HIV-associated motor neuron disease

HERV-K activation and response to antiretroviral therapy

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ABSTRACT

Objective: To determine whether there is activation of human endogenous retrovirus K (HERV-K) in amyotrophic lateral sclerosis in HIV infection and whether it might respond to treatment with antiretroviral drugs.

Methods: In this case series, we present 5 patients with HIV infection who subsequently developed motor neuron disease involving both upper and lower motor neurons. We monitored HERV-K levels in plasma of 4 of these patients.

Results: Three patients who received antiretroviral therapy had reversal of symptoms within 6 months of onset of neurologic symptoms and the other 2 had slow neurologic progression over several years. Three patients in whom the levels were measured at onset of neurologic symptoms showed elevated HERV-K levels that responded to optimization of antiretroviral therapy for CNS penetration.

Conclusions: Thus, motor neuron disease in individuals with HIV infection may a treatable entity, but early treatment with CNS-penetrating antiretroviral therapy may be necessary. Monitoring of HERV-K levels may help guide treatment. *Neurology*® 2016;87:1756–1762

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ARV** = antiretroviral; **CPE** = CNS penetration efficacy; **HERV-K** = human endogenous retrovirus K; **MND** = motor neuron disease; **NCV** = nerve conduction velocities.

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease with a mortality rate of nearly 90% within 5 years. The underlying cause remains unknown, although several genetic forms have been identified. An ALS-like syndrome may also occur in some patients with HIV infection with neurologic manifestations that are indistinguishable from idiopathic ALS except that it may occur at a younger age, and may be accompanied by neurologic findings typically attributed to HIV infection alone. Of interest, the majority of these patients show variable degrees of response to antiretroviral (ARV) drugs with nearly complete reversal in some.[1–7] However, in these case reports, long-term follow-up is not available and the pathophysiology is unknown.

It is known that reverse transcriptase activity can be found in the brain and blood of patients with ALS.[8–11] However, a search for exogenous retroviruses has been negative.[9,12] We found activation of a human endogenous retrovirus K (HERV-K) in the brain and cortical neurons of these patients.[13,14] Endogenous retroviruses constitute approximately 8% of the human genome. Most of these are highly mutated and do not form functional genes. However, the HERV-K group of retroviruses is the most recently acquired and is integrated into the genome at multiple sites. They have intact open reading frames for some or all genes.[15] Expression of the virus or its envelope protein in neurons was cytotoxic, and transgenic mice with the envelope protein developed features characteristic of ALS.[14] HERV-K can also be activated by the Tat protein of HIV.[16] We present 5 patients with HIV infection who developed motor neuron disease (MND) and were treated with ARV and monitored for HERV-K activity in the blood.

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Supplemental data at Neurology.org

From the Section of Infections of the Nervous System, National Institute of Neurological Diseases and Stroke (L.N.B., R.T., W.L., T.A., B.S., A.N.), and National Institute of Allergy and Infectious Diseases (M.W.), NIH, Bethesda, MD; and National Neurological AIDS Bank and Department of Neurology (E.J.S.), University of California, Los Angeles.

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METHODS **Standard protocol approvals, registrations, and patient consents.** All patients were studied at the NIH Clinical Center in Bethesda, MD, and the case series received approval by the institutional review board. The clinical profile of the patients is presented in table 1 and neurologic course is shown in the figure. We used the CNS penetration efficacy (CPE) method[17] that assigns a value of 1 (below average), 2 (average), 3 (above average), and 4 (much above average) to each ARV agent. A drug's CPE reflects its estimated effectiveness in the CNS.[18]

RESULTS **Case 1.** A 29-year-old man with hemophilia type A and HIV infection developed progressive weakness. He acquired HIV and hepatitis C shortly after birth and was treated with ARV therapy until 2001 when he self-discontinued the therapy. In November 2004, he developed right hand weakness followed by left hand and right leg weakness over 3 months. Examination showed prominent weakness in the right arm and left leg with atrophy of the right hand without fasciculations. Sensory examination, deep tendon reflexes, and plantar responses were normal. MRI of the brain and cervical spine was unremarkable. EMG and nerve conduction velocities (NCV) showed widespread acute denervation and no sensory involvement consistent with MND (table e-1 at Neurology.org).

He restarted ARV therapy (table 1). His strength improved and in May 2006, his neurologic examination was unremarkable other than brisk reflexes. His $CD4^+$ cell count was 402 cells/mm^3 and the plasma HIV was undetectable. A telephone interview in December 2015 indicated that he had occasional fasciculations in the upper limbs without weakness. He continues on the same ARVs and the plasma HIV remains undetectable.

