Perspective

Vitamin D and HIV: Letting the Sun Shine In

Vitamin D is important for cell growth, immunity, and metabolism. Deficiency has classically been associated with rickets and decreased bone density and more recently with increased risk and severity of autoimmune diseases, cancers, myocardial infarction, diabetes, and infectious diseases. How vitamin D can affect these diverse conditions is the subject of much research. The active form of vitamin D (vitamin D_3) has been implicated recently in an intracellular process known as autophagy. In addition to its role in maintaining cellular homeostasis during conditions of stress, autophagy plays an important role in the control of many intracellular microorganisms including Mycobacterium tuberculosis*. Recent work has identified that HIV-1 reduces autophagy during permissive infection and that agents that induce autophagy, including vitamin D_3, can inhibit HIV-1 replication. These findings help provide a biological explanation for the increased risk of more rapid disease progression observed in HIV-infected persons with low levels of vitamin D or with genetic variants within the vitamin D receptor that alter binding to vitamin D. Controlled trials are needed to determine the potential for therapeutic benefit of vitamin D supplementation in HIV disease. This article summarizes a presentation by Stephen A. Spector, MD, at the IAS–USA continuing medical education program held in Chicago in April 2010.*

Vitamin D is important for cell growth, immunity, and metabolism, and vitamin D deficiency is common in developed as well as developing countries. Despite much research, there is still disagreement as to the optimal level of vitamin D needed for health. 25-hydroxyvitamin D is the metabolite usually measured in serum, with lower limits of "normal" considered to be between 20 nmol/L and 38 nmol/L. However, optimal bone health may require levels of at least 50 nmol/L to 80 nmol/L (20–32 ng/mL) in adults.[1] Vitamin D deficiency is classically associated with rickets, which still occurs in developed countries and remains an important problem in resource-poor countries, and with decreased bone mineral density. It is also associated with increased risk and severity of bone diseases, autoimmune disease, cancer (of the colon, prostate, and breast), myocardial infarction, infectious diseases, and possibly diabetes. Evidence indicates that vitamin D deficiency is also associated with increased risk of HIV infection and disease progression.

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Vitamin D Sources

Lanolin in the skin is converted to 7-dehydrocholesterol, which is converted to pre–vitamin D with exposure to ultraviolet (UV) rays from the sun. Pre–vitamin D enters the circulation and is metabolized to 25-hydroxyvitamin D, the major circulating form of the vitamin (which has a circulating half-life of approximately 15 days). It is subsequently converted to the active form, 1,25-dihydroxyvitamin D_3 (called vitamin D_3), in the kidneys. In addition to exposure to sunlight, vitamin D sources include natural foods such as salmon and other "oily" fish, cod liver oil, shiitake mushrooms, and egg yolk, as well as fortified foods and vitamin supplements (Table 1).[2]

The main factors affecting an individual's vitamin D status are the extent of sunlight exposure, degree of skin pigmentation, use of sunscreen (with sun protection factor [SPF] ≥ 8), latitude and season of the person's locale, time spent outdoors, use of protective clothing, body mass and percentage of fat (which are inversely related to vitamin D levels), diet (specifically the intake of fish oil, oily fish, and foods with vitamin D supplementation), and vitamin D supplementation. Persons with HIV infection frequently have low vitamin D levels.[3-6] Moreover, patients treated with nonnucleoside reverse transcriptase inhibitors and protease inhibitors are at increased risk of vitamin D deficiency.[4,7-9] Thus, vitamin D deficiency is common in HIV-infected persons regardless of treatment status, viral load, or CD4+ lymphocyte count.

Vitamin D and Autophagy

In 1903, Niels Ryberg Finsen was awarded a Nobel Prize in Medicine and Physiology in part for showing that extensive exposure to sunlight was frequently effective in treating "lupus vulgaris," (ie, cutaneous tuberculosis [TB]). This effect is now known to be associated with the role of vitamin D in autophagy, a critical process in cell death and survival. Under normal conditions involving infection with many intracellular pathogens, the organism is taken into an endosome that joins with an autophagosome in the cytoplasm of a macrophage. The autophagosome fuses with a lysosome, acidifying the autophagosome to form an autolysosome; the autolysosome exerts antimicrobial activity and kills the microorganism.

