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## Retroviruses and amyotrophic lateral sclerosis

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### Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive, invariably fatal neurologic disorder resulting from upper and lower motor neuron degeneration, which typically develops during the sixth or seventh decade of life, and is diagnosed based on standard clinical criteria. Its underlying cause remains undetermined. The disease may occur with increased frequency within certain families, often in association with specific genomic mutations, while some sporadic cases have been linked to environmental toxins or trauma. Another possibility, first proposed in the 1970s, is that retroviruses play a role in pathogenesis. In this paper, we review the published literature for evidence that ALS is associated either with infection by an exogenous retrovirus or with the expression of human endogenous retroviral (HERV) sequences in cells of the central nervous system. A small percentage of persons infected with the human immunodeficiency virus-1 (HIV-1) or human T cell leukemia virus-1 (HTLV-1) develop ALS-like syndromes. While HTLV-1 associated ALS-like syndrome has several features that may distinguish it from classical ALS, HIV-infected patients may develop neurological manifestations that resemble classical ALS although it occurs at a younger age and they may show a dramatic improvement following the initiation of antiretroviral therapy. However, most patients with probable or definite ALS show no evidence of HIV-1 or HTLV-1 infection. In contrast, recent reports have shown a stronger association with HERV, as analysis of serum samples, and postmortem brain tissue from a number of patients with a classical ALS has revealed significantly increased expression of HERV-K, compared to controls. These findings suggest that endogenous retroviral elements are involved in the pathophysiology of ALS, but there is no evidence that they are the primary cause of the syndrome.

### Keywords

human endogenous retrovirus; transposons; amyotrophic lateral sclerosis; reverse transcriptase; human immunodeficiency virus

### 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder, in which increasing muscle weakness leads to respiratory failure and death. The disease is diagnosed clinically, based on a standard set of neurologic findings known as the

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El Escorial criteria (Table 1). ALS most commonly begins during the sixth or seventh decade of life, leading to death in 3–5 years, with an annual worldwide incidence of approximately 2 per 100,000 population (Logroscino et al, 2010). Some 5– 10% of cases have a familial basis (fALS), while the remainder are sporadic (sALS). Once considered a pure motor disorder, affecting only upper and lower motor neurons, recent findings suggest that ALS actually involves multiple systems and neuronal groups in the brain (Ferrajuolo et al, 2011).

Despite extensive research, the etiology of ALS remains unexplained. Mutations in specific genes have been identified in just over half of familial and about 10% of sporadic cases (Lattante et al, 2012). Those most frequently detected involve the genes encoding C9ORF72, superoxide dismutase-1 (SOD1) and the TAR-DNA-binding protein (TARDBP). Mutations in gene C9ORF72 involve repeat expansion of a hexanucleotide GGGGCC and are strongly associated with ALS cases in which motor neuron degeneration is accompanied by frontotemporal dementia (De Jesus-Hernandez et al, 2011; Renton et al, 2011). In Guam, an ALS-like syndrome associated with Parkinsonism and dementia has been linked to exposure to a toxin in cycad seeds (Reed et al, 1987). Clusters of cases have also been reported in football and soccer players, suggesting the possibility of trauma as a triggering event.

Viral infection has also long been suspected to play a role in ALS, in part because of the marked similarities in the histopathologic and neuroanatomic findings in ALS and poliomyelitis (Norris, 1977). Retroviruses have been a particular focus of inquiry since the 1970s, when the first human retrovirus, human T-lymphotropic virus-1 (HTLV-1) was discovered, and reverse transcriptase (RT) activity was detected in the postmortem brain tissue of two Guamanian ALS patients (Viola et al., 1975). Retroviral involvement in ALS could potentially take two forms: infection by an exogenous agent, such as the human immunodeficiency virus-1 (HIV-1), HTLV-1 or a human foamy virus (HFV), or the expression of a human endogenous retroviral (HERV) sequences in motor neurons or other cells of the central nervous system.

In this paper, we review the published medical literature for evidence that exogenous or endogenous retroviruses play a role in the pathogenesis of ALS. We first summarize reports of the detection of RT expression in patients who met the El Escorial criteria for probable or definite ALS. We then review the occurrence of ALS-like syndromes in persons infected with HIV-1, HTLV-1 or HFV, noting that most such cases differ from “classic” ALS in their earlier age at onset, variable course and, in the case of HIV-1 infection, frequent improvement during antiretroviral therapy. We then review evidence of HERV gene expression in patients with probable or definite ALS, including our own recent observations of HERV-K polymerase gene transcripts in postmortem brain tissue (Douville et al., 2011). We conclude by suggesting promising directions for further research on the role of exogenous and endogenous retroviruses in degenerative motor neuron disease.