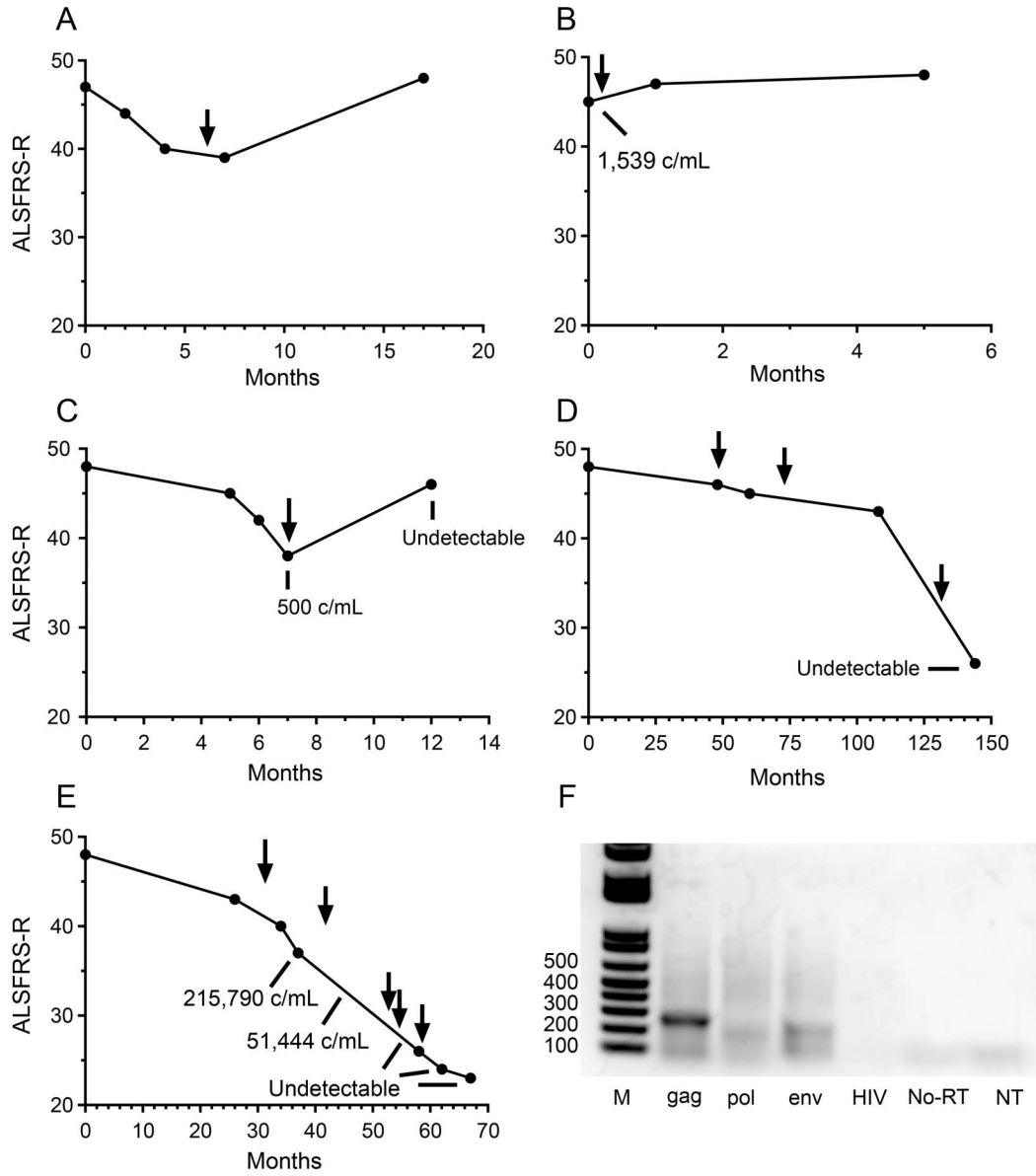
Case 2. A 32-year-old man developed HIV-related opportunistic infections and left upper extremity weakness in July 2014. He had active pulmonary enterovirus and rhinovirus infections, cytomegalovirus retinitis and colitis being treated with ganciclovir, candida esophagitis treated with fluconazole, and facial and oral Kaposi sarcoma. He was diagnosed with HIV infection in 2012, and was treated with ARV therapy (table 1) until June 2013 but stopped the therapy because of a rash. Ten days before presentation, he noted weakness of proximal arms, predominantly left-sided, which progressed to difficulty with writing. On presentation, he had bilateral upper extremity muscular atrophy with prominent winging of the right scapula. Lower extremity strength was normal with no fasciculations. Bulbar muscle evaluation was limited because of right facial Kaposi sarcoma. Reflexes were 3+ in upper extremities, 1+ at the knees, and absent at the ankles. MRIs of the brain and cervical cord were unrevealing, and CSF testing for opportunistic infections was negative. The $CD4^+$ cell count was 6 cells/mm^3 and the plasma HIV was 36,924 RNA copies/mL. EMG and NCV showed active denervation and chronic neurogenic changes (e-Methods). The combination of upper and lower