In latent *Mycobacterium tuberculosis* infection, however, the organism impairs the recruitment of hepatocyte growth factor–regulated tyrosine kinase substrate (Hrs), which plays a central role in late endosome sorting and autophagosomal maturation (Figure 1).[10] This effect leads to the inhibition of autophagy and thus, the retention of live organisms in autophagosomes. Under such conditions, autophagy in cells can be induced by certain means—for example, through cell starvation,

by drugs, and from environmental stress—so that the autophagosome containing the bacteria fuses with the lysosome, forming the autolysosome and resulting in bacterial killing.

Autophagy is often referred to as programmed cell death-2 (PCD-2), in distinction to apoptosis (which is considered programmed cell death-1, or PCD-1), although some believe that once cells are programmed for death, autophagy and apoptosis are indistinguishable. Under conditions of infection or other stress, cells proceed down one of the PCD pathways. The apoptosis pathway invariably leads to cell death. However, the autophagy pathway is primarily involved in processes of adaptation and survival through the recycling of cytoplasmic proteins and organelles in an attempt to promote cell survival and function. Too much or too little autophagy in response to challenges can result in cell dysfunction and eventually cell death.

In addition to playing a role in innate immunity by clearing or destroying intracellular organisms, autophagy is important in adaptive immunity by assisting with major histocompatibility complex class I and II antigen presentation.[11,12] Microorganisms under the control of autophagy include numerous bacteria, such as *M tuberculosis*, and viruses, including, Dr Spector and colleagues believe, HIV-1 (Table 2).

Vitamin D plays an important role in the killing of microorganisms through autophagy.[13,14] The induction of autophagy by 1,25-dihydroxyvitamin D_3 is the subject of much investigation. At least 2 overlapping pathways appear to be involved with the induction of autophagy by vitamin D. The first involves 1,25-dihydroxyvitamin D_3 binding to the vitamin D receptor (VDR), which promotes the formation of the PI3KC3 kinase complex and leads to autophagosome elongation and subsequent fusion of the autophagosome with a lysosome. In the second pathway, after binding of 1,25-dihydroxyvitamin D_3 to the VDR, there is upregulation of the antimicrobial peptide cathelicidin, resulting in the fusion of autophagosomes with lysosomes. The induction of autophagy through both pathways ultimately leads to the elimination of microorganisms such as *Mycobacterium* species.

Table **1.** Dietary, Supplemental, and Pharmaceutical Sources of Vitamin D_2 and Vitamin D_3

Source	Approximate Vitamin D Content
Natural Sources	
Salmon	
Fresh, wild (3.5 oz)	600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	250 IU of vitamin D_3
Tuna, canned (3.6 oz)	230 IU of vitamin D_3
Cod liver oil (1 tsp)	400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	100 IU of vitamin D_2
Sun-dried (3.5 oz)	1600 IU of vitamin D_2
Egg yolk	20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)	3000 IU of vitamin D_3
Fortified foods	
Fortified milk	100 IU/8 oz, usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz, usually vitamin D_3
Fortified butter	50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	100 IU/serving, usually vitamin D_3
Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/mL
Over the counter	
Multivitamin	400 IU vitamin D (D_2 or D_3)
Vitamin D_3	400, 800, 1000, and 2000 IU

Adapted from Holick.[2]

Vitamin D and HIV

There is growing recognition of an association between vitamin D deficiency and the pathogenesis and course of HIV disease. Vitamin D deficiency is common in HIV infection. It is present in 25% to 75% of infected persons and has been associated with more rapid disease progression. Infants born to HIV-infected women with vitamin D deficiency are at increased risk of infection and have decreased survival.

Persons in resource-limited regions often have low vitamin D levels. In addition, darkly pigmented skin reduces the amount of UV light available in the skin for production of pre–vitamin D. Numerous studies of black people in the United States and Africa have shown an increased risk of vitamin D deficiency, suggesting that insufficient levels of vitamin D may be one of several other risk factors contributing to the severity of HIV disease in persons living in many developing countries.

