Nicotinamide: An Oral Antimicrobial Agent with Activity against Both *Mycobacterium tuberculosis* and Human Immunodeficiency Virus

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Coinfection with *Mycobacterium tuberculosis* and human immunodeficiency virus (HIV) is responsible for one-third of all deaths due to acquired immunodeficiency syndrome. More than 99% of cases of HIV–*M. tuberculosis* coinfection occur in the developing world, where limited resources add urgency to the search for effective and affordable therapies. Although antimicrobial agents against each of these infections are available, single agents that have activity against both *M. tuberculosis* and HIV are uncommon. The activity of nicotinamide has been evaluated in 2 different eras: in anti–*M. tuberculosis* studies performed during 1945–1961 and in anti-HIV studies performed from 1991 to the present. This review brings together these 2 bodies of inquiry and raises the possibility that, with more study, this small molecule could emerge at the beginning of the 21st century either as a therapeutic agent in itself or as the lead compound for a new class of agents with activity against both *M. tuberculosis* and HIV.

The story of nicotinamide's antimycobacterial capacity is unknown to many, because the literature predates the careers of most people currently involved in the treatment of these infections as well as the National Institutes of Health PubMed database [1]. In 1945, the first trials of streptomycin that involved humans were taking place in the United States [2], and a worldwide search for other effective anti–*Mycobacterium tuberculosis* therapies was underway. That year, in Paris, Ernst Huant [3] reported a serendipitous discovery regarding the use of nicotinamide for the treatment of patients undergoing radiation therapy for "lung tumors." He found that nicotinamide therapy, which he had initiated in an attempt to protect patients' mucous membranes from the effects of radiation, shrunk those lung infiltrates that were caused by *M. tuberculosis*. This report complemented another report from France by Chorine [4], who suggested a new role for nicotinamide, distinct from its known vitamin effect, as an anti–*M. tuberculosis* therapy. McKenzie et al. [5], who apparently were screening compounds without knowledge of either Huant or Chorine's work, independently confirmed these findings.

Two structurally related compounds, pyrazinamide and isoniazid, were found to be effective anti–*M. tuberculosis* therapies in the period from 1945 through 1951; these discoveries were made, in part, through the use of nicotinamide as a lead compound (figure 1) [6, 7]. Nicotinamide monotherapy resulted in clinical improvement for up to 64% of *M. tuberculosis*–infected patients described in published reports [8]. However, interest in nicotinamide as a treatment for *M. tuberculosis* faded rapidly when one of the foremost research groups of the day reported antagonism between nicotinamide and isoniazid when they were used together as a 2-drug therapeutic regimen [9].

By the 1990s, all of this information had fallen into relative obscurity. In fact, a comprehensive review of nicotinamide's pharmaceutical effects, published in 1991

Received 17 September 2002; accepted 18 November 2002; electronically published 31 January 2003.

Financial support: Foundation for Innovative Therapies (Cambridge, Massachusetts).

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Clinical Infectious Diseases 2003;36:XXX–XXX

1058-4838/2003/3604-00XX$15.00

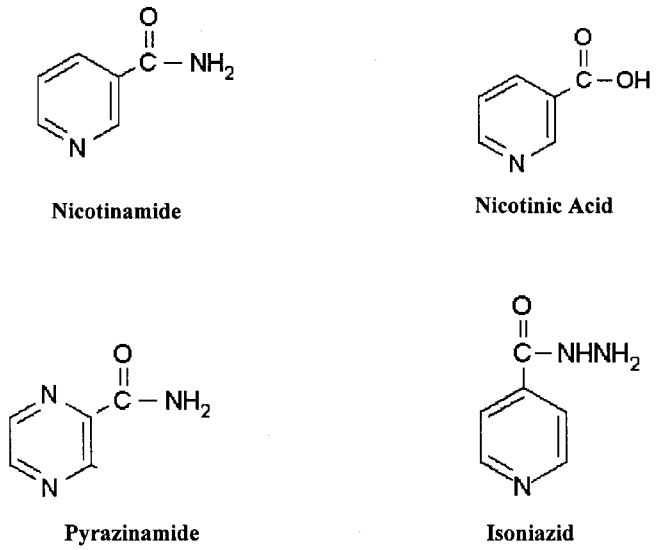

Figure 1. Structure of nicotinamide and related compounds

(the year of the first reported use of nicotinamide in HIV research), makes no mention of its effects against *M. tuberculosis* [10].