Table 1 Clinical characteristics of the patients

Case	Sex	Age at symptom onset, y	Age at HIV infection	Clinical symptoms	ARV therapy	Symptom response to treatment	HERV-K plasma levels
1	M	29	Birth	Weakness in hands and shoulder, right greater than left	Indinavir/ritonavir/emtricitabine/tenofovir (6 mo after symptoms; CPE = 9)	Return of full strength	Not tested
2	M	32	30	Bibrachial atrophy and weakness	Efavirenz/emtricitabine/tenofovir (stopped 1 year before symptoms; CPE = 7); abacavir/lamivudine/dolutegravir (1 mo after symptoms; CPE = 9)	Recovery of upper extremity strength following ARV therapy	1,539 copies/mL
3	M	62	54	Loss of proximal arm strength and hand strength; progression to legs	Lopinavir/ritonavir/emtricitabine/tenofovir (5 y before symptoms; CPE = 8); lopinavir/ritonavir/abacavir/lamivudine (2 y before symptoms, noncompliant; CPE = 9); lopinavir/ritonavir/abacavir/lamivudine (7 mo after symptoms, compliant; CPE = 9); IVIg (11 mo after symptoms)	Medication compliance with improvement in symptoms	500 copies/mL (undetectable ARV compliance)
4	M	33	32	Atrophy and fasciculations in legs, especially feet and thighs; progressed to shortness of breath and dysphagia	Ritonavir/atazanavir/emtricitabine/tenofovir (59 mo after symptoms; CPE = 7); efavirenz/emtricitabine/tenofovir + IVIg (92 mo after symptoms; CPE = 7); dolutegravir/emtricitabine/tenofovir (155 mo after symptoms; CPE = 8)	Slow progression of neuromuscular weakness over 13 y; wheelchair-bound	Undetectable 13 y after symptom onset
5	M	47	42	Fasciculations, extremity weakness predominantly in legs; progression to shortness of breath and dysphagia	Raltegravir/emtricitabine/tenofovir (15 mo after symptoms; CPE = 7); darunavir/ritonavir/abacavir/lamivudine/raltegravir (37 mo after symptoms; CPE = 12); abacavir/lamivudine/raltegravir (41 mo after symptoms; CPE = 8); darunavir/ritonavir/abacavir/lamivudine/raltegravir (55 and 59 mo after symptoms; CPE = 12)	Continued slow progression 5 y later; wheelchair-bound	215,790 copies/mL (undetectable after new ARVs)

Abbreviations: ARV = antiretroviral; CPE = CNS penetration efficacy; HERV-K = human endogenous retrovirus K; IVIg = IV immunoglobulin.

Figure Effect of antiretroviral therapy in patients with HIV and motor neuron disease



Disease duration is measured against the ALSFRS-R[19] for each patient represented in graphs (A–E). Arrows denote time of initiation or change of antiretroviral therapy and thick lines denote HERV-K viral load in plasma. (F) For case 5, the PCR amplicons for HERV-K gag, pol, and env primers were resolved on a 2% agarose gel along with the no template (NT) and no reverse transcriptase (No-RT) controls. For size determination, a 1-kb ladder (M) was run next to the PCR products. The amplicons for HERV-K gag, pol, and env were extracted from the gel and sequenced. ALSFRS-R = ALS Functional Rating Scale; HERV-K = human endogenous retrovirus K.

motor neuron findings was thought consistent with MND. He began ARV therapy (table 1). By August 2014, he had improved, with near normal strength. His reflexes were brisk and plantar responses were up going. Plasma HERV-K levels were 1,539 copies/mL. He was lost to further follow-up.