A number of studies have indicated associations between low vitamin D levels and HIV disease. One such study performed in white injection drug users with HIV infection in Spain showed that persons with vitamin D receptor variants associated with reduced vitamin D binding (ie, people homozygous for the BB allele) had a statistically significant increased risk of progression to AIDS (adjusted hazard ratio [HR], 1.7; $P = .036$) and were statistically significantly more likely to have a CD4+ cell count less than 200/μL (HR,

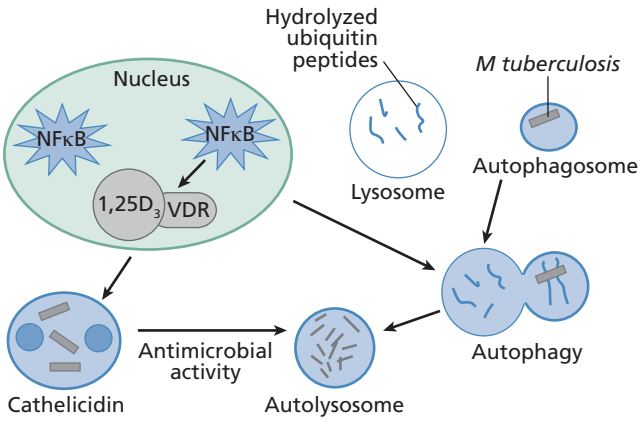

Figure **1.** A simplified schematic of a macrophage, showing the role of vitamin D in the killing of microorganisms. 1,25-dihydroxyvitamin D_3 ($1,25D_3$) binds to the vitamin D receptor (VDR) and through mechanisms not fully identified upregulates the production of cathelicidin and transcription factors that promote autophagy. In infections with *Mycobacterium tuberculosis*, an endosome (autophagosome) containing the organism is induced to fuse with a lysosome, leading to acidification of the fused autophagosome–lysosome complex (autolysosome), resulting in killing of the *M tuberculosis* organism. Cathelicidin, an antimicrobial peptide, also contributes to mycobacterial killing. NF-κB indicates nuclear factor κB.

2.1; $P = .004$) than were those with alleles Bb or bb, which are associated with better binding.[15]

A recent study in HIV-infected women in Tanzania who gave birth showed a striking relationship between lower vitamin D levels and increased risk of HIV disease progression and all-cause mortality (Figure 2).[16] Among infants born to women with low vitamin D levels in this study, multivariate analysis showed a statistically significant increased risk of HIV transmission through breast-feeding among children known to be HIV uninfected at 6 weeks of age (relative risk [RR], 2.03; $P = .03$). It also showed a statistically significant increased risk of HIV infection at 24 months (RR, 1.46; $P < .01$), death among live births (RR, 1.61; $P < .01$), overall mortality (RR, 1.58; $P < .01$), and overall HIV infection or mortality (RR, 1.50; $P < .01$).[17]

Potential Effects of Vitamin D on HIV-1 Infection

The viral products released by HIV-infected CD4+ lymphocytes (eg, gp120) induce programmed cell death of uninfected lymphocytes. In fact, during acute infection, bystander lymphocytes are killed more rapidly than infected cells.[18] Although programmed cell death through apoptosis has been the mechanism most commonly described, recent studies suggest that autophagy may play an important role in bystander CD4+ cell death.[19-21]

In contrast to CD4+ lymphocytes that are killed during HIV-1 infection, infected macrophages are productively infected by HIV-1 but not killed by the virus. Based on Dr Spector and colleagues' recent laboratory findings, it appears that HIV infection of macrophages and CD4+ T lymphocytes results in a downregulation of autophagy that permits viral replication but also allows sufficient autophagy for cell survival.[22]

Regarding other potential effects of autophagy in HIV disease, Spector and Zhou hypothesize that toxins produced by HIV replication in microglial cells (eg, viral products, neurotoxins, and cytokines) cause increased autophagic dysfunction and eventually cell death of neurons, which plays a role in HIV neurocognitive impairment.[23] This premise is supported by postmortem findings that brains of patients with HIV encephalopathy contain higher levels of indicators of autophagy than do those of HIV-seronegative persons or HIV-infected persons without HIV encephalopathy.[24] These findings suggest that aberrant autophagy may be important in the pathogenesis of HIV-associated neurocognitive disorders.