In the past decade, 3 different hypotheses have prompted the testing of nicotinamide for use as therapy for HIV. First, several groups studied the effects of treatment with nicotinamide for HIV, giving attention to its inhibitory activity against the nuclear enzyme poly-ADP ribose polymerase (PARP) [11, 12]. Second, in 1995, when we reported that nicotinamide was an inhibitor of HIV [13], our hypothesis was generated out of interest in potential correlations between pellagra and AIDS [14]. Third, Cossarizza et al. [15] pursued studies of nicotinamide in the context of its antioxidant properties, and they reported inhibition of HIV-induced cellular damage. Of interest, these hypotheses were all pursued without reference to the anti–*M. tuberculosis* data that preceded them by 30–50 years.

Single agents with activity against both HIV and *M. tuberculosis* are rare. Any such agent stirs interest both as a potential therapy and as a window on pathogenesis. Although some of the nucleoside reverse-transcriptase inhibitors have been shown to have antibacterial inhibitory effects in addition to their known antiretroviral effects, this antibacterial activity does not extend to mycobacteria [16]. A number of cytokines have been shown to be significant in both infections, and therapeutic cytokine delivery for these infectious diseases is an area of active investigation [17, 18]. Nicotinamide is neither a reverse-transcriptase inhibitor nor a cytokine. Although nicotinamide is an inexpensive and orally available agent without significant side effects that has been in use for 65 years, there remain many unanswered questions regarding its unusual antimicrobial spectrum.

NICOTINAMIDE AS A DRUG

Niacin is the generic name for 2 compounds: nicotinamide and nicotinic acid. Both nicotinamide and nicotinic acid were first used clinically in 1937, when these newly purified compounds were each shown to act as "pellagra-preventive" factors [19]. Niacin, also known as vitamin B_3, is considered part of the B vitamin complex. Niacin can either be synthesized in the body or acquired directly from dietary sources; in fact, by some definitions, niacin is not a vitamin, given that its synthesis in the human body is achievable. The majority of preformed dietary niacin is nicotinamide, not nicotinic acid, although both compounds are readily transported across the gastrointestinal epithelium [10]. In the body, nicotinic acid is converted to nicotinamide in hepatocytes and erythrocytes, and nicotinamide can then be transported in plasma to be used by all cells for the synthesis of nicotinamide nucleotides (i.e., nicotinamide adenine dinucleotide [NAD] and nicotinamide adenine dinucleotide phosphate) [20]. To fulfill routine dietary requirements, only 20 mg of niacin is required on a daily basis. When this dietary requirement is significantly exceeded, then niacin in either form is considered to be a pharmacological agent or drug. Although nicotinamide and nicotinic acid can be used interchangeably to treat diet-associated pellagra, their other pharmacological activities often differ (table 1) [10].

A recent study of the use of nicotinamide for the treatment of HIV-positive patients confirmed that dosages of 3 g/day could be well tolerated [22]. Studies of the use of nicotinamide for the treatment of *M. tuberculosis* have used similar dosages (e.g., 50 mg/kg/day) without attributable toxicity [9]. The pharmacokinetics of nicotinamide have been studied in humans; a study of twice-daily administration of oral nicotinamide in a total daily dose of 25 mg/kg revealed a plasma half-life of 3.5 h, and the mean maximum plasma concentration was 42.1 μg/mL (0.3 m*M*) [24].

M. TUBERCULOSIS AND NICOTINAMIDE

Additional clinical trials of the use of nicotinamide monotherapy for humans followed Huant's original observation. These studies were published as small series or case reports and occurred primarily in Europe [25]. Tanner [8] described 11 patients with pulmonary *M. tuberculosis* infection, most of whom had experienced failure of therapy with streptomycin, para-aminosalicylic acid, or both. He treated these patients with nicotinamide monotherapy for an average of 112 days, noting clinical

Table 1. Effects of niacin compounds (nicotinamide [NAm] and nicotinic acid [NAc]) against HIV and *Mycobacterium tuberculosis.*

