Ototoxicity Associated with Use of Nucleoside Analog Reverse Transcriptase Inhibitors: A Report of 3 Possible Cases and Review of the Literature

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Although a variety of adverse effects have been attributed to treatment with nucleoside analog reverse transcriptase inhibitors (NRTIs) for human immunodeficiency virus type 1 (HIV-1) infection, only 5 cases of ototoxicity have been reported in the literature. We describe 3 additional cases of possible NRTI-associated ototoxicity in HIV-1–infected patients, all of whom were aged >45 years, had a history of noise-induced hearing loss, and reported tinnitus and deterioration in hearing in the setting of antiretroviral therapy. Reductions in mitochondrial DNA content induced by NRTIs, as well as mitochondrial DNA mutations associated with aging and HIV-1 infection, all may contribute to auditory dysfunction in older patients with HIV-1 infection. Prospective studies are necessary to determine the incidence of tinnitus and hearing loss among HIV-1–infected patients and their relationship to the use of NRTIs.

The use of nucleoside analog reverse transcriptase inhibitors (NRTIs) to treat HIV type 1 (HIV-1) infection has evolved during the last 13 years from zidovudine (ZDV) monotherapy to complex treatment regimens that often consist of ≥2 NRTIs in combination with other antiretroviral drugs. Currently, 6 NRTIs are approved for the treatment of HIV-1 infection by the US Food and Drug Administration. Although a variety of adverse effects have been associated with the use of these agents, ototoxicity has been reported only rarely. Here we describe 3 cases of auditory dysfunction possibly associated with the use of NRTIs in patients infected with HIV-1 who were treated at an infectious disease clinic at the Denver Veterans Affairs Medical Center (VAMC) during the past 4 years.

CASE REPORTS

Patient 1. A 53-year-old man presented to the Denver VAMC in July 1996 for treatment of HIV-1 infection. The infection had been diagnosed in 1987 and during 1988–1996 the patient had received ZDV monotherapy. In early 1996, ritonavir had been added to his regimen. At the time he first presented to the Denver VAMC, he had a plasma HIV-1 RNA level of <500 copies/mL and a CD4+ T cell count of 474 cells/mm³. In addition to his antiretroviral medications, he was taking 325 mg aspirin daily and received monthly testosterone injections. He had a history of high-frequency hearing loss dating to the late 1970s, which was thought to be related to occupational noise exposure. During his initial visit to the Denver VAMC, he reported he
had first developed tinnitus in 1991, and then difficulty hearing conversations in 1993. He had a history of exposure to aircraft and construction noise in his work as a hospital corpsman, from which he had retired in 1995. Review of prior audiology results from 1986 and 1995 revealed that his hearing had declined from the upper limits of normal to severe bilateral sensorineural hearing loss during this 9-year period. Testing in 1996 suggested further progression of hearing loss (table 1). He had no history of opportunistic infections and no family history of hearing loss, and his rapid plasma reagin test was nonreactive. He was fitted with bilateral hearing aids.

In December 1996, the patient developed a deep venous thrombosis. Because of difficulties achieving anticoagulation due to interactions between warfarin and ritonavir, his antiretroviral therapy was changed to didanosine (ddl), stavudine (d4T), and nevirapine, and aspirin was discontinued. His plasma HIV-1 RNA level was well controlled on this regimen, and his CD4+ T cell count remained >400 cells/mm³. Over the next 6 months, he noted a marked decline in his hearing, and in June 1997, he asked his physician whether the antiretroviral drugs could be precipitating his hearing loss. Audiologic testing performed then and during the next 2 years revealed fluctuations in his hearing, but overall progression of his hearing loss was evident (table 1). He continues to take antiretroviral medications, including NRTIs. His profound hearing loss seriously impairs his ability to socialize.

**Patient 2.** A 47-year-old man presented to the Denver VAMC in 1992 for treatment of HIV-1 infection. He was unable to tolerate antiretroviral therapy until 1996, when he initiated treatment with indinavir, d4T, and lamivudine (3TC). His CD4+ T cell count was 52 cells/mm³, and his plasma HIV-1 RNA level was 274,000 copies/mL at the time he began therapy. Within 2 months of initiating therapy, the patient’s plasma HIV-1 RNA level dropped to <400 copies/mL, and his CD4+ T cell counts increased to >300 cells/mm³. He subsequently experienced multiple side effects attributed to indinavir, including nausea, bloating, and 2 episodes of renal colic. During the next 2 years, he continued d4T and 3TC therapy in combination with various HIV-1 protease inhibitors.

The patient initially complained of hearing loss to his physician in 1997 and was referred for audiologic testing. He had no history of opportunistic infections and no family history of hearing loss, and his rapid plasma reagin test was nonreactive. He reported that he had experienced stable, mild hearing loss and tinnitus beginning in 1966, when he had been exposed to machine-gun fire while on military duty in Vietnam. More recently, however, he thought his hearing was deteriorating. Audiologic testing revealed moderately severe bilateral hearing loss, which was substantially greater than a previous audiologic examination in 1985, which had demonstrated mild to moderate hearing loss (table 1).

