ciency. Pregnant women who have iron deficiency are at higher risk for preterm birth, a low-birth-weight infant, and maternal death, which are factors that must be considered in balancing the potential risks and benefits of iron supplementation during HIV infection [3]. In developed countries, the epidemiology of anemia, nutritional status, and oxidative stress has changed with the advent of highly active antiretroviral therapy [4, 5], and further evaluation is needed to characterize the relationship between iron status and HIV disease severity in the era of highly active antiretroviral therapy [3]. Clinical trials are currently in progress to determine directly the risks and benefits of iron supplementation for adults with iron deficiency anemia and HIV infection.

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Ototoxicity May Be Associated with Protease Inhibitor Therapy

Sir—Simdon et al. [1] report 3 cases of ototoxicity associated with the use of nucleoside reverse-transcriptase inhibitors (NRTIs) in patients infected with HIV type 1 (HIV-1). They report that this brings to 8 the number of such cases reported in the literature, and they propose that mitochondrial toxicity, which is currently implicated in a wide variety of adverse conditions associated with NRTI therapy [2], is a possible cause. In support of this, they note the absence of case reports of ototoxicity associated with protease inhibitor use. I report here, however, a case in which auditory dysfunction was temporally associated with the use of lopinavir-ritonavir.

A 44-year-old Hispanic man had HIV infection diagnosed in 1995, with a baseline CD4 count of 21 cells/mm³. His past medical history included Pneumocystis carinii pneumonia, disseminated Mycobacterium avium complex infection, cerebral and pulmonary nocardiosis, idiopathic thrombocytopenic purpura, and chronic neutropenia. Since 1995, he had had extensive exposure to all currently available antiretroviral agents; virologic control has been poor, regardless of the regimen.

In November 2000, after review of genotypic and phenotypic data, the patient restarted therapy with standard dosages of stavudine, lamivudine, and abacavir, all of which he had received in the past without adverse effect, and lopinavir-ritonavir (400 mg b.i.d. and 100 mg b.i.d., respectively), which he had not received previously. Before he restarted therapy, his CD4 count was 2 cells/mm³, and his plasma HIV RNA level was 89,000 copies/mL. Concomitant medications included azithromycin, ethambutol, granulocyte colony-stimulating factor, acyclovir, omeprazole, dronabinol, clonazepam, hydrocodone, and loratidine, all of which had been taken consistently at the same dosages for many months. Within 3 months after he started the new regimen, the patient’s CD4 count had increased to 58 cells/mm³, and his plasma HIV RNA level had decreased to 7400 copies/mL.

Four weeks after starting the new regimen, the patient reported decreased auditory acuity accompanied by an intermittent lancinating pain in his left ear and a sensation of hearing in a “vacuum” or “tunnel.” Audiologic testing performed 7 weeks later indicated mild to moderate bilateral sensorineural hearing loss (speech reception threshold, 40-decibel hearing level [dBHL] bilaterally). On the same day, he discontinued the antiretroviral regimen without medical advice, and he reported subjective improvement in his hearing during the following week. One week later, he restarted antiretroviral therapy with the same NRTI regimen and substituted efavirenz for lopinavir-ritonavir. Two weeks later, he reported continued improvement in auditory acuity and continued following the new regimen. Audiologic testing was performed 20 weeks after he discontinued taking lopinavir-ritonavir, and it revealed borderline normal auditory acuity (speech reception threshold, 15 dBHL bilaterally).

The etiology of sensorineural loss associated with antiretroviral therapy is not known. Although it is possible that drug interactions between lopinavir-ritonavir and other medications in the patient’s regimen could have precipitated the problem, none of the nonantiretroviral medications in the regimen are known to be associated with ototoxicity.

Previous case reports have implicated NRTIs alone, perhaps because they are the most prevalent components of highly active antiretroviral therapy regimens. The circumstantial evidence from this case suggests that protease inhibitors may have an independent role in causing the ototoxicity associated with highly active antiretroviral therapy. Because a deleterious effect of protease inhibitors on mitochondrial function has not yet been

References

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documented, it seems less likely that mitochondrial dysfunction is implicated, as proposed by Simdon et al. [1].

