. Multiple biopsies of an ulcer are necessary to exclude infectious etiologies.

Tuberculous lesions usually appear as shallow ulcers with a necrotic base, ranging in size from small mucosal defects to large linear ulcerations. Probing the ulcer base may reveal a fistulous tract. Alternatively, the only endoscopic feature may be an extrinsic compression of the lumen, with no mucosal lesions.⁴⁸ Specimens from biopsied lesions should be sent for acid-fast stain and mycobacterial culture, in addition to routine histologic studies.

Treatment

Candidiasis: Unlike oropharyngeal disease, non-systemic therapy (eg, nystatin and clotrimazole troches) is mostly ineffective in the treatment of *Candida* esophagitis. Of the antifungal agents, three drugs have been extensively investigated and used: ketoconazole, fluconazole, and itraconazole (see Table 3). Randomized trials have shown fluconazole to be superior to capsules of ketoconazole⁴⁹ and itraconazole⁵⁰ for esophageal candidiasis, making it the antifungal agent of choice. The stated superior efficacy of fluconazole and itraconazole over ketoconazole might be qualified by the greater speed of response, or apparent potency of the former over the latter, while their relative difference in effectiveness may not be so great. As the absorption of

ketoconazole and itraconazole is pH-dependent, these agents should be avoided in patients requiring anti-acid therapy, especially in view of some degree of hypochlorhydria seen in patients with AIDS. Ketoconazole and itraconazole are known to have interactions with commonly prescribed drugs like terfenadine, cisapride, ritonavir, indinavir, saquinavir, carbamazepime, phenytoin, phenobarbital, and the rifamycins.⁴² The response rate with fluconazole tends to be very rapid, with most patients experiencing significant clinical improvement within five days. An important therapeutic issue is the optimal duration of therapy before considering the patient a non-responder. Wilcox et al have suggested that assessment as early as one week may be accurate in predicting those patients who are likely to have underlying ulcerative esophagitis.⁵¹ Oral solution forms of both fluconazole and itraconazole are available. Greater efficacy has been inferred for the itraconazole oral solution over the capsules. Oral solution has been shown to be equivalent to fluconazole in the management of esophageal candidiasis.⁵² The same equivalence has not been demonstrated for itraconazole capsules. Similarly, for fluconazole-refractory oral candidiasis, itraconazole solution appears to have greater efficacy. The oral solution formulations also have an additional topical antifungal effect.⁵³

Azole-resistant strains of *Candida* are an emerging problem. Risk factors for acquiring resistance include advanced immunosuppression, relapsing oropharyngeal candidiasis with repeated courses of treatment, and chronic (maintenance) suppressive therapy with azole drugs.⁵³ Resistance may in some cases be overcome by increasing the dose of the azole, but switching to amphotericin B (either topically or as a last resort intravenously) may be required in some cases.⁴² Some of the investigational azoles hold promise for the management of fluconazole-refractory oral candidiasis,

including posaconazole and voriconazole. Optimal antiretroviral therapy, possibly by increasing the CD4 cell count and immune function, may also lead to clearance of refractory candidiasis.

Amphotericin B is effective against all strains of *Candida*. Due to its toxicity profile, it is generally reserved for oropharyngeal and/or esophageal candidiasis that has shown clinical or microbiologic resistance to one of the azole agents.⁵⁴

Cytomegalovirus: Antiviral agents available for CMV esophagitis include intravenous ganciclovir, foscarnet, and more recently, cidofovir. Due to its efficacy, tolerability, and cost, ganciclovir is usually the first-line therapy. Oral ganciclovir has been evaluated mainly in the setting of maintenance therapy of AIDS-related CMV retinitis. Its efficacy for induction therapy for any of the forms of CMV disease is unknown but doubtful, given its low bioavailability and sub-optimal blood levels compared to intravenous ganciclovir. Ganciclovir has been shown to cause significant neutropenia in 25 percent to 68 percent of patients, and thrombocytopenia in 5 percent, necessitating discontinuation of therapy, especially in patients who are also on AZT.⁵⁵ This problem can be treated with addition of granulocyte colony-stimulating factor or by substituting ganciclovir with foscarnet. Valganciclovir, an oral pro-drug of ganciclovir, is a newer agent that has a much higher bioavailability than oral ganciclovir. It is presently being used for the treatment of CMV retinitis in patients with AIDS and will likely prove to be effective in the treatment of CMV esophagitis in the future. Foscarnet also represents an effective treatment for cases that are refractory to ganciclovir. Due to its ability to inhibit the reverse transcriptase of HIV-1, the effect of AZT and foscarnet on HIV may be additive.⁵⁵ This possible additive antiviral effect of foscarnet appeared to be encouraging in the pre-HAART era, but it is outweighed by the current available array of antiretrovirals that have considerably greater potency and much less toxicity. The principal side effects of foscarnet include renal toxicity and electrolyte disturbances such as hypocalcemia and hypophosphatemia. Adequate hydration with saline prior to drug administration can be helpful in preventing renal dysfunction. Seizures and genital ulcers are less commonly reported side effects.⁵⁶ Cidofovir is effective for CMV retinitis and recent case reports have documented its efficacy for esophageal disease.⁵⁷

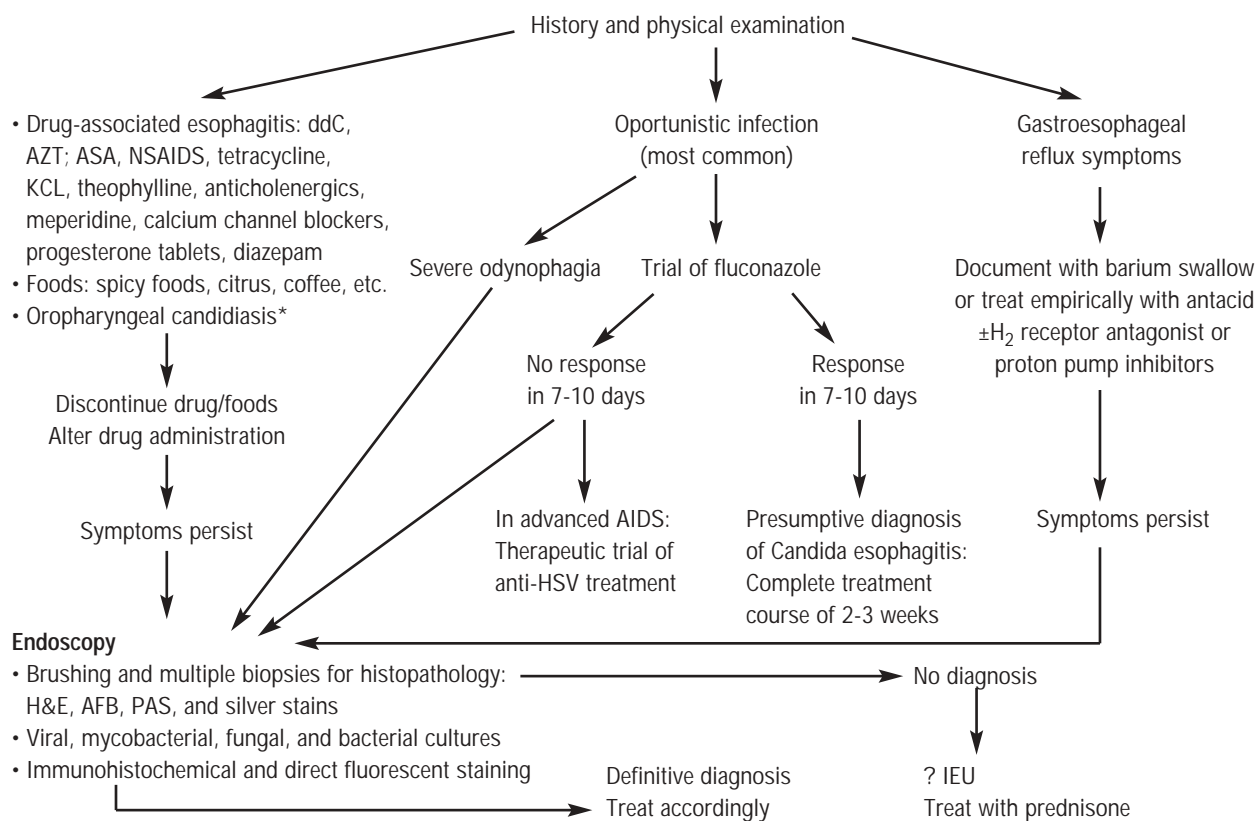
A commonly used policy is to administer intravenous ganciclovir, assuming there are no major contraindications such as pancytopenia. Most patients respond clinically within first week of therapy, and the relapse rate of 30 percent to 60 percent is similar for esophageal and colonic CMV disease.⁵⁸ This relapse rate was identified