It thus appears that HIV controls autophagy in infected macrophages and, to some extent, in infected lymphocytes. That is, the virus, by altering autophagy within the cells, allows the lymphocyte to survive longer than uninfected bystander cells undergoing programmed cell death from viral products. Moreover, the drug rapamycin, which induces autophagy (via inhibition of the mammalian target of rapamycin [mTOR] pathway), inhibits HIV replication in monocytes.[22] Similarly, calcitriol, the active form of vitamin D_3, can also inhibit viral replication.

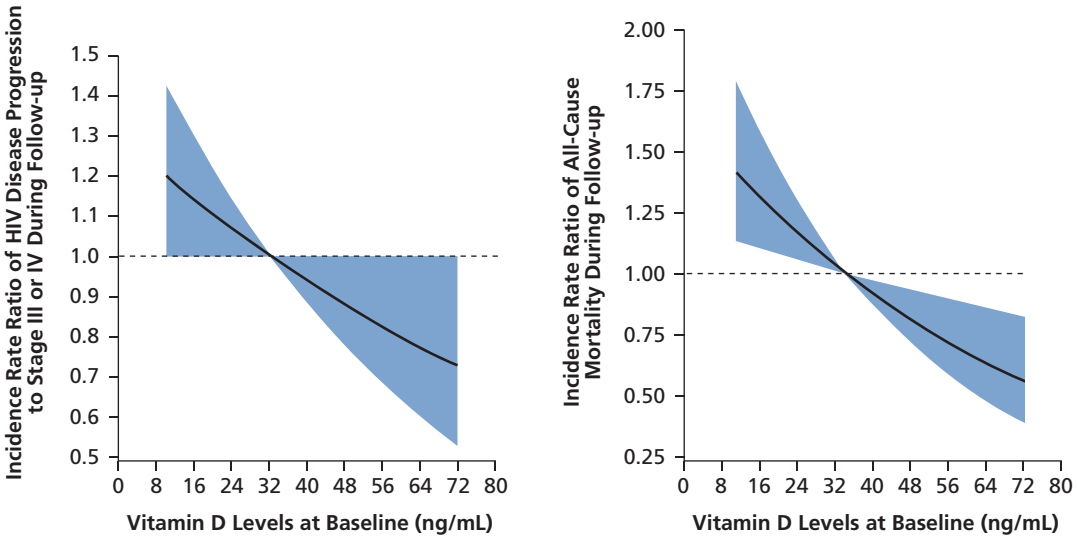

Figure **2.** Association of vitamin D status with HIV disease progression (left) and all-cause mortality (right) in HIV-infected women in Tanzania. Shaded areas represent confidence intervals. Adapted from Mehta et al.[16]

Table 2. Microorganisms Under the Control of Autophagy

Bacteria
Brucella abortus
Chlamydia trachomatis
Coxiella burnetii
Legionella pneumophila
Listeria monocytogenes
Myobacterium tuberculosis
Porphyromonas gingivalis
Salmonella species
Shigella flexneri
Staphylococcus aureus
Streptococcus pyogenes
Viruses
Coxsackievirus
Cytomegalovirus
Dengue virus
Herpes simplex virus
HIV-1
Influenza A virus
Poliovirus
Respiratory syncytial virus
Varicella zoster virus
Parasites
Schistosoma haematobium

Controlled trials of vitamin D supplementation have yielded favorable outcomes in patients with bacterial infections such as TB (in 3 of 4 studies) and *Helicobacter pylori* (in a single study); viral upper respiratory tract infection (in 2 of 4 studies) and influenza (in a single study); and parasitic infection with *Schistosoma haematobium* (in a single study). Favorable outcomes have not been detected, however, in patients demonstrating immune responses to hepatitis B virus or influenza virus vaccines.