**Table 1.** Audiologic test results in 3 HIV-1–infected patients with possible nucleoside analog reverse transcriptase inhibitor–associated ototoxicity.

<table>
<thead>
<tr>
<th>Patient, date of examination</th>
<th>Hearing acuity, dBHL</th>
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<tbody>
<tr>
<td></td>
<td>Right ear</td>
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<tr>
<td>1 20 Aug 1986</td>
<td>25</td>
</tr>
<tr>
<td>6 Jun 1991</td>
<td>30</td>
</tr>
<tr>
<td>7 Sep 1995</td>
<td>78</td>
</tr>
<tr>
<td>22 Jul 1996</td>
<td>92</td>
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<tr>
<td>23 Jul 1997</td>
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<tr>
<td>29 Oct 1997</td>
<td>103</td>
</tr>
<tr>
<td>12 Jun 1998</td>
<td>110</td>
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<tr>
<td>20 Dec 1999</td>
<td>108</td>
</tr>
<tr>
<td>2 5 Jun 1986a</td>
<td>53</td>
</tr>
<tr>
<td>24 Dec 1997</td>
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<td>28 May 1998</td>
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<td>75</td>
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<tr>
<td>3 27 Sep 1999</td>
<td>28</td>
</tr>
<tr>
<td>22 Dec 1999</td>
<td>26</td>
</tr>
</tbody>
</table>

**NOTE.** Complete audiologic assessments were performed and pure tone threshold averages at 2, 3, and 4 kHz are presented here in decibels hearing level (dBHL). A dBHL level of 0–25 indicates hearing within normal limits; 26–40 dBHL indicates mild loss of hearing; 41–60 dBHL indicates moderate loss of hearing; 61–80 dBHL indicates moderately severe loss of hearing; 81–90 dBHL indicates severe loss of hearing; and >90 dBHL indicates profound loss of hearing.

*a These tests were not performed at the Denver Veterans Affairs Medical Center.*

In May 1998, the patient was found to have a borderline vitamin B₁₂ level of 209 pg/mL, and replacement therapy was begun. In September 1998, the protease inhibitor was discontinued from his regimen because of intolerance, and ddl, hydroxyurea (HU), and efavirenz (EFV) were added to d4T and 3TC. In January 1999, he reported the simultaneous onset of burning pain in his feet and severe tinnitus and asked whether the antiretroviral agents could be causing his symptoms. At the time he developed these symptoms, he was taking acyclovir for recurrent genital herpes, sodium valproate for manic depression, trazodone for insomnia, propoxyphene napsylate and acetaminophen for chronic right foot pain, testosterone injections, and vitamin B₁₂. His antiretroviral medications were discontinued; both the peripheral neuropathy and the tinnitus improved but did not completely resolve.

In April 1999, antiretroviral therapy with ZDV, 3TC, abacavir, and EFV was reinitiated. Both the neuropathy and tinnitus rapidly worsened. The patient has continued to receive
This therapy and maintains an undetectable plasma HIV-1 RNA copy level. Audiology testing in December 1999 revealed severe hearing loss without evidence of significant progression during the past 2 years (table 1). The patient now wears bilateral hearing aids and reports that the tinnitus is intolerable.

**Patient 3.** A 49-year-old veteran with a history of HIV-1 infection for at least 13 years presented to the Denver VAMC in October 1998 for treatment. He had never taken antiretroviral medications. His CD4+ T cell count was 225 cells/mm³, his CD4+ lymphocyte percentage was 13%, and his plasma HIV-1 RNA level was 4604 copies/mL. He had no history of opportunistic infections and no family history of hearing loss, and his rapid plasma reagin test was nonreactive. He had a history of stable hearing loss in the left ear since the early 1970s, when a machine-gun shell exploded near his ear while he was on active duty in Vietnam.

Treatment was initiated with EFV, d4T, 3TC, and trimethoprim (160 mg daily) and sulfamethoxazole (800 mg daily), and the patient rapidly achieved and maintained an HIV-1 RNA level of <50 copies/mL. Approximately 4 months after starting antiretroviral therapy, he noted the new onset of tinnitus and worsening hearing in the left ear. His symptoms progressed from intermittent to constant tinnitus during a 2-month period, and the hearing loss subjectively worsened as well. On a routine clinic visit, he asked the physician whether the medications could be causing the “buzzing” in his ear. At that time, the physician discontinued d4T and started ZDV. One month later, the patient reported some improvement of both the tinnitus and the hearing loss, although not complete resolution. He had no symptoms or signs of neuropathy. Audiology testing revealed mild hearing loss in the right ear and moderately severe hearing loss in the left ear, which was unchanged during a 2-month period (table 1). No prior audiology results were available. The patient continues to take antiretroviral medications, and his tinnitus and hearing loss persist.