in the pre-HAART era, and may have declined considerably with the effective use of HAART. Ophthalmologic examination is mandatory at the time of diagnosis of CMV infection to exclude retinal disease. If retinal disease is absent and a complete symptomatic and endoscopic response is documented after induction, therapy is stopped and the patient observed. Endoscopic re-examination with biopsy of any mucosal abnormality is indicated in those patients who continue to have persistent symptoms following therapy. For patients with major contraindications or failure to respond to ganciclovir, foscarnet is usually effective. Combination therapy with ganciclovir and foscarnet may be as effective as induction therapy and maintenance therapy with a single drug, and is also efficacious for ganciclovir failures.^{59,60} For patients with the first episode of CMV esophagitis and relapses of it, anti-CMV therapy and an emphasis on initiating or revising HAART is recommended to attempt partial immune reconstitution, rather than considering poorly tolerated and aggressive combination therapy with ganciclovir and foscarnet.

Herpes simplex virus: HSV esophagitis should be initially treated with intravenous acyclovir. Therapy with oral acyclovir may then be continued for a total of two weeks.⁶¹ Famciclovir and valacyclovir are equally effective oral agents. Complete resolution is reported in 70 percent of patients treated with acyclovir, but relapse occurs in 15 percent within four months.³⁶ Due to its side effects, foscarnet is generally reserved for patients with acyclovir resistance. Although ganciclovir may not have proven efficacy in this setting, this does not necessarily imply inefficacy.

Idiopathic esophageal ulcer: HIV-infected patients with IEUs have improved on systemic steroid therapy in more than 90 percent of cases.⁶² Because oropharyngeal and/or esophageal candidiasis may complicate steroid use and confuse the therapeutic response, short courses of concomitant azole therapy are recommended.⁵ Steroids may also increase the risk of clinical CMV disease in patients with AIDS.⁴² Before contemplating steroid therapy, a thorough search for treatable infectious etiologies must be undertaken. Recently, thalidomide, which has immunomodulatory activity, has been reported to improve IEUs in HIV-infected patients.⁶³ However, the drug has not been approved for this indication. Common side effects of thalidomide include somnolence, peripheral neuropathy, and a skin rash. Use in pregnancy is contraindicated because of a strong association with birth defects. Regardless of the initial therapy, the relapse rate of IEU is approximately 40 percent to 50 percent.⁵⁸ It is quite likely that this figure has declined considerably in the present HAART era, but this is not well-described.

Figure 1. Suggested algorithm for initial diagnosis and management of new-onset esophageal symptoms in HIV-infected patients



* Oropharyngeal candidiasis may have a positive predictive value ($\leq 90\%$) for esophageal candidiasis, although thrush may be absent in one-third of patients with esophageal candidiasis.

Mycobacteria: In the absence of drug resistance, a nine-month course of multi-drug therapy generally cures esophageal tuberculosis and often closes fistulas. If fistulas do not close with medical therapy, surgical intervention is required.⁵⁴ MAC is difficult to treat and requires long-term therapy. Commonly used agents include clarithromycin, ethambutol, amikacin, ciprofloxacin, and rifabutin. Current recommended therapy for MAC is a combination of clarithromycin plus ethambutol. Amikacin and ciprofloxacin are second-line agents, which seldom need to be considered except in the setting of clarithromycin-resistant MAC disease. It has been shown that a macrolide (clarithromycin)-containing multi-drug regimen is superior to a non-macrolide containing regimen in the treatment of MAC disease.⁶⁴

Prophylaxis

Despite the frequency of oropharyngeal and esophageal candidiasis in HIV-infected patients, primary prophylaxis is not widely administered. These disorders are not life-threatening, therapy is usually very effective, and there is concern that widespread use of primary prophylaxis will exacerbate the problem of drug resistance.⁵ Secondary

prophylaxis (with fluconazole 50 to 100 mg/day or 150 mg once weekly) is commonly given for patients with multiple recurrences of oropharyngeal and/or esophageal candidiasis. For CMV disease, primary prophylaxis with oral ganciclovir has been recommended with severe immunodeficiency (CD4 cell count less than 50/mm³). Although efficacious in the prophylaxis of CMV retinitis, no definite data exist on the effectiveness of primary prophylaxis for decreasing gastrointestinal CMV disease in HIV-infected patients.⁶⁵ Secondary prophylaxis with intravenous ganciclovir or foscarnet did not affect disease progression among HIV-infected patients with gastrointestinal CMV disease.⁶⁶ Primary prophylaxis against HSV disease is not currently recommended. Patients with frequent relapses of genital, oropharyngeal, or esophageal disease usually benefit from secondary prophylaxis with acyclovir (400 to 600 mg daily).⁶¹

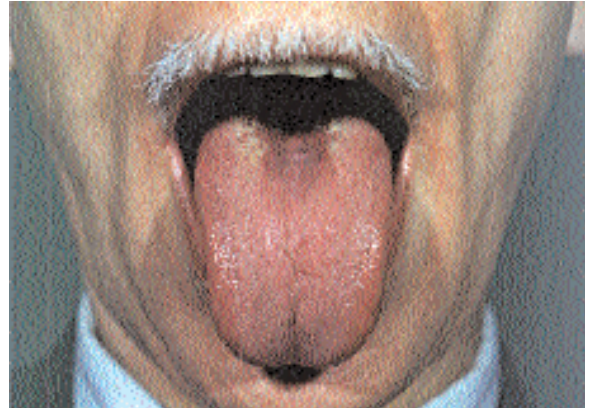
Management of the HIV-infected patient with esophageal disease

In the HIV-infected patient presenting with new onset esophageal symptoms, history and physical examination may help in formulating a rational approach toward

Gallery. Oral candidiasis has more than one clinical appearance, which may coexist. These clinical photographs identify four manifestations.