Case 3. A 62-year-old man with HIV infection presented with progressive weakness in July 2013. He was diagnosed with HIV infection in 2007 and started ARV therapy within a year of diagnosis. Other comorbidities included hepatitis C, prior cocaine and methamphetamine use, chronic alcohol use, and pernicious anemia.

In December 2012, he noted mild weakness of the right arm. By June 2013, he had dysphagia and strength was diminished in the distal arms and legs. Deep tendon reflexes were diminished in the upper limbs, brisk at the knees, and absent at the ankles. Hoffmann reflex was present. Fasciculations were noted in both calves. Extensive neuroimaging studies, autoantibody testing, and CSF studies were unrevealing. EMG/NCV was consistent with MND (e-Methods). At the time of our evaluation in July

2013, his $CD4^+$ count was 889 cells/mm^3, and plasma HIV was 75 RNA copies/mL. He was on ARV therapy but was noncompliant. He had upper extremity spasticity and progression of motor weakness over the prior 3 months with gait instability due to bilateral foot drop. There was prominent atrophy in the hands, triceps, and tibialis anterior muscles and the plantar responses were extensor. His plasma HERV-K levels were 500 copies/mL. HIV was undetectable in the CSF. However, CSF had pattern 3 oligoclonal banding with no pleocytosis or albuminocytologic dissociation. EMG/NCV confirmed the presence of active denervation and chronic neurogenic changes with reduced recruitment in at least 3 body segments, sparing sensory responses, and supporting the diagnosis of clinically definite ALS. Plasma HIV genetic testing did not show drug resistance mutations, and he was urged to improve compliance with his ARV medications. Follow-up 1 month later showed improvement in fine motor control and ambulation without return of full strength. He continued to have dysphagia. Follow-up HERV-K levels were undetectable in plasma. He continues to have fasciculations and cramps in his arms and legs with return of near-normal strength.

Case 4. A 46-year-old man with HIV infection was seen in December 2015 with a diagnosis of HIV-associated MND. He had likely contracted HIV infection in 2001 and a year later, developed muscle pain, twitching, and fatigue. He initially had left foot weakness, which progressed to the right and then proximally over 2 years. By August 2005, he had diffuse fasciculations in both thighs and mild generalized atrophy. EMG/NCV showed chronic motor denervation and reinnervation with fasciculation potentials (e-Methods). He was diagnosed with HIV infection in September 2005. The $CD4^+$ cell count was 467 cells/mm^3, HIV in plasma was 15,125 RNA copies/mL, and CSF was 5,700 RNA copies/mL. He was treated with ARV therapy (table 1).

In March 2007, he had brisk upper but diminished lower extremity reflexes with a new extensor plantar response on the left. By March 2008, he developed shortness of breath and decreased exercise tolerance. HIV in CSF was <50 copies RNA/mL and serum creatine phosphokinase was 531 U/L. Since 2005, the creatine phosphokinase levels had ranged from 300 to 900. By December 2008, he developed difficulty in climbing stairs independently. EMG and NCV showed progression of active denervation and reinnervation in all muscles sampled compared to a study in 2005. In January 2009, he began wearing leg braces intermittently and had difficulty lifting his arms above his head. In May 2009, he had a 20% decrease in forced vital capacity as compared to 2006. In July 2009, he was treated twice with IV immunoglobulin but his neurologic status continued to decline.

His ARV therapy was changed (table 1) in August 2009. By November 2012, he was using a wheelchair when he left the house but continued to ambulate independently at home. By December 2013, he had complete loss of strength in both anterior tibialis muscles. Throughout 2014, he had only slight progression of muscular weakness. In October 2014, he was treated with a 6-month course of IV immunoglobulin and his ARV regimen was changed (table 1). By January 2015, he was using a wheelchair intermittently and had developed more persistent shortness of breath and worsening of bilateral arm weakness. He was areflexic in upper and lower limbs. By December 2015, he was fully wheelchair-bound but able to stand for short amounts of time independently.

Case 5. A 50-year-old man with HIV infection was evaluated for signs of a progressive MND. He was diagnosed with HIV-1 infection in March 2010 but declined ARV therapy. In June 2010, he developed intermittent left arm fasciculations, which spread to all 4 extremities. In September 2011, the $CD4^+$ cell count was 9 cells/mm^3 and plasma HIV viral load was 14,362 RNA copies/mL. He was started on ARV therapy (table 1), and HIV plasma viral load was undetectable. By the summer of 2012, he had diminished dexterity of the hands and was unable to lift objects weighing 10 pounds or more. By August 2012, he noted dyspnea especially with exertion. EMG/NCV showed active denervation and chronic reinnervation with reduced recruitment in the left arm, leg, and thoracic paraspinal muscles consistent with early MND. In April 2013, he was started on nightly BiPAP (bilevel positive airway pressure). In June 2013, his ARV was changed (table 1).