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Reply

Str—We read with interest the letter from Dr. Williams [1] regarding our article on ototoxicity associated with the use of nucleoside analog reverse-transcriptase inhibitors [2]. Dr. Williams reports the case of a patient with AIDS who was receiving multiple medications and whose auditory acuity decreased bilaterally, accompanied by intermittent lancinating pain in his left ear, 4 weeks after potent antiretroviral therapy was initiated. Both the auditory dysfunction and the lancinating pain resolved when the patient discontinued his antiretroviral regimen 7 weeks after starting therapy. Symptoms did not recur when he resumed therapy at week 8, substituting efavirenz for lopinavir-ritonavir in his antiretroviral regimen. Dr. Williams concludes that lopinavir-ritonavir was the most likely cause of the patient’s transient auditory dysfunction [1].

We believe that several aspects of the case reported by Dr. Williams suggest diagnoses other than lopinavir-ritonavir ototoxicity. The patient was receiving other medications that have been associated with auditory dysfunction—most notably, azithromycin, which was presumably prescribed for disseminated Mycobacterium avium complex (MAC) infection. Reversible ototoxicity is a common complication of azithromycin given at the dosages used to treat disseminated MAC infection, with a reported incidence ranging from 14% to 26% [3–5]. As evidence that these other medications were not the cause of the patient’s audiologic symptoms, Williams [1] notes that the patient’s treatment with other medications had been stable for months, during which time symptoms were absent. However, azithromycin ototoxicity rarely manifests early during treatment [3, 4]. In one study of individuals infected with HIV type 1 (HIV-1) and treated with azithromycin for MAC infection or toxoplasmosis, azithromycin ototoxicity became manifest at a mean of 7.6 weeks after initiation of azithromycin treatment (range, 1.5–20 weeks) [4].

Poor adherence to medications is strongly suggested by the patient’s history of “extensive exposure to all currently available antiretroviral agents with poor virologic control, regardless of regimen” [1]. It seems possible that the patient discontinued azithromycin in addition to lopinavir-ritonavir when he changed regimens. Alternatively, lopinavir-ritonavir may have augmented azithromycin concentrations. Substantial increases in azithromycin levels have been shown to occur in the presence of nelfinavir [6], although the impact of other protease inhibitors on azithromycin concentrations has not been evaluated, to our knowledge. It has been hypothesized that the mechanism of augmentation of azithromycin levels may be nelfinavir-induced inhibition of P-glycoprotein (Pgp), which is important in azithromycin metabolism [6]. Ritonavir has been reported to be a potent inhibitor of Pgp [7], and lopinavir may be an inhibitor of Pgp as well, according to un-published data from Abbott Laboratories. Therefore, we believe that azithromycin ototoxicity, possibly augmented by lopinavir-ritonavir, is an important diagnostic consideration in the case described by Williams [1].

Another feature of this case that suggests diagnoses other than lopinavir-ritonavir ototoxicity is the lancinating pain in the patient’s ear. Lancinating pain is not typically associated with ototoxic agents. Instead, it suggests a local process near the ear. The patient was being treated with loratidine, which indicates that he may have had upper respiratory symptoms, possibly due to allergic rhinitis or sinusitis. Furthermore, his very low CD4+ T cell count, as well as his history of infections with Pneumocystis carinii, MAC, and Nocardia species (all of which have been reported to involve the ear in HIV-1–infected individuals [8]), raise the possibility of an opportunistic infection. Alternative scenarios to the proposed protease inhibitor–associated ototoxicity are an allergic rhinitis or an infection involving either the sinuses or the ears. Although improved auditory function was temporally associated with a change in antiretroviral therapy, it may have been merely coincidental with the resolution of a separate allergic or infectious process.

Regardless of whether the transient audiologic dysfunction of Dr. Williams’ patient was caused by lopinavir-ritonavir therapy, this does not diminish the significance of data presented in our paper concerning the association between nucleoside reverse-transcription inhibitors (NRTIs) and ototoxicity. One of the subjects described in our paper had never received a protease inhibitor, and, for the other 2 subjects, the worst symptoms of tinnitus and hearing loss developed when protease inhibitors were discontinued and NRTI therapy was intensified. Ototoxic agents do not continue to produce ototoxicity once administration has been stopped. Thus, even if protease inhibitors do cause ototoxicity, our data do not sug-