Palatal erythematous candidiasis (note the satellitism)



Median glossitis, or atrophic lingual candidiasis



Angular cheilitis (also seen with vitamin B12 deficiency, or as herpes labialis)



Diffuse pseudomembranous oral candidiasis

Photos courtesy of D. William Cameron

management (Figure 1). Patients should be questioned about the use of any medications linked to drug-induced esophagitis, such as AZT, ddC, aspirin, NSAIDS, particularly at bedtime or prior to assuming the supine position for prolonged periods. Discontinuation of the drug or a change in its administration may benefit the patient. Physical examination may reveal oropharyngeal candidiasis or CMV retinitis, suggesting esophageal involvement by these pathogens.

Because candidiasis is the most common cause of esophageal disease in AIDS, an empiric trial of fluconazole is commonly used for new onset esophageal complaints in these patients.^{2,5,51,53} This approach may not be appropriate for patients with severe odynophagia, since such individuals are more likely to have ulcerative lesions present. A loading dose of 200 mg/day followed by 100 mg/day for a 14- to 21-day period is usually given. A prospective study comparing empirical fluconazole with

endoscopy has shown the former to be the best initial management, documenting safety and effectiveness.⁵¹ If symptoms abate, the diagnosis of candidiasis can be established empirically. The failure of symptoms to respond by day seven of empirical therapy necessitates further diagnostic testing, preferably endoscopy with mucosal biopsy. Most patients who do not respond to antifungal therapy have esophageal ulceration, rather than evidence of persistent esophageal candidiasis. If *Candida* is the only pathogen identified during endoscopy, then fluconazole is usually continued. If symptomatic improvement does not follow fluconazole therapy within a few weeks, the patient should undergo another endoscopy, and amphotericin B should be given if *Candida* is again the only pathogen identified.⁶⁷ Antifungal drug susceptibility testing may be useful at this point, in view of possible azole-resistant candidiasis, although the technique is not available in all microbiology laboratories. The predictive value of susceptibility data for individual patients can

be influenced by various host and pharmacokinetic factors, and *in vitro* susceptibility does not always predict successful therapy. Overall, clinical usefulness of antifungal susceptibility studies is limited.⁵³

Endoscopy is recommended for all HIV-infected patients with symptoms refractory to antifungal therapy or with upper gastrointestinal bleeding. According to a study by Bashir et al, symptom-specific use of endoscopy, particularly in patients with refractory symptoms such as odynophagia and upper gastrointestinal bleeding, had the highest diagnostic yield with a corresponding response to therapy.⁶⁸ Endoscopy was found to be less useful for the evaluation of abdominal pain or nausea and vomiting. Overall, pathologic findings were identified in refractory esophageal symptoms (82 percent), upper gastrointestinal bleeding (92 percent), abdominal pain (39 percent), and nausea and vomiting (27 percent). In addition, a CD4 cell count less than 100/mm³ was found to be an independent predictor of opportunistic disorders diagnosed by endoscopy, with a sensitivity of 98 percent and a positive predictive value of 83 percent.⁶⁸

The use of empirical antiviral therapy, such as acyclovir and ganciclovir, has not proven to be safe and effective and should be discouraged.⁶⁹ Treatment regimens for CMV and HSV esophagitis have been discussed earlier. As a general rule, lesions that do not respond to appropriate therapy should be re-evaluated by endoscopy with biopsy and culture to confirm the diagnosis, and if indicated, to perform drug susceptibility testing. Additional diagnostic procedures are usually not required, but may be useful in special circumstances when there is a clinical suspicion of esophageal dysmotility.

In patients who present with symptoms suggestive of gastroesophageal reflux, an empirical trial of H₂-receptor blockers or proton pump inhibitors is warranted. If no pathogen is found on multiple adequate biopsies of an esophageal ulcer, and after thorough review by an experienced pathologist, the patient could be treated with oral prednisone 40 mg/day which can be tapered to 10 mg/week after symptoms improve.⁴² Treatment of underlying HIV disease remains an important adjunct to therapy for any esophageal disorder. ■

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A clinical review of micronutrients in HIV infection

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Abstract

This article reviews current literature on the role of micronutrients in human immunodeficiency virus (HIV) infection. Deficiencies of micronutrients are common in HIV-infected persons. They occur due to malabsorption, altered metabolism, gut infection, and altered gut barrier function. There is a compelling association of deficiencies of micronutrients in HIV-infection with immune deficiency, rapid disease progression, and mortality. Also, there is increased risk of vertical HIV transmission from mother to child with deficiency of vitamin A, and of neurological impairment with vitamin B₁₂. The last five years have been exciting in micronutrient research, and there is promise that some micronutrients may be key factors in maintaining health in HIV immunodeficiency, and in reducing mortality. Selenium appears important in reducing virulence of HIV and slowing disease progression. Vitamin A supplementation in pregnant women with HIV may reduce maternal mortality and improve birth outcomes. Supplementation in children with HIV may accelerate growth. Carotenoid supplementation is being evaluated. Vitamin B₁₂ may slow HIV immune deficiency disease progression, and reverse neurological compromise. Clinical benefit of supplementation with some micronutrients may be measurable in the presence of pre-existing deficiency. Apart from improved general nutrition, the impact of micronutrient supplements on health and their optimal use in HIV infection is controversial because there are so few controlled clinical trials. Further research is needed to elucidate the role of micronutrient deficiencies on the course of HIV infection, and the preventive and therapeutic role of supplementation in its clinical management. Nevertheless, current knowledge supports the use of routine multivitamin and trace element supplementation as adjuvant to conventional antiretroviral drug treatment as a relatively low-cost intervention.

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JIAPAC 2002;1(2):63-75. © 2002 IAPAC.

Key words: AIDS, HIV, micronutrients, trace elements, vitamins

Introduction

In recent years, the importance of nutrition in human health has received growing attention. Therapeutic and preventive supplementation with vitamins has been used successfully for a long time for many clinical conditions. This includes vitamin A for maintenance of vision, beta-carotene in erythropoietic protoporphyria, vitamin C in scurvy, niacin in pellagra, and others. *In vitro* and animal studies have shown immunostimulatory and anti-cancer properties of several micronutrients, leading to several large epidemiological trials of micronutrient supplementation. However, these trials did not show effect on incidence and outcomes of cancer, stroke, and heart disease.¹⁻⁴ Nonetheless, a protective effect of combined supplementation with beta-carotene, vitamin A, and selenium on incidence of stroke was seen in an undernourished population in China.⁵

Supplementation with vitamin A has reduced morbidity and mortality from childhood infectious diseases, such as measles, diarrhea, and acute respiratory infections.⁶⁻¹⁰ In trials of zinc supplementation, significant reductions were seen in severity of diarrhea, acute respiratory infections, and malaria.¹¹ Selenium was shown to have a protective effect against certain cancers, particularly in the presence of low dietary intake.¹²

Assessment and correction of nutritional status in HIV infection is being recognized as an important part of comprehensive care of persons infected with HIV. This article reviews the current published literature on micronutrients in HIV infection, examines the role of supplementation with individual and combined micronutrients, and attempts to recommend direction that future research must take in order to define the place of nutrition in HIV infection.