Effect	NAc	NAm	Comment	First author [reference]
Improved serum lipid profile	+	−	Effects limited to NAc; accounts for most common pharmacological use of niacin compounds	DiPalma [10]
Pruritus	+	−	Limits use of NAc for some patients, not seen with NAm	DiPalma [10]
Flushing	+	−	Limits use of NAc for some patients, not seen with NAm	DiPalma [10]
Insulin resistance	+	+	Potential additive or synergistic problem if combined with HIV protease inhibitors	Dube [21]
Increased plasma level of tryptophan in HIV-positive patients	?	+	Small trial of NAm only, NAc's effects unstudied	Murray [22]
In vitro anti-HIV activity	−	+	Despite a lack of in vitro effects, NAc may have in vivo activity, given its routine conversion to NAm in the liver	Murray [13]
In vivo anti–*M. tuberculosis* activity	?	+	Animal models in the 1940s and 1950s suggested an effect for NAm but not for NAc; however, further study is warranted	Tanner [8]
Preserves β cell function in patients with new-onset type I diabetes	?	+	Under continued study	Pozzilli [23]

NOTE. +, Positive; −, no effect; ?, untested/unknown.

or bronchoscopic improvement in 7 of the 11 patients. Although apparently no head-to-head trials involving humans compared nicotinamide monotherapy with other therapies for *M. tuberculosis,* the effect of nicotinamide against *M. tuberculosis* was compared in the mouse model, where it exceeded the effect of para-aminosalicylic acid and was greater than or equal to the effect of streptomycin [26, 27], although nicotinamide was 7-fold less effective than pyrazinamide [28].

In 1953, soon after the first clinical use of isoniazid, it became apparent that this drug had adverse effects on the normal metabolism of 2 B complex vitamins: B_6[29] and niacin [30]. To this day, isoniazid remains better known for its more commonly observed effects on vitamin B_6 and the resultant peripheral neuropathy that can occur in patients who do not receive adequate amounts of vitamin B_6. It is less well known by clinicians that isoniazid can also significantly affect niacin metabolism and that it has been observed to induce clinical pellagra (i.e., niacin depletion) [31]. One link between vitamin B_6 and nicotinamide is the tryptophan oxidation pathway, which uses vitamin B_6 as a cofactor in the routine conversion of 1%–2% of dietary tryptophan to nicotinamide and nicotinamide nucleotides (figure 2). Studies of uninfected animal models have shown that isoniazid inhibits enzymes in the tryptophan oxidation pathway of the host [32]. In addition, in the absence of adequate amounts of available vitamin B_6, tryptophan's conversion to NAD is inhibited [33].

In 1961, on the basis, in part, of studies that successfully used the nicotinamide-derived drug pyrazinamide in combination with isoniazid [34], Jordahl et al. [9] tested the combination of isoniazid and nicotinamide for the treatment of humans. Their published study of 33 patients with pulmonary *M. tuberculosis,* 32 of whom had cavitary disease, showed that the use of nicotinamide and isoniazid as combination therapy resulted in a "reversal of infectiousness" significantly lower than that experienced by historical controls described in a study published 3 years earlier [35]. Only 27% of the patients receiving dual treatment, compared with 72% of the controls treated with isoniazid monotherapy, achieved clearing of mycobacteria from the sputum at 6 months after the initiation of therapy. At the time of this study, many had concluded that "any regimen containing isoniazid is superior to all others" [36, p. 75], and, so, these results essentially brought the clinical use of nicotinamide in mycobacteriology to a halt.

The antimycobacterial mechanism of action of isoniazid remained unclear for almost half a century, despite widespread use of the drug. In 1998, Rozwarski et al. [37] published evidence of a mechanism based on isoniazid covalently binding to the nicotinamide ring of NADH within the active site of the drug target. It is reasonable to speculate that the observed antagonism between nicotinamide and isoniazid could result from nicotinamide competing with NADH for isoniazid binding (figure 3), and one might also expect pyrazinamide, although structurally related, to be a less efficient inhibitor of isoniazid, given the alteration of its 6-member ring structure. Regardless of the precise mechanism of the mutual antagonism, one could expect clinical failures