There are few data on the use of vitamin D supplementation in HIV disease. One study showed that the combination of alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV disease.[25] A study of vitamin D as supplementary treatment for TB in HIV infection showed no benefit, although the dose used in the study (100,000 IU of cholecalciferol at baseline, 5 months, and 8 months) is considered likely to be too low to provide a therapeutic response.[26]

In addition to improved bone health, the potential benefits of vitamin D supplementation in HIV disease may include improved control of HIV replication, increased CD4+ cell count, slower rate of disease progression, improved control of opportunistic infections, decreased risk of HIV-related neurocognitive impairment, and improved overall survival. It remains unclear what the optimal dosage of vitamin D supplementation might be to provide some level of benefit for prevention or treatment of HIV or other infectious diseases. Current recommended dietary allowances (RDA) of vitamin D are 600 IU for persons 1 year to 70 years old and 800 IU for individuals older than 70 years. An adult therapeutic dose of cholecalciferol could be as high as 10,000 IU daily. Controlled clinical trials are needed to determine the optimal dosage of vitamin D supplementation and its potential benefits for HIV-infected persons.

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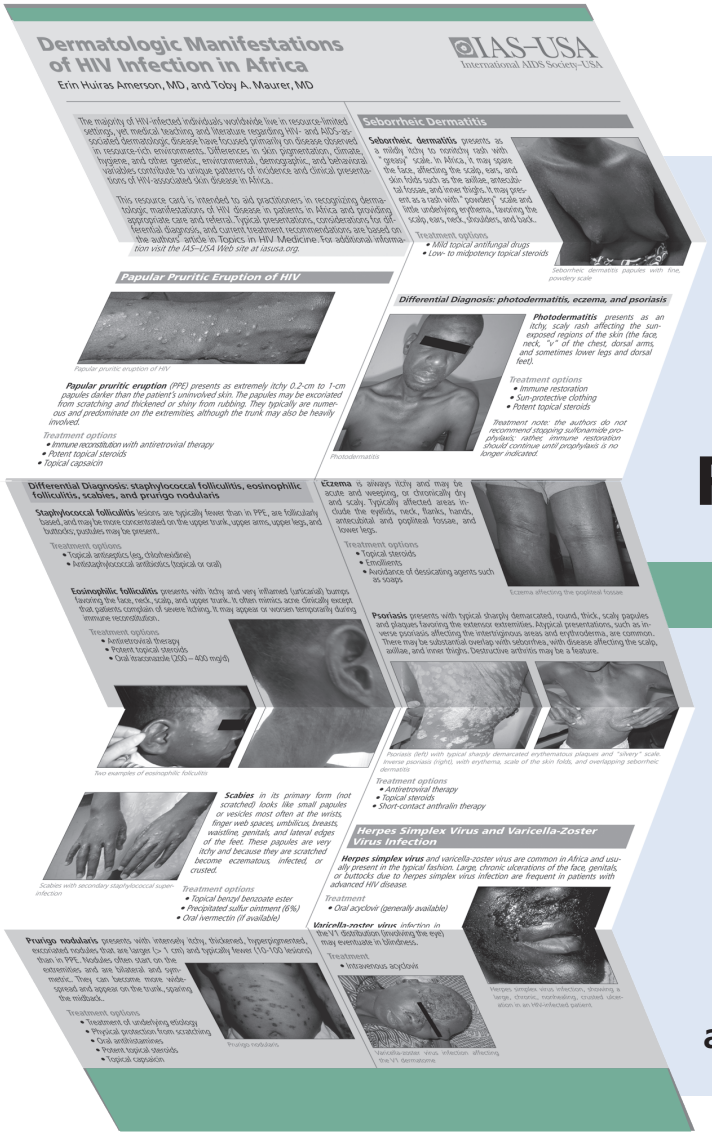

Dermatologic Manifestations of HIV Infection in Africa Resource Card

Cards Available

Based on the *Topics in HIV Medicine* article from February/March 2010, this folding card is available on request by visiting www.iasusa.org. Included are brief descriptions of selected dermatologic manifestations, along with their differential diagnoses and treatment options.