Micronutrients

Deficiency of micronutrients

Micronutrient deficiencies are common in HIV infection, and occur at all stages of immune deficiency, including asymptomatic infection.¹³⁻¹⁵ Serum levels of fat-soluble

micronutrients and of selenium are reduced more than of others, and serum carotene levels are reduced more than any other micronutrient.^{16,17} Tomaka et al found no difference in prevalence of micronutrient deficiencies in patients with CD4 cells greater than 500, between 200 and 500, and fewer than 200 cells/ μ L.¹⁸

Helper/inducer (CD4) T-lymphocytes, disease progression, and mortality: An association was demonstrated between micronutrient deficiencies and rapid disease progression in prospective observational studies. Higher intake of micronutrients, which included riboflavin, thiamine, and niacin, was associated with higher CD4 cell counts at baseline.¹⁹⁻²¹ In a study of intravenous drug users, follow-up for 18 months showed an association between declining CD4 cell counts and development of deficient levels of vitamin A or B₁₂. Higher CD4 cell counts were seen in those without deficient levels.²² Low serum levels of vitamin E²³ and B₁₂²⁴ were measured in those with development of acquired immunodeficiency syndrome (AIDS). A similar association was not demonstrated for vitamin A.²³

Micronutrient supplementation

Multivitamin and trace element supplementation is common in 63 percent to 73 percent of the HIV-infected population in North America. Although multivitamin and trace element supplementation resulted in elevation of levels of micronutrients at all stages of the disease, levels in HIV-seropositive subjects were seen to be lower than in HIV-negative controls. Even with supplementation, 29 percent of HIV-infected persons had deficient levels of one or more micronutrient.²⁵

Disease progression and mortality: Multivitamin use and intake of vitamin E, riboflavin, vitamin C, thiamine, and vitamin A were associated with slower disease progression in HIV.¹⁹ Tang et al observed slower progression of disease with moderate increase in intake of vitamins B₁, B₂, B₆, and C, and reduced risk of mortality with all of these except vitamin C. Benefit was not significant with a great increase in intake of these micronutrients.²¹ These studies were observational in design, and residual confounding cannot be excluded as an explanation of results.

Birth outcomes: In a randomized, placebo-controlled trial in Tanzania, birth outcomes were studied in HIV-infected women. The women were supplemented with vitamin A and/or multivitamins (vitamins B₁, B₂, B₆, B₁₂, C and E, and niacin and folate, but not vitamin A) in a factorial study design. They were given routine ferrous sulphate, and folate supplements daily, and weekly prophylactic chloroquine. A statistically significant reduction of 39 percent in risk of fetal loss was observed with multivitamin supplementation, and a 40 percent

reduction in low birth weight, severe pre-term birth, and small-for-dates birth. A significant improvement in CD4, CD8, and CD3 cell counts was also seen. Vitamin A supplement had a smaller treatment effect that was not statistically significant.²⁶

Vitamin A

Deficiency of vitamin A

Studies have shown vitamin A deficiency is common in various stages of HIV infection,^{13-15,22,27-31} even in 12 percent to 19 percent of asymptomatic HIV-positive persons.^{13,22} Levels appear to become lower as the disease progresses,²² may be more prevalent in women than in men,³² and may occur in the presence of adequate nutrition.³⁰

Sixty-three percent of 474 HIV-positive pregnant women in Malawi had deficient levels of vitamin A, and 70 percent of their babies born with or without HIV infection had deficient levels of vitamin A, compared with age-matched maternal controls.³³ Children in one study were shown to develop deficiency prior to development of AIDS.³⁴ In general, deficiencies of fat-soluble micronutrients occur in HIV infection due to fat malabsorption, general malabsorption, diarrhea, gut infection, altered gut barrier function, and altered metabolism.³⁵

CD4 lymphocytes, disease progression and mortality:

Baum et al demonstrated an association over an 18-month period between the development of vitamin A deficiency and a significant decrease in CD4 cell count.²² Semba et al demonstrated that low vitamin A levels were an independent predictor of death from AIDS-related causes. They also showed that over a four-year period, vitamin A deficiency occurred in 20 percent of those who died from AIDS or infection, and in only 7 percent of matched HIV-positive controls who survived.³¹ In another study, serum retinol (vitamin A) levels were shown to be inversely associated with the risk of mortality in HIV-infected intravenous drug users.¹⁴

Vertical HIV transmission:

A significant inverse relationship of prenatal vitamin A levels and viral load in breast milk of mothers with CD4 cell count below 400 cells/mm³ was demonstrated in a cross-sectional study.³⁶ Low vitamin A levels and increased shedding of virus in vaginal secretions were demonstrated in another study.³⁷

In an observational study of 133 HIV-infected mothers, women who were vitamin A deficient prenatally were found to be 3.69 times more likely to transmit the virus to their children. Progressively increasing rates of HIV transmission were seen with decreasing levels of vitamin A in the HIV-infected mother. Multivariate analysis

showed a three- to four-fold increase in the risk of transmission. Infants of women with the lowest vitamin A levels died within one year of birth.³⁸ Lower serum levels of vitamin A were associated with higher risk of viral transmission,^{39,40} and with having a dead or HIV-positive baby.⁴¹ This association between low vitamin A levels and risk of vertical transmission was not seen in two observational studies with 334 and with 95 HIV-positive pregnant women.^{42,43}

Vitamin A supplementation

Viral load: In a small placebo-controlled trial of vitamin A and beta-carotene in HIV-infected pregnant women, no effect was seen on viral load.⁴⁴ Similarly, no effect was seen on viral load with vitamin A⁴⁵ and beta-carotene⁴⁶ supplements in HIV-infected patients in two separate studies.

Vertical viral transmission, maternal mortality, and birth outcomes: Randomized controlled trials of supplemental vitamin A in pregnant women at various stages of HIV infection have shown no overall effect on vertical viral transmission. In a randomized, placebo-controlled trial of prenatal supplementation with 10,000 IU of vitamin A or placebo in 700 HIV-infected pregnant women in Malawi, treatment had no effect on viral transmission at six weeks and 12 months.⁴⁷ Prenatal supplementation with 5,000 IU of vitamin A and 30 mg beta-carotene or placebo in 750 women in South Africa in factorial design showed no effect of treatment on viral transmission, although a small but statistically insignificant reduction in premature births was observed. Among preterm births, women on supplements were less likely to transmit virus than women on placebo.⁴⁸ In a large randomized, placebo-controlled trial in Tanzania, vitamin A and multivitamins (excluding vitamin A) were administered prenatally. Follow-up showed no effect on vertical transmission compared with controls on placebo in the prenatal or intrapartum periods, or for up to six weeks of breastfeeding.⁴⁹

In a placebo-controlled trial, 20,000 pregnant women in Nepal were supplemented with a weekly dose of 23,300 IU vitamin A or beta-carotene. Up to 50 percent reduction in maternal mortality was observed in both HIV-infected and uninfected women.⁵⁰ In the same population, no effect of supplementation with the two micronutrients was seen on outcomes relating to birth weight, prematurity, and small-for-gestational-age births.⁵¹

Vitamin A supplementation in children: In a randomized, placebo-controlled trial in Durban, vitamin A was given in single age-adjusted doses to children of HIV-positive mothers at one and three months (50,000 IU), six and nine months (100,000 IU), and at 12 and 15 months

(200,000 IU). At 16 months, the treated group showed reduction in diarrhea by 28 percent, 40 percent shorter bouts of diarrhea, and reduction in hospitalization for diarrhea by 77 percent. Treatment effect was shown by multivariate analysis to be confined to children who tested HIV-seropositive.⁵² In a randomized, placebo-controlled study from Tanzania, 687 children between 6 and 60 months old were admitted for pneumonia, and supplemented with 200,000 IU vitamin A (half that if under 12 months old). The dose was repeated the next day, and at four and eight months. This resulted in a significant increase in linear growth in children with HIV infection, ponderal growth in children with malaria, and reduced stunting in children with persistent diarrhea.⁵³

Oxidative stress and antioxidants: Antioxidant imbalances in the host play a role in apoptosis that may lead to progression in HIV-infection.⁵⁴⁻⁵⁶ This apoptosis is induced by reactive oxygen species (ROS) by damage to lipid membranes, intracellular proteins, and DNA.¹⁷ ROS can activate the latent HIV state by stimulating oxygen-responsive transcription factors, especially NF- κ B, which induces HIV replication in the infected T-lymphocyte.⁵⁷ Addition of antioxidant vitamins may inhibit HIV replication, and reduce ROS.