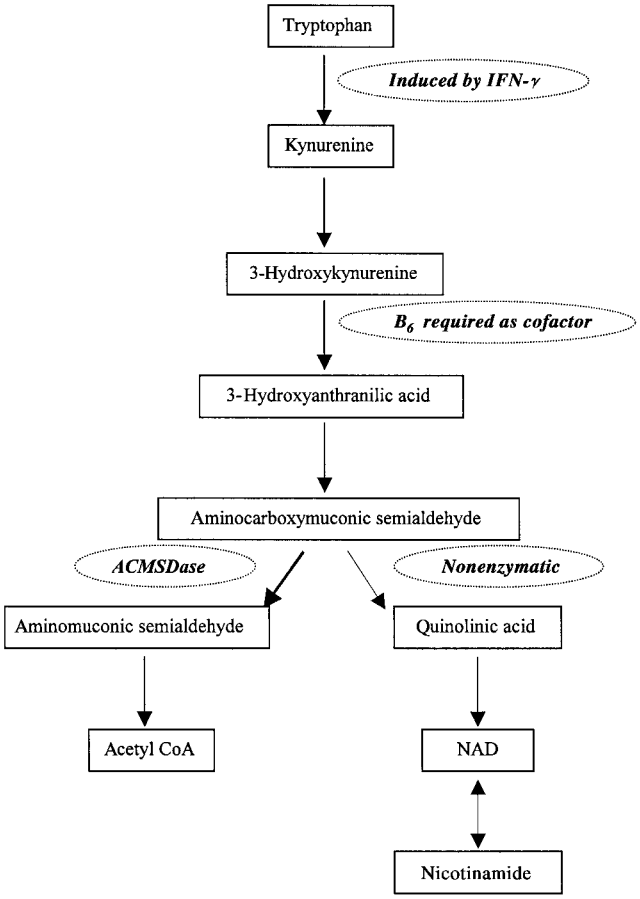

Figure 2. Oxidative metabolism of tryptophan. Less than 2% of dietary tryptophan is routinely converted to niacin and nicotinamide nucleotides in uninfected humans. The remainder of dietary tryptophan is used in protein production, serotonin synthesis, and the acetyl coenzyme A (CoA) arm of this pathway. ACMSDase, aminocarboxymuconic semialdehydase; NAD, nicotinamide adenine dinucleotide.

as well as the emergence of drug-resistant *M. tuberculosis* to be risks of combining isoniazid and nicotinamide, because standard doses of antagonistic therapies lead to subtherapeutic "effective concentrations" of those medications.

Pyrazinamide apparently is not antagonized by nicotinamide. These agents, however, share a cross-resistance mechanism through the inactivation of the mycobacterial enzyme nicotinamidase, which is also known as pyrazinamidase [38]. Therefore, although the combination of these drugs does not appear to be contraindicated, the standard recommendations for 3- and 4-drug therapies aimed at avoiding the emergence of resistance should not be altered outside of a controlled clinical trial [39].

HIV-1 AND NICOTINAMIDE

The first study of nicotinamide against HIV was published in 1991 [11]. This study showed the efficacy of nicotinamide and other PARP inhibitors as antiretroviral agents. Also, in 1991, Yamagoe et al. [12] reported that nicotinamide could inhibit the HIV long terminal repeat in an inducible in vitro system. Furlini et al. [40] demonstrated that HIV infection was associated with an increased intracellular ADP ribosylation of proteins. PARP activity recently was shown to be critical to efficient HIV integrase action, and inhibition of this enzyme with nicotinamide may cause inhibition at the point of proviral integration [41], although nicotinamide's activity in a postintegrational HIV model system suggests that other points in the virus's life cycle are also affected.

We have postulated that HIV induces niacin depletion. This is based on 4 observations: a pentad of features common to HIV and pellagra (table 2), the existence of a model for clinically significant infection-induced vitamin deficiency (i.e., measles and vitamin A) [42], the existence of other inducible nondietary niacin deficiency states (table 3), and the lack of any specific dietary niacin deficiency in HIV-positive patients [43]. Plasma tryptophan deficiency, which is 1 of 5 shared features of HIV and pellagra, has been demonstrated in HIV-positive patients by several groups. In a test of the use of pharmacological doses of nicotinamide for HIV-infected persons, we found a specific and significant increase in plasma tryptophan levels after 2 months of treatment with high-dose nicotinamide [22]. Further study is needed to determine whether this therapy has effects on virus load, immune function, or clinical outcomes.