**DISCUSSION**

All patients described here had a history of noise-induced hearing loss that reportedly worsened in association with tinnitus in the setting of antiretroviral therapy. Hearing loss due to noise exposure does not progress after the exposure ceases [1]. Thus, prior noise exposure cannot explain subsequent hearing loss or tinnitus in these patients. Patient 1 developed tinnitus and moderately severe hearing loss between 1986 and 1995, a time during which he was diagnosed with HIV-1 infection, initiated ZDV monotherapy, and experienced occupational noise exposure. It is very unlikely, however, that the level of noise that he was exposed to in his job as a hospital corpsman would produce the magnitude of hearing deficits that developed. Even after his retirement in 1995, his hearing continued to decline, with a 30–decibels hearing level (dBHL) loss in his right ear and a 15-dBHL loss in his left ear during the next 4 years. Although he was taking 325 mg aspirin daily, this dosages does not usually cause ototoxicity, and his hearing loss continued to progress even after the aspirin was discontinued in 1996, when he started d4T and 3TC. Thus, these data suggest that ZDV and subsequently d4T and 3TC may have played a role in this patient’s progressive auditory dysfunction.

Patient 2 experienced a decrease in hearing of ~25 dBHL bilaterally between 1985 and 1999, a period when he was not experiencing noise exposure but during which he became infected with HIV-1 and began antiretroviral therapy. This patient had a history of borderline vitamin B₁₂ deficiency as well as exposure to trazodone and valproic acid, all of which have been implicated rarely in hearing loss and tinnitus [2–4]. Thus the evidence is not definitive that his progressive hearing loss was caused by antiretroviral therapy. However, the acute onset several months after initiation of HU and multiple NRTIs of severe tinnitus and peripheral neuropathy, the latter of which is a well-known toxicity of NRTIs [5] that is exacerbated by HU [6], suggests that antiretroviral therapy may have been a precipitant of his tinnitus. The partial improvement in both symptoms with cessation of antiretroviral therapy, and subsequent worsening with reinitiation of antiretroviral therapy, further implicate antiretroviral therapy as a cause of his severe tinnitus.

For Patient 3, acoustic trauma occurred >25 years before the onset of symptoms of worsening auditory function, and he was not taking any other ototoxic medications. It is impossible to verify his subjective sensation of worsening hearing because there is no audiologic examination available before the onset of his symptoms. His tinnitus, however, was a distinctly new symptom, and in the absence of other obvious causes, it is suggestive of ototoxicity due to antiretroviral therapy.

An increased incidence of auditory dysfunction among patients infected with HIV-1 has been documented in several studies [7–13]. Multiple causes for auditory dysfunction have been described, including otitis media due to bacterial pathogens [14–16] and, rarely, *Pneumocystis carinii* [15, 17, 18]; opportunistic infections of the CNS [15, 16, 19, 20], such as toxoplasmosis, cytomegalovirus, tuberculosis, and cryptococcosis; neurosyphilis [21, 22]; malignancies, including Kaposi’s sarcoma [16] and lymphoma [15]; HIV-1 infection [23]; and treatment with ototoxic drugs [15, 24, 25]. HIV-1 protease inhibitors and non-NRTIs have never been reported to cause ototoxicity. Five previous case reports have associated NRTIs with hearing loss; hearing loss was attributed to dideoxycytidine for 3 patients [26–28], ddI for 1 patient [29], and the combination of ddI and ZDV for 1 patient [30]. A study of 99 HIV-1–infected patients who attended an outpatient clinic in Seattle found that 29% demonstrated abnormalities on screening audiometry [12]; use of NRTIs within...
the previous 6 months was significantly associated with hearing loss in patients aged >35 years, but not in those aged <35 years.

All 3 of the patients with progressive auditory dysfunction presented here were older than the average HIV-1-infected patient at the Denver VAMC. In all instances, at the time they began to experience worsening auditory function, their antiretroviral regimens contained NRTIs, including ZDV monotherapy, d4T-3TC, and d4T-3TC-ddI-HU. The cases reported here are consistent with the previous literature, in that they suggest an association between NRTIs and ototoxicity in older HIV-1-infected patients, and they implicate NRTI combinations that have not been previously described. These cases also suggest a possible association between antecedent hearing loss and NRTI-induced ototoxicity that has not been reported previously. These patients’ prior hearing deficits may have been an indicator that they were more susceptible than others to ototoxicity. Alternatively, their deficits may have made them more sensitive to NRTI-associated hearing loss that could be occurring on a subclinical level in others. In either case, these data suggest that NRTIs should be used sparingly in patients with preexisting hearing loss.

Many of the toxicities of NRTIs, including hearing loss, have been ascribed to mitochondrial toxicity [12, 31–33]. Aging [34–37], HIV-1 infection [38], and hearing loss [39–42] have been associated with mitochondrial DNA mutations. If NRTIs cause hearing loss through mitochondrial toxicity, it is possible that they synergize with mitochondrial abnormalities induced by HIV-1 infection and age to produce greater auditory dysfunction in older HIV-1–infected patients. As the population infected with HIV-1 survives longer because of the success of potent combination antiretroviral therapy, more cases of NRTI-associated ototoxicity may occur. Prospective studies are needed to confirm whether NRTIs are associated with auditory dysfunction and, if so, to identify the NRTIs most likely to induce ototoxicity and determine which patients are most susceptible.

References