Safety of vitamin A: There is known toxicity with long-term and high-dose use of vitamin A, and there is the theoretical risk of HIV-1 expression.⁵⁸ Toxicity manifests itself as hypervitaminosis A and increase in bone fractures.⁵⁹ However, the risk of toxicity in the presence of HIV infection is not known.

It is believed that benefit of supplementation with vitamin A may only occur when there is pre-existing deficiency. No benefit was observed with vitamin A supplements in a largely replete population of HIV-positive American men.²³ Further investigation of treatment with vitamin A is needed into the differential treatment effect of vitamin A with or without deficiency.

Carotenoids

Carotenoids are increasingly being used in studies as a substitute for supplemental vitamin A. There are more than 600 naturally occurring carotenoid pigments, of which 50 are biologically active. Some are precursors of vitamin A, including beta-carotene that is the principal carotenoid. Many of them, including beta-carotene, are antioxidants. The provitamin carotenoids are converted to vitamin A in the jejunal mucosa and absorbed, or absorbed unchanged, while other carotenoids are absorbed unchanged. Carotenoids have been shown to be non-toxic with prolonged use,⁴ except for possible adverse effect of beta-carotene on cancer incidence in smokers in one trial.³ There is no recommended daily allowance (RDA) or daily limit on intake.

Carotene deficiency

Deficiencies of carotene and other carotenoids are common in HIV infection,^{17,18,60} are more marked than of other micronutrients,¹⁷ and occur even in the absence of symptoms or diarrhea.⁶⁰ Long-standing fat malabsorption occurs even in early HIV disease due to villous atrophy and impaired enterocyte function in the absence of gut infection.⁶¹ Scavenging of singlet oxygen by carotene leads to depletion of carotene.⁶² The prevalence of low serum carotene levels is between 30 percent and 77 percent of adult patients with HIV disease.^{15,60,63} A correlation was demonstrated between serum carotene levels and CD4 cell counts, and serum carotene and CD4/CD8 ratio, in 116 HIV-infected individuals in various stages of HIV disease.⁶⁰

Twenty-five HIV-infected patients in early-stage, and 18 patients in late-stage HIV immune disease, were followed for six months. Low serum carotene levels and plasma carotenoids were observed in all patients. Paradoxically, persons in US Centers for Disease Control and Prevention (CDC) stage II had a more rapid fall in serum carotene levels than persons in CDC stage IV.⁶⁴ The authors hypothesized that this paradox may be due to higher anti-oxidant activity at the early stage, and increased consumption of carotene by oxygen free radicals. Lacey et al demonstrated low levels of several carotenoids in 35 HIV-positive individuals. While correlation of some carotenoids with CD4 cell counts was demonstrated, similar correlation with CD4 cells was not demonstrated with beta-carotene, and vitamins A, C, and E.¹⁷

In one study, low serum vitamin A levels were observed in 37 percent of HIV-positive women in the third trimester of pregnancy. Serum carotene and vitamin A concentrations correlated significantly with percentage of CD4 lymphocytes, absolute CD4 cell counts, and CD4/CD8 ratios.⁶⁵

Carotene deficiency in children: In a study of 15 African-American and Hispanic HIV-infected children, a correlation was observed between severity of disease and serum carotene levels. Those with HIV infection had a 6.5-fold decrease from baseline in serum carotene levels, compared with age-matched controls, whereas children with AIDS had a 13-fold decrease. However, vitamin A and E levels did not vary with severity of disease.⁶⁶ Periquet et al described low levels of lycopene (a carotenoid) and retinol (vitamin A) in ten children with AIDS, but no deficiency of carotene.³⁴

Carotenoids supplementation

CD4 lymphocytes: Supplementation in 17 healthy HIV-negative volunteers with 180 mg (30,000 IU) beta-carotene daily for 14 days showed a 30 percent elevation of CD4 cells.⁶⁷ In another study, seven AIDS patients

showed a transient lymphocyte count increase of 66 percent when they were treated with 60 mg beta-carotene twice daily for four weeks, and followed for another six weeks.⁶⁸

Garewal et al observed significant increases in Leu 11 (a marker for natural killer cells) with beta-carotene supplementation, and elevations in Ia antigen transferrin receptor and measurements of lymphocyte activation. Sixty mg beta-carotene was administered daily for four months to HIV-positive veterans. No changes were observed in lymphocyte percentages of CD4, CD8, or CD11.⁶⁹ Eleven HIV-seropositive subjects with oral candidiasis were treated with 60-120 mg beta-carotene daily for three to seven months. Treatment showed no improvement in the infection or in lymphocyte counts or percentages.⁷⁰

A 60-mg dose of beta-carotene or placebo was administered randomly daily for four weeks to HIV-positive patients in a crossover trial. In both cases, the treatment group showed significant increases in leucocyte counts and CD4/CD8 ratio.⁷¹ A prospective, placebo-controlled, randomized study compared beta-carotene plus multivitamins and trace elements, to multivitamins and trace elements for three months,⁷² in which Coodley et al were not able to replicate the results of their earlier study.⁷¹ The authors hypothesized that vitamin A in the multivitamins given to both groups in the second study may have resulted in reduction of the apparent treatment effect of beta-carotene.

These studies of beta-carotene supplementation are small and findings range from no effect to varying and transient increase in immune cells. No definite conclusions can be drawn from them of the effect of beta-carotene supplementation on immune cells.

Disease progression and mortality: In a study of 11 patients with AIDS-related complex symptoms, treatment with 60 mg beta-carotene daily for 20 days per month resulted in alleviation of symptoms in all the patients over a period of 24 to 36 months. Two patients progressed to AIDS, while the others showed an increase in CD4 cell count.⁷³

A randomized, placebo-controlled, double-blind, clinical trial of natural mixed carotenoids was conducted in patients with advanced AIDS on antiretroviral therapy. They were all given a specially designed multivitamin and trace element preparation, including vitamin A (see Table 1). Further study is required to corroborate and investigate findings that suggested an effect of carotenoids on survival.⁷⁴

Oxidative stress: Delmas-Beauvieux et al randomized 52

Table 1. Ingredients of a specially designed multivitamin and mineral supplement used for all participants in the randomized, controlled, double-blind trial of natural, mixed carotenoids in AIDS.*74