Observational studies of niacin (i.e., pooled nicotinic acid and nicotinamide) intake among HIV-infected persons in the United States have suggested that even modest increases in niacin intake are associated with beneficial outcomes. Abrams et al. [44] observed that higher niacin intake was associated with higher CD4 cell counts. When Tang et al. [45] studied the Multicenter AIDS Cohort Study cohort with use of time to death as the clinical endpoint, they observed that a daily niacin intake equaling 3–4 times the US recommended daily allowance correlated, as an independent variable, with slower progression and improved survival. These data imply that increasing the niacin intake from the US recommended daily allowance of 20 mg/day (~0.3 mg/kg/day) to >64 mg/day (~1 mg/kg/day), independent of other interventions, may prolong the life of HIV-infected patients (figure 4). Although this dosage of niacin would not be expected to yield plasma concentrations comparable to the observed in vitro antiviral threshold, the effects of niacin

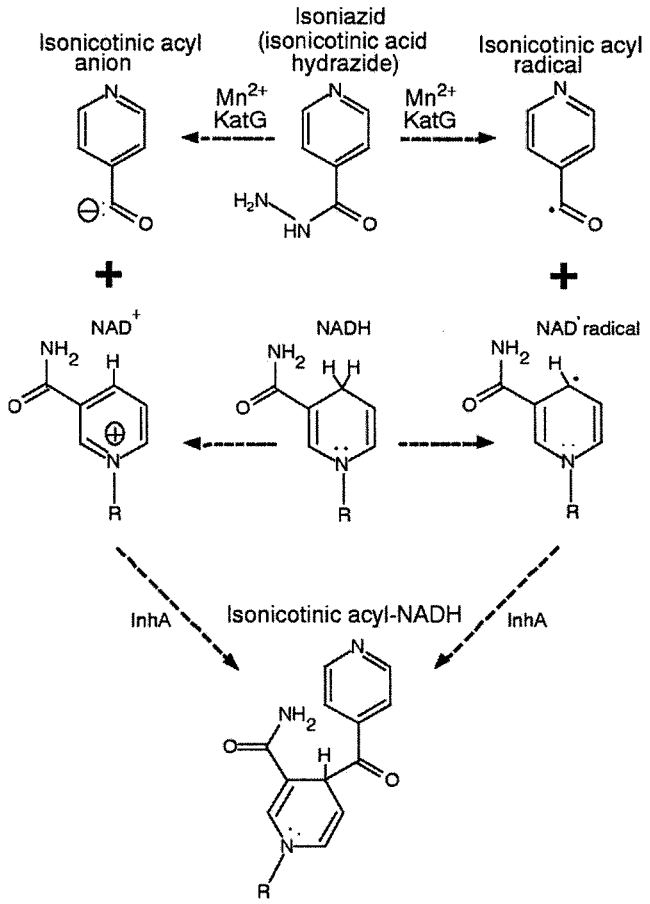

Figure 3. Proposed pathway for formation of the isonicotinic acyl-NADH inhibitor of InhA. Reprinted with permission from [37].

observed by Tang et al. [45] and Abrams et al. [44] may be the result of benefits other than direct antiviral effects, such as the repletion of intracellular NAD concentrations in uninfected non–T lymphocyte "bystander cells" [46].

NICOTINAMIDE'S ANTIMICROBIAL MECHANISM OF ACTION

Nicotinamide's antimicrobial mechanism of action is not currently known. Its activity may come to be understood as that of an indirect antimicrobial that has primarily a prohost effect. Among the reasons to suggest a prohost effect is the body of literature that reports an immunomodulatory role for nicotinamide in a wide variety of experimental systems [47–51]. One specific immunomodulatory effect is a change in HLA-DR expression [52]. Of interest, the expression of HLA-DR on T cells is doubled in patients with *M. tuberculosis* monoinfection and is tripled in patients with *M. tuberculosis*–HIV coinfection [53]; the effect of nicotinamide on T cell HLA-DR in patients with either *M. tuberculosis* or HIV has not yet been studied. Other potentially important immunomodulatory effects of nicotinamide include modulation of cytokine action [54], alterations in nitric oxide production [55], and regulation of the intercellular adhesion molecule [56]. Recent studies lay the groundwork for examining a role for nicotinamide in reversing an arrest in T cell proliferation linked to tryptophan depletion [57].