On evaluation at the NIH in July 2013, he had progression of motor symptoms with mild shortness of breath, bilateral upper and lower extremity atrophy, weakness and fasciculations, as well as upper and lower extremity hyperreflexia. His HERV-K plasma levels were 215,790 RNA copies/mL. Sequencing of the *gag* gene product showed complete homology to HERV-K sequence from chromosome 22q 11.21. In July 2013, ritonavir-boosted darunavir was added to his ARV regimen. He discontinued the darunavir and ritonavir after several months. HERV-K levels in plasma in April 2014 were 51,444 copies/mL and were undetectable in November 2014. Examination in April 2015 showed slow progression, predominantly in the lower extremities with no bulbar signs, with occasional wheelchair use. He restarted darunavir and ritonavir. HERV-K levels remained undetectable upon retesting in April and

October 2015. By January 2016, he was wheelchair-bound, with little use of both hands and occasional dysphagia.

In summary, cases 1 through 5 showed either recovery or slow progression in motor symptoms as measured by the revised ALS Functional Rating Scale[19] (figure). In cases where treatment with combination ARV therapy was initiated within 6 months of symptom onset, they had nearly complete motor recovery (figure, A–C). Case 1 had weakness of upper and lower limbs and was treated with indinavir, ritonavir, and emtricitabine/tenofovir (figure, A). Case 2 had weakness of both upper limbs only and was treated with abacavir, lamivudine, and dolutegravir. His HERV-K viral load was 1,539 copies/mL at the time of onset of symptoms and clearance was not confirmed as he was lost to follow-up (figure, B). Case 3 had upper and lower extremity weakness with dyspnea and became compliant with lopinavir, ritonavir, abacavir, and lamivudine. His HERV-K viral load was 500 copies/mL at the time of onset of symptoms and became undetectable after treatment (figure, C). Cases 4 and 5 had gradual decline in neurologic function despite treatment with combined ARV therapy but are long-term survivors. Case 4 was treated with ritonavir, emtricitabine, tenofovir, and atazanavir initially but then switched to dolutegravir, emtricitabine, and tenofovir. On follow-up 13 years after symptom onset, his HERV-K viral load was undetectable (figure, D). Case 5 had dyspnea and orthopnea with limb involvement at time of onset and was treated with raltegravir, emtricitabine, and tenofovir initially but HERV-K viral load despite treatment was 215,790 copies/mL in plasma. He was later switched to abacavir, lamivudine, darunavir, ritonavir, and raltegravir. The HERV-K viral load progressively deteriorated and became undetectable (figure, E).

DISCUSSION We present 5 patients with HIV infection who developed signs and symptoms of MND. All patients had upper and lower motor neuron involvement and several patients had serial EMG/NCV performed by different operators at different institutions suggesting the results were consistent over time. None of these patients had evidence of HIV myelopathy.[20,21] Although all patients had symptoms, signs, and neurophysiologic evidence of ALS, we have used the term MND for patients with comorbid HIV infection. Because ALS has always been a universally fatal disease and patients with HIV-associated MND have shown an improvement in motor symptoms when treated with ARV therapy, we prefer to distinguish the diagnoses.

MND is a rare manifestation of HIV infection. In a prior literature review, we had identified 29 cases.[1] Since then, one case of HIV infection and ALS-like disorder[22] and another 7 cases with a lower motor neuron disorder have been reported.[22,23] In one study of 1,700 patients with HIV infection, the prevalence of HIV-associated ALS was estimated as 3.5 cases/1,000 patients.[22] In comparison, the incidence of ALS in the general population is approximately 1 or 2 cases per 100,000/year and the prevalence is 4 to 6 cases per 100,000.[24] While the clinical presentation of HIV-associated MND is indistinguishable from sporadic ALS, the patients with HIV are typically younger, nearly all the cases are younger than 40 years of age at the time of onset of neurologic symptoms, and most of these patients are male.[1] Similarly, all the patients reported here are male. This likely reflects the epidemiology of HIV infection in the United States. In comparison, the male to female ratio for sporadic ALS is 1.3 to 1. Together, these observations suggest that the coexistence of MND with HIV infection cannot be by chance alone but is driven by HIV infection.