<i>Micronutrient or trace element</i>	<i>Weight/tablet</i>
Vitamin A (retinol palmitate 1,500 IU/tablet, 500,000 IU/gm)	3 mg
Vitamin D ₃ (cholecalciferol 800K IU/gm, 56.2 IU/tablet)	0.071 mg
Vitamin C (ascorbic acid 56.2 mg/tablet, 10% LF)	62.5 mg
Vitamin E (d-alpha tocopherol acetate 1210 IU/gm, 56.2 IU/tablet)	45.5 mg
Vitamin B ₁ (thiamine hydrochloride)	9.38 mg
Vitamin B ₂ (riboflavin)	4.68 mg
Vitamin B ₂ (riboflavin-5' phosphate sodium)	2.25 mg
Vitamin B ₃ (niacin)	3.75 mg
Vitamin B ₃ (niacinamide)	9.38 mg
Vitamin B ₅ (d-calcium pantothenate)	18.75 mg
Vitamin B ₆ (pyridoxine hydrochloride)	9.38 mg
Vitamin B ₆ (pyridoxine-5'-phosphate)	3 mg
Folic acid (folacin)	0.08 mg
Biotin	0.06 mg
Magnesium (chelate, 20% Mg ⁺⁺ , 37.5 mg/tablet)	187.5 mg
Zinc (methionate, 20% Zinc, 7.5 mg/tablet)	38 mg
Iron (glycinate sulfate, 16% Fe ⁺⁺ , 1.5 mg/tablet)	9.38 mg
Copper (citrate, 16% Cu ⁺⁺ , 0.38 mg/tablet)	2.35 mg
Manganese (citrate, 30% Mn ⁺⁺ , 1.5 mg/tablet)	5 mg
Potassium (chloride, 52% K ⁺ , 9.38 mg/tablet)	18 mg
Chromium (picolinate, 12% Cr ⁺⁺⁺ , 18 mcg/tablet)	0.16 mg
Selenium (citrate, 0.2% Se, 18 mcg/tablet)	9.38 mg
Molybdenum (citrate, 0.2% Mo, 9.38 mcg/tablet)	4.69 mg
Vanadium (citrate, 0.2% V, 9.38 mcg/tablet)	4.69 mg
Choline bitartrate	9.38 mg
Iodine (kelp, 0.18% I ₂ , 9.38 mcg/tablet)	10.5 mg
N-acetyl-1-cysteine	150 mg
Glutathione (reduced)	37.5 mg

*Dosage: 4 tablets/day.

HIV-seropositive persons into three groups to receive 250 µg/L selenomethionine daily, or 30 mg beta-carotene twice daily, or placebo. At 12 months, neither treatment group showed improvement in CD4 cell counts, compared to controls. However, glutathione levels were significantly higher, and malondialdehyde levels were significantly lower in both treatment groups. Glutathione indicates increased anti-oxidant activity, and malondialdehyde is an indicator of lipid peroxidation. The authors reported that median serum carotene levels increased from 3 µg/L to a surprising 305 µg/L with 30 mg beta-carotene administered twice daily.⁷⁵

In another study, 36 HIV-positive subjects were divided into three groups. Each group received 250 µg of selomethionine daily, or 30 mg beta-carotene twice daily, or placebo, for 12 months. Other indicators of endothelial damage remained unchanged in all groups, but stable

levels of thrombomodulin and von Willebrand factor (markers of endothelial damage) were reported in both treatment groups. These were elevated in controls, and believed by the authors to be evidence of possibly antioxidant-mediated prevention of endothelial damage.⁷⁶

Further studies are needed to evaluate carotenoids as vitamin A precursors, and to evaluate treatment effects in relation to deficiencies, and in relation to antiretroviral therapy.

B-complex vitamins

Deficiency of B-complex vitamins

Deficient serum levels of vitamins of the B-complex occur in HIV disease, even in early disease and in the absence of symptoms.²² Beach et al assessed micronutrient concentrations in HIV, and found low riboflavin levels in 26 percent, low B₆ levels in 53 percent, and low B₁₂

levels in 23 percent men belonging to CDC stage III.¹³ Low choline levels,²⁵ and low vitamin B₁₂ and B₆ levels⁷⁷ were shown in HIV-infected men and women. Low erythrocyte and serum folate levels were seen in 64 percent of 74 HIV-infected persons at all stages of the infection.⁷⁸

Supplementation with B-complex vitamins

In a study of micronutrient supplementation, Abrams et al showed an inverse relationship between increased intake of thiamine and niacin and progression to AIDS.¹⁹ Significantly slower disease progression to AIDS was also observed with increased intake of B-complex vitamins in other studies.^{20,79}

Vitamin B₆

Deficiency of vitamin B₆

Vitamin B₆ deficiency was shown to be common in CDC stage III HIV-infected persons with adequate nutrition. Thirty-four percent of 44 persons were deficient in vitamin B₆, and another 30 percent had marginally deficient levels. Patients who were deficient showed decreased lymphocyte mitogen responsiveness and reduced natural killer cell cytotoxicity, compared with HIV-positive persons who were not deficient.⁸⁰

Vitamin B₁₂

Deficiency of vitamin B₁₂

Deficiency of vitamin B₁₂ is common in HIV infection, and its prevalence varies between 10 percent and 35 percent, depending on the stage of the disease.^{78,81-85} Deficiency was more common in HIV-infected individuals than in those not infected,^{13,77,86-88} even in early and asymptomatic disease.^{13,24,27,82,83,90,91} Deficiency is attributed to malabsorption due to gastric and parietal cell antibodies, duodenal and colonic inflammation,⁹² and gastric cell acid hyposecretion.⁹³ It is possible that increased lymphocyte turnover in HIV infection might deplete vitamin B₁₂, just as fetal growth can deplete vitamins B₁₂ and folate to produce the megaloblastic anemia of pregnancy.

Disease progression and mortality: Follow-up for two years showed that HIV-seropositive persons with deficiency of vitamin B₁₂ had 50 percent mortality, compared with 22 percent among persons without deficiency. However, the latter group had more AIDS patients, and the groups may not be comparable. A significant association was demonstrated between low serum B₁₂ levels and lower hemoglobin, leucocytes, CD4 cell counts, and CD4/CC8 cell ratios, compared with normal B₁₂ levels.⁹⁴

Baum et al, in a follow-up of 108 HIV-positive men, showed a significant association between the development of B₁₂ deficiency and declining CD4 cell count. There was a significant increase in CD4 cell counts in those who

had normalization of serum vitamin B₁₂. Low baseline serum B₁₂ levels were shown to be significant predictors of AIDS.²² In an observational study of 310 homosexual men, after adjusting for confounders, lower levels of serum vitamin B₁₂ significantly increased the risk of progression to AIDS by 89 percent, compared with normal levels of B₁₂.²⁴

Although the studies that link B₁₂ deficiency with HIV disease progression are observational by design, and confounding of associated factors may explain results, the association is strong. Randomized, controlled clinical trials must elucidate if low B₁₂ levels are just a marker of advanced disease, or actually cause disease progression, and confirm if supplementation can slow disease progression.