With regard to both *M. tuberculosis* and HIV infection, it has been observed that the host response includes an elevation of blood niacin levels [58, 59]. The methodology used to measure blood levels of niacin in these studies pools nicotinic acid together with nicotinamide, so that the contribution of the individual compounds to the overall elevation is not known. Although studies of uninfected healthy subjects demonstrate that nicotinamide makes up >80% of circulating niacin, further study is needed to determine whether the same 4:1 ratio of nicotinamide to nicotinic acid is maintained in infected persons [60]. The degree of elevation of blood levels of niacin in patients with both infections is similar: in patients with *M. tuberculosis* infection, the elevation is 22% greater than that in controls [58], and, in patients with HIV infection, the elevation is 17% greater than that in controls [59]. When elevated blood levels of niacin were first observed in patients with *M. tuberculosis* in the 1950s, it was proposed that this elevation could be attributable to the direct production of nicotinic acid by mycobacteria; however, the fact that HIV cannot synthesize niacin casts doubt on microbial niacin production as the complete explanation for elevated levels. Studies of blood levels of niacin in coinfected patients have not been reported to date. In both infections, there is evidence for activation of tryptophan's oxidative metabolism in response to infection; this response can raise blood concentrations of niacin independent of microbial metabolism (figure 2). More study of the innate drive to increase blood levels of niacin during these infections will likely contribute to our understanding of exoge-

Table 2. Pentad of shared features of classical dietary pellagra and HIV infection.

Shared feature
Plasma tryptophan depletion
Intracellular nicotinamide adenine dinucleotide depletion
Idiopathic dermatitis
Idiopathic diarrhea
Idiopathic dementia

Table 3. Dietary and nondietary causes of pellagra.

Cause
Dietary
Niacin deficiency
Tryptophan deficiency
Nondietary
Hartnup disease
Carcinoid tumors
Drug induced (e.g., isoniazid)

nous nicotinamide's antimicrobial mechanism of action.

The beneficial effects of nicotinamide for the treatment of HIV infection appear to be linked to cellular utilization of NAD. Nicotinamide appears to be void of any cell-free reverse-transcriptase inhibition or virucidal activities [13]. However several cell-associated observations link HIV, nicotinamide, and NAD. HIV-infected cells demonstrate an increase in the ADP ribosylation of proteins, a phenomenon in which NAD is used as the ADP-ribose donator to covalently modify proteins [40]. As a general feature, nicotinamide inhibits ADP ribosylation reactions. Protein ADP ribosylation can occur in the nucleus, in the cytoplasm, and on the cell surface of lymphocytes. PARP is a nuclear enzyme that catalyzes the formation of ADP-ribose polymers that attach to multiple different proteins. The activity of PARP is critical to the integration of foreign DNA, including proviral DNA; inhibition or absence of this enzyme interrupts the HIV life cycle [41]. Along with poly-ADP ribosylation, monoribosylation steps also involve proteins in cells, including the ADP ribosylation of both HIV Tat protein [61] and cellular defensins [62, 63]. The antimicrobial action of nicotinamide might also work through the modulation of certain histone deactylase reactions (i.e., Sir2 proteins) that use NAD in the silencing of chromosomal DNA expression [64].

CONCLUSION

More work is needed to define the exact mechanism of action of nicotinamide; however, it appears clear that increasing nicotinamide concentrations through pharmacological supplementation is consistent with the natural host response to both *M. tuberculosis* and HIV. It cannot, however, be assumed that infected patients would benefit simply from pharmacological doses of any or all "natural products." In patients with HIV infection, increased levels of zinc appear to be a risk for progression of disease [45], and vitamin A appears to have a deleterious effect at the extremes of the average dose range and a benefit in the middle dose range [45]. Vitamin D has been shown to benefit patients with *M. tuberculosis,* but it appears to stimulate HIV production in vitro [33, 65, 66]. Vitamin B_6 generally is thought to be critical to immune function [45, 67], and its benefit may be derived, in part, from its function as a cofactor in the production of nicotinamide and nicotinamide nucleotides from tryptophan [68, 69].