The neurologic symptoms in patients with HIV infection and MND tend to progress rapidly, but the majority of these patients respond to ARV therapy.[1] In the present case series, 3 patients showed improvement in symptoms after either initiation of or increased compliance of their ARV regimen. Two others showed prolonged survival although the symptoms continued to progress. Case 1 remains asymptomatic except for occasional fasciculations 10 years since symptom onset; cases 4 and 5 are wheelchair-bound and have respiratory involvement but remain alive 13 and 6 years, respectively, following symptom onset.

The mechanism by which HIV infection leads to MND is unclear. HIV infects infiltrating macrophages, microglia, and astrocytes but does not infect neurons, hence the effect is likely indirect.[25,26] We have previously shown that patients with sporadic ALS have activation of an HERV-K in cortical neurons and anterior horn cells.[13,14] Furthermore, expression of HERV-K or its envelope protein in neurons in culture or in vivo in experimental animals causes degeneration of motor neurons producing a phenotype that is indistinguishable from ALS.[14] It has also been shown that the HIV-Tat protein can be released extracellularly from HIV-infected cells,[27] taken up by uninfected cells, and transactivate HERV-K.[28] HIV-Tat can also be detected in the brains of HIV-infected individuals.[27,29] It is our hypothesis that controlling HIV infection within the CNS would indirectly control HERV-K activation in neurons and result in clinical improvement. In 2 patients in whom HERV-K levels were measured in the plasma, high levels of activation were detected at the onset of neurologic symptoms, and in one

patient in whom HERV-K was measured repeatedly, the levels gradually fell and became undetectable following a change in ARV therapy. However, it remains unknown whether the ARV drugs can directly control HERV-K expression. In these patients, we optimized therapy with combination ARV drugs that target different parts of the HIV life cycle and have the best penetration into the CNS.[30] However, CPE values only provide a rough estimation of the ability of the drugs to penetrate the brain, because most of the data are based on CSF ARV levels and the efficacy of the drugs may vary in different cell types.[31] Some drugs, despite poor uptake in the CNS, can adequately control HIV replication as determined by CSF viral load.[17] Thus, the most optimal regimen for treatment of CNS manifestations of HIV infection remains unknown. In case 5, HERV-K levels remained elevated despite optimal control of plasma HIV viral load, and additional ARV therapy appeared to control the HERV-K levels. The timing of ARV therapy in relationship to the patients' MND symptoms remains unclear; however, it is notable that in the 3 patients who had at least improvement in their MND symptoms following ARV therapy, they initiated or increased compliance with the therapy within 6 months of symptom onset. It is our hypothesis that within this time window, the neurons are functionally impaired and not irreparably damaged. It is possible that similar windows of opportunity exist in other forms of ALS and should be considered when designing clinical trials.

HERV-K has multiple copies within the human chromosome.[32] To determine whether there was a particular site that was preferentially activated, we sequenced the HERV-K gag PCR product from case 5. The sequence had 100% homology to HERV-K on chromosome 22 at locus q11.21. This is a human-specific provirus that was one of the most recently acquired germline integrations and has complete open reading frames for some proteins. The HERV-K provirus identified from patient 5 has a 292 base pair deletion that results in a messenger RNA encoding a 9-kDa fusion protein, Np9, of unknown function.[15] However, the deletion also disrupted the *env* and *pol* genes such that the env and reverse transcriptase proteins cannot be formed at this site.[15] Thus, a complete viral particle can only be formed by a recombination event whereby the env and reverse transcriptase proteins would come from other loci of HERV-K in the genome.

In conclusion, MND, although rare, may be a treatable complication of HIV infection with optimization of ARV CNS penetration. Monitoring of HERV-K levels may be necessary since optimal control of HIV may not be sufficient for controlling HERV-K replication.

AUTHOR CONTRIBUTIONS

Avindra Nath: study concept and design, acquisition of data, critical revision of manuscript for intellectual content. Lauren N. Bowen: analysis and interpretation of data, acquisition of data, critical revision of manuscript for intellectual content. Richa Tyagi: study concept and design, acquisition of data. Wenxue Li: study concept and design. Tariq Alfahad: study concept and design, acquisition of data. Bryan Smith: study concept and design, critical revision of manuscript for intellectual content. Mary Wright: acquisition of data. Elyse J. Singer: critical revision of manuscript for intellectual content, acquisition of data.

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DISCLOSURE

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