Neurological impairment: In 64 asymptomatic HIV-seropositive subjects, a significant association was found between low levels of vitamin B₁₂ and cognitive impairment, such as deficits in information-processing time and visual-spatial problem-solving skills.⁸⁷ In another study of 64 HIV-positive persons, peripheral neuropathy and myelopathy were associated with low serum B₁₂ levels. A positive Schilling test or a low serum B₁₂ level was reported in 20 percent of patients.⁸⁵

No association between neurological abnormalities and B₁₂ deficiency was demonstrated in some studies. Keating et al found no association between serum vitamin B₁₂ levels and low cerebrospinal fluid methylation ratios in HIV positive patients, indicating that myelopathy was probably due to a mechanism other than vitamin B₁₂ deficiency.⁹⁵ In another study of 153 HIV-seropositive subjects, no association was found between low serum vitamin B₁₂ levels or impairment of B₁₂ metabolism, and neuropsychiatric disturbances such as peripheral neuropathy, mood disturbances, and dementia in subjects.⁹⁶

In a longitudinal observational study of 84 HIV-infected homosexual men, the association between cognitive function and low levels of serum vitamin B₁₂ was examined in four groups of subjects, based on vitamin B₁₂ levels, at six monthly intervals over a period of 18 months. Normalization of serum B₁₂ levels resulted in improved speed of retrieving over-learned information from long-term memory, although the clinical significance of this finding has not been explained.⁹⁷ All the studies of association between vitamin B₁₂ levels and neurological impairment are observational in design, and all except one are cross-sectional, implying the presence of confounding influences.

Vitamin B₁₂ treatment

In separate case reports of vitamin B₁₂ injection

treatment, one patient with AIDS-related dementia showed improvement in dementia over a two-month period,⁹⁷ five of eight patients showed improvement of neuropathic symptoms,⁸⁵ and CSF methylation ratios normalized in patients with B₁₂ deficiency.⁹⁵ The evidence for reversal of neurological deficit with B₁₂ treatment is based largely on case reports. Randomized, controlled trials are needed to confirm this effect. Controversy surrounds oral versus parenteral use of vitamin B₁₂. However, parenteral administration is recommended in conditions that need specific vitamin B₁₂ therapy.⁹⁸

Interaction of vitamin B₁₂ and zidovudine therapy:

There may be increased toxicity of zidovudine (AZT) therapy in the presence of vitamin B₁₂ deficiency, as each is associated with bone marrow depression manifested as anemia and neutropenia. In a placebo-controlled trial of AZT therapy, AIDS patients with lower baseline levels of B₁₂ had increased incidence of hematological side effects of AZT therapy, such as anemia, leukopenia, and neutropenia. No benefit of vitamin B₁₂ injection in reducing hematological toxicity of AZT therapy was seen in other small studies.⁹⁹⁻¹⁰¹

Vitamin E

Deficiency of vitamin E

Low serum concentration of vitamin E was seen in observational studies. In a study of 100 asymptomatic HIV-seropositive men, 26 percent had intake of vitamin E that was 50 percent less than RDA, and 27 percent had overt or marginal deficient levels.¹³ In another study, 50 percent of 18 AIDS patients, 58 percent of 12 ARC patients, and 38 percent of 13 HIV-positive persons had intake of vitamin E less than 50 percent of RDA.¹⁰²

Oxidative stress: Oxidative stress in HIV infection and opportunistic infections results in high level of free radicals and depletion of vitamin E. Resulting deficiency of vitamin E may then increase susceptibility to further infection.¹⁰³

Vitamin E supplementation

Viral load and oxidative stress: In a randomized, placebo-controlled clinical trial, supplementation of 40 HIV-seropositive persons with 800 IU vitamin E and 1000 mg vitamin C, resulted in a significant reduction in oxidative stress and viral load, compared with the placebo group.¹⁰⁴ In another study, significant reduction in viral load was seen with large doses of vitamin E and C.¹⁰⁵

Disease progression and mortality: Among 296 HIV-seropositive men followed for six years, doubled intake of vitamin E showed a decreased risk of progression to AIDS.¹⁹ Among 310 HIV-seropositive homosexual men

studied over nine years, subjects in the highest quartile of serum vitamin E had a significantly decreased risk of progression to AIDS, compared to subjects in all other quartiles combined after adjusting for several confounders. An increase in serum levels of vitamin E was also seen with vitamin E or multivitamin supplements.²³

Few controlled clinical trials have been done with vitamin E, but they support the immunostimulatory and antioxidant effects demonstrated in animal studies. Further research is needed to establish the role of vitamin E deficiency in disease progression, and the therapeutic effect of restoring normal levels with vitamin E supplements.

Selenium

Deficiency of selenium

In different studies in HIV, both plasma and red blood cells were found to be deficient in selenium. This was reported in both HIV-positive and AIDS patients,¹⁰⁶⁻¹⁰⁸ and occurred even in early disease when malabsorption and malnutrition were unlikely contributors.¹⁰⁹ In another study, deficient levels were found in 15 percent, and marginally low levels in 57 percent of 54 asymptomatic HIV-infected males.¹¹⁰ In a study of 23 HIV-infected children, 61 percent had low selenium levels which correlated with weight, serum albumin, and CD4 cell counts.¹¹¹

Disease progression and mortality: Association of lower selenium levels with progression of disease was found in several studies. It was independent of malabsorption and correlated with CD4 cell counts.^{107,108,112} Constans et al also demonstrated correlation between both CD4 cells and serum selenium with mortality and opportunistic infections in 95 HIV-positive individuals.¹¹³

Baum et al showed that HIV-positive patients with low levels had a significant 20-fold risk of death from HIV-related causes than those with adequate serum levels. The risk was 16 times greater than of low CD4 cell count, and greater than with any other micronutrient.¹¹⁴ In a study of 24 HIV-infected children, investigators showed that low plasma selenium concentration and CD4 cell count below 200/ μ l were independent predictors of mortality and faster disease progression.¹¹⁵

Selenium supplementation

CD4 cells and clinical improvement: Administration of 80 μ g selenium and 25 mg vitamin E to eight patients with advanced AIDS and three patients with symptomatic HIV infection, resulted in a doubling of serum selenium levels, but no improvement in CD4 cells.¹⁰⁸ Supplementation with 400 μ g of yeast-based selenium for 70 days in 19 symptomatic HIV and AIDS patients resulted in elevation of serum selenium levels, while there was no difference in the control group.

Fourteen of the subjects reported improvement of symptoms.¹¹⁶ In another study, ten patients with cardiomyopathy, eight of them selenium-deficient, were supplemented with 360 µg selenium for 15 days, followed by 180 µg for eight days. This resulted in normalizing of left-ventricle shortening in six patients, while one patient died.¹¹⁷

Anti-oxidant activity: In a study of supplementation of 14 HIV-positive persons with 100 µg selenium, results were compared with 18 HIV-positive persons on placebo, and with 26 HIV-negative healthy persons on no supplementation. Significantly lower baseline glutathione levels were observed in both the HIV-infected groups. On follow-up for one year, the treated group showed significantly higher glutathione peroxidase and reduced glutathione levels than each of the other groups.⁷⁵

All the studies of selenium in HIV-infection are small and observational in design, making confounding a possible explanation of findings. Randomized controlled trials are needed to investigate the association of deficiency with poor outcome, and possible therapeutic effect of supplementation.