In the conquest of tuberculosis, as in the conquest of most diseases, some therapeutic leads have been abandoned to focus resources on the most promising therapies. The abandonment, in 1961, of nicotinamide as therapy for *M. tuberculosis* infection seemed reasonable in its day, but, with the new perspective of its activity against HIV disease, its use will require reevaluation. Although nicotinamide therapy generally is accessible without prescription, there are significant medical concerns that warrant its pharmacological use only within supervised clinical trial settings until more information is available. Most significant among those con-

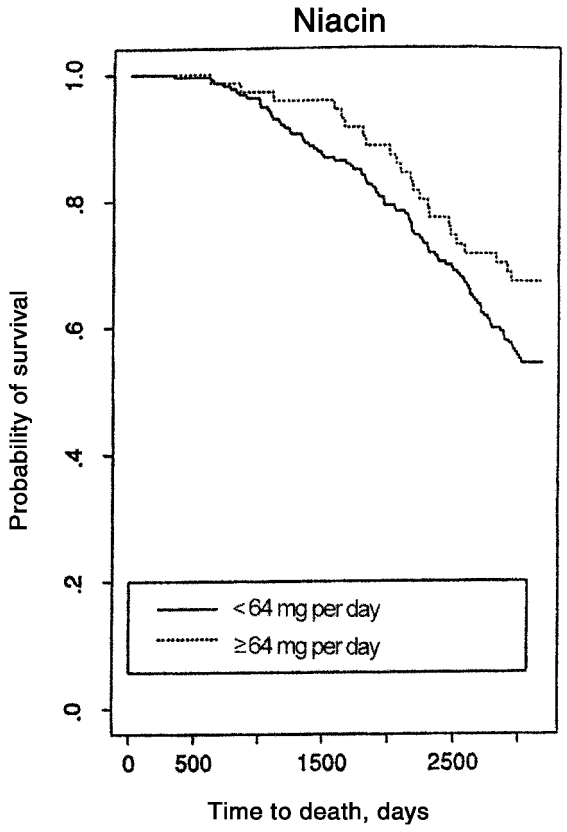

Figure 4. Kaplan-Meier survival curve demonstrating improved survival of HIV-infected patients with a daily niacin intake of ⩾64 mg/day (relative hazard, 0.57). The patient group ($n = 281$) was followed for 8 years (1984–1992). Reprinted with permission from [45].

cerns is the antagonism of isoniazid therapy and the potential for the emergence of drug-resistant *M. tuberculosis*—including primary nicotinamide resistance, pyrazinamide cross-resistance, and isoniazid resistance secondary to antagonism.

There is interest in nicotinic acid as a lipid-modulating agent for HIV-infected patients receiving HAART, and several clinical trials have been initiated [21, 70]. Nicotinic acid used in pharmacological doses would be expected to raise circulating nicotinamide concentrations in participating patients via conversion in the liver and red blood cells. Although it is possible that these clinical trials may shed light on the use of niacin compounds for the treatment of HIV-infected patients, drawing conclusions from the secondary analysis of any study always requires caution.

The death toll associated with HIV–*M. tuberculosis* coinfection was estimated to be 1 million deaths in 1999 [71]. Although nicotinamide, compared with most pharmacological agents, is a relatively weak inhibitor in both infections, there are several reasons to pursue evaluation of its potential use: it is nontoxic, orally available, and inexpensive, and it appears to have pro-host effects. Nicotinamide exists in food, but, unlike other vitamins, it can also be synthesized in the human body; therefore, it can be viewed as a vitamin or nutritional supplement in low concentrations or a drug when used in pharmacological concentrations. As with any drug, the use of nicotinamide needs to be monitored for potential associated side effects. Nicotinamide, a "pellagra-preventive" agent first used in 1937, may eventually contribute to therapeutic approaches of the 21st century as part of regimens used as "AIDS-preventive" agents [72] and "tuberculosis-preventive" agents.

Acknowledgments

I thank J. C. Sacchettini, D. P. Rogers, R. R. MacGregor, and M. M. Murray for their helpful comments and critical review of the manuscript.

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