Zinc

Zinc deficiency

Zinc deficiency is common in the HIV-infected population.¹¹⁸ Zinc levels are known to be depressed during acute phase reaction to infections, reflecting increased uptake by the liver,¹¹⁹ In a cross-sectional study of 228 hospitalized AIDS patients, 29 percent had low zinc levels and another 21 percent had levels characterized as marginal. A higher incidence of bacterial infections was reported in persons with low zinc levels.¹²⁰

Malabsorption, altered metabolism, anorexia, and diarrhea may produce low levels of micronutrients and trace elements.¹²¹ Low zinc levels were also seen in early disease, and in the absence of symptoms.^{13,64,122} Some studies reported no effect on serum zinc levels in HIV infection,¹²³⁻¹²⁵ and others reported lower levels with more advanced stages of the disease.^{122,126}

Disease progression and mortality: In a large study, a positive association was seen between dietary intake of zinc and CD4 cell counts, but no association was demonstrated with progression to AIDS.¹⁹ Progression to AIDS was associated with lower baseline serum zinc levels, as compared both to those who did not develop AIDS and to those who were HIV-negative.¹²² In another study, an association was demonstrated between low baseline zinc levels and AIDS mortality among men in Miami. When adjusted for baseline CD4 cell counts and serum concentrations of other nutrients, this association lost statistical significance.¹¹⁴

Since zinc deficiency and zinc-dependent immunity are responsive to acute and subsequent chronic phase reaction,¹²⁷ levels of thymulin (a thymic hormone activated only by binding with zinc ions) may be a more sensitive marker of deficiency than serum zinc levels.¹²⁸ Thymulin levels have been shown to be low even in the presence of normal serum zinc levels.¹²⁷

Zinc supplementation

CD4 cells: Eleven men with AIDS, whose baseline zinc levels did not differ from controls, were treated for ten months with 0.4 mg/kg/day. This was shown to result in significant increase in CD4 cell counts, a significant increase in CD3 cells, and a mean increase in weight of seven pounds that could not be explained by caloric intake alone.¹²⁹

CD4 cells in children: Oral zinc supplements of 1.8-2.2 mg/kg/day were given for three to four weeks to 13 stable HIV-infected children with a mean age of six years. The number of children with normal levels of zinc increased from six at baseline to nine, two children showed significant increases in CD4 counts, and four showed improved clinical scores.¹³⁰ In another small trial, supplementation of HIV-seropositive children with 2 mg zinc per day for three weeks showed significant increases in total lymphocyte count, and a doubling of CD4/CD8 ratio.¹³¹

Zinc safety: There is some concern surrounding supplementation with zinc. Intake of zinc beyond 11.6 mg/day in 281 HIV-1 seropositive men was associated with increased relative risk for disease progression after controlling for confounders.²⁰ The findings of this study were controversial and uncorroborated, and in other studies, zinc supplementation did not show increased disease progression with high doses.^{19,122}

Interaction between antiretroviral therapy and zinc: There is a suggested relationship between AZT treatment and zinc deficiency. In one study, 64 percent of those who were treated with AZT had a deficiency of zinc, compared with 24 percent of those who were not treated with AZT.⁹⁰ Treated patients not deficient in zinc had significant mitogen response while treated patients who were zinc deficient did not. Mocchegiani et al followed HIV patients on 12 mg elemental zinc supplements daily for 30 days. Eighteen patients were on AZT monotherapy, and 28 were on two nucleoside analogue drugs and one protease inhibitor. Of the 18 patients on AZT, there was a lower risk of opportunistic infections with supplement than without. In patients on three-drug HIV treatment, there was no increased risk of opportunistic infection in those unsupplemented with zinc. These patients also had improved zinc absorption, and higher serum zinc levels that might be

attributed to improved intestinal mucosal absorptive function.¹³²

Observational studies show that zinc deficiency is common in HIV infection. It is associated with opportunistic infections, and also with lower CD4 cell counts. The role that correction of deficiency may have in prevention or amelioration of HIV immune deficiency needs investigation in randomized, controlled trials.

Magnesium

Studies have variously reported no deficiency,¹²⁴ low serum levels in 30 percent to 65 percent of subjects,^{133,134} and low levels correlated with CD4 cell counts.¹³³ In one study, 59 percent of 64 HIV positive persons in all stages of infection showed deficiency of magnesium unrelated to stage of the disease, compared with 9 percent in HIV-negative controls.²⁵

Discussion

The results of micronutrient treatment studies are difficult to interpret due to various study designs, doses, lengths of follow-up time, and study outcomes. Serum micronutrient levels are used to characterize micronutrient deficiencies, but they may not be a true reflection of nutritional status. Micronutrient levels are influenced by factors such as gender, time of day of measurement, acute infection, liver disease, technical parameters, and recent intake. There may be interaction between micronutrients,¹³⁵ and between micronutrients and concomitant antiretroviral drug treatment therapy, making generalization of findings to diverse populations difficult.

It remains unclear if supplementation with micronutrients has any measurable impact on the clinical course of HIV disease. Further research is needed to elucidate clinical benefit of supplementation in different clinical settings, and with different micronutrients. Still, there is considerable collective evidence that nutritional compromise adversely affects the course of HIV disease. It has also been shown that micronutrient supplements may alleviate symptoms, delay progress to AIDS, reduce mortality, accelerate growth in children, improve birth outcomes, and reduce maternal mortality.

Ideally, every individual diagnosed with HIV infection should be screened for micronutrient deficiencies, and a nutritionist consulted, especially in later stages of disease. However, this is not always feasible. Multivitamin and trace element supplements should be considered for all persons with HIV infection. Priestley et al reported that multivitamin supplementation of HIV-infected patients resulted in stabilization of CD4 cell counts and improved survival, compared to survival of patients with similar counts in other studies.¹³⁶ Rigorous

evaluation is still needed with controlled clinical trials.

The routine use of multivitamin supplementation in the general population is considered more beneficial than harmful.¹³⁷ Thirty percent of the population of the United States takes multivitamin supplements.¹³⁸ Multivitamin use is also common in the HIV-infected population in North America, and between 63 percent and 73 percent take such supplements.^{25,139,140} The guidelines of the Institute of Medicine list RDAs and upper limits of micronutrients for different life stages.¹⁴¹ The RDAs of micronutrients are used in the currently available multivitamin preparations. However, RDAs refer to requirements for healthy individuals, and may not constitute appropriate supplementation in HIV infection.

Baum et al showed that even with the consumption of vitamins at or above RDA, deficiencies of vitamins B₆, B₁₂, B₂, A, C and E may occur in those with HIV infection. They recommended that HIV-infected patients take doses higher than RDA, especially of these vitamins.¹⁴² Risk of toxicity of nutrients in HIV infection is not known, and could well be lower than in those not infected. Table 1 shows the specially designed multivitamin and trace element supplement, given with additional natural mixed carotenoids, which is being evaluated in patients with advanced AIDS.⁷⁴ There is a need to formulate a micronutrient plus trace element supplement for use in HIV infection, with caution against potential toxicities of excessive vitamin A, selenium, and zinc.

There is the possibility of inadequate utilization of the micronutrients in a supplement due to malabsorption. Still, routine use of one of the currently available multivitamins and trace element preparations is advisable for HIV-positive patients until a specific co-formulation is developed. This should be considered as adjuvant to conventional antiretroviral therapy, and may prove to be a relatively low-cost intervention. ■

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Editor's Note: This acknowledgement was to have appeared in "Hospitalization in HIV in Chicago," by Renslow Sherer, MD, et al in the Winter 2002 issue of JIAPAC, Vol. 1, No. 1.

Acknowledgements:

The Authors gratefully acknowledge the contributions of the following individuals to this work: Bonnie Lubin, PhD, Grants Administrator, Hektoen Institute; Aaron Rothenberg, Data and Computer Consultant; Patty Magana, Administrative Assistant; Kathi Braswell, RN, Executive Director, the CORE Center; and Robert A. Weinstein, MD, Chief Operating Officer, The CORE Center for the Prevention, Care, and Research of Infectious Disease.