## 2. Reverse transcriptase activity in ALS

A defining characteristic of all retroviruses is that they possess an enzyme, reverse transcriptase (RT) that has the ability to convert RNA into complementary DNA (Temin and Mizutani, 1970). Therefore, detection of RT has been used as a generic retroviral screening method that requires no previous knowledge of viral genome nucleotide sequence. Studies demonstrating the association of RT with ALS are summarized in Table 2. The first demonstration of retroviral involvement in ALS dates back to 1975 when Viola et al found RT activity in cytoplasmic particulate fraction from two Guamanian ALS but not in brains from two control individuals. At that time, a growing interest was in finding the retroviral

origin of RT in patients with ALS. In the 1980s, with the discovery of HTLV-1 and HIV, ALS-like syndromes in patients with HTLV-1 and HIV were described, and hence believed to be the source of RT. However, one group tested sALS patients, who were seronegative for both HTLV-1 and HIV, for RT activity (Andrew et al, 2000). They used a novel approach in the form of product enhanced reverse transcriptase (PERT) assay, which is highly sensitive for detecting RT activity (Yamamoto et al, 1996). Much higher proportion of sALS patient (59%) had RT activity in the serum compared to healthy controls (5%) which raised the question as to the source of this RT activity. This finding was confirmed in three independent studies (see Table 2). Unexpectedly, the prevalence of PERT positivity in the serum was similar in those with ALS and their healthy blood relatives, 47% vs. 43%, respectively (Steele et al, 2005). The blood relatives comprised seven children (three PERT positive), one sibling (one PERT positive), four parents (one PERT positive), one aunt (one PERT positive), and one cousin (zero PERT positive). Authors in this study argued that if this ALS-associated RT activity had been caused by an exogenous retrovirus, one might expect to have found an increased prevalence of RT activity in the spouses of ALS patients because sexual transmission is characteristic of exogenous retrovirus infections in humans. However, spousal controls in this study did not display an increased prevalence of serum RT activity and therefore provide no support for the existence of an exogenous ALS-associated retrovirus. The amount of RT activity seen in sALS matched that measured in serum from HIV-infected patients. RT activity was found to be higher in controls when multiple sclerosis (MS) was used as non-sALS control suggesting a contribution of increased HERV expression to the total RT activity given that HERV expression is known to be increased in MS (Christensen T, 2005).

## 2.1. Comments

These studies showed RT involvement in sALS, or a subset of sALS, with prevalence of 53% (average in 131 ALS cases) versus 12.25% (average in 152 non-related healthy controls). Many reasons could explain the lack of detecting RT in 100% of serum samples from ALS cases. First, the level of serum RT activity in some ALS patients may fall below the lower detection limit of the current PERT assay, depending on several factors like time of the day, stage of ALS, and concurrent use of other medications/herbs. Second, RT activity might not be increased in a subset of sALS. The two studies that looked at RT activity in CSF gave contradictory results (39% vs. 4% in ALS cohorts). One difference is that the first study obtained CSF and serum from the same patients, while the second study, CSF samples and serum samples were not obtainable from the same patients for testing concurrently. It's important to note that ALS is not a leptomenigeal disease and, hence, the acute phase reactants associated with it are likely to appear in the blood much more than in the CSF. A close example would be in cases of HIV infection where the concentration of HIV in CSF is significantly lower (often undetectable) than the concentration in serum, even in patients with HIV-related neurologic complications. The increased RT activity is likely part of a cascade of events involved in the pathogenesis of sALS, and some other disorders like MS, and not an evidence that sALS is a retroviral disease.

## 3. ALS-like syndromes in patients infected with exogenous retroviruses

### 3.1. Human Immunodeficiency Virus

Upon development of a diagnostic serologic test for HIV-1 in 1985, Hoffman et al. (1985) reported the first case of HIV-associated ALS (HALS). Moulignier et al (2001) retrospectively identified six cases of HALS among 1700 HIV-infected patients over a 13-year period suggesting ALS frequency of 3.5 per 1000 HIV-infected persons. To date, at least 29 cases of HALS patients have been reported (see Table 3 for details & Table 4 for summary). HALS occurred at a younger age (range 22–61 years, mean 40 years) compared

with sALS in which more than 75% occurred in patients older than 55 years old. The male to female ratio, excluding suspected ALS category, was 4.8: 1 for HALS, compared to 1.3: 1 for ALS and 1: 1.5 for HIV. According to the El Escorial criteria (see Table 1), 72% of HALS cases were classified as either clinically definite ALS (41%), or clinically probable/possible ALS (31%). Another 8 cases were classified as clinically suspected ALS.

Contrary to a review on HALS cases that mentioned isolated lower motor neuron (LMN) syndrome to be the predominant variant of sALS (Verma and Berger, 2006), our review suggests that pure LMN syndrome was only present in 32% of HALS, while mixed UMN and LMN was present in 57%. In around 38% of reported HALS, HIV was newly discovered suggesting that HALS can develop at any stage of HIV infection. Severity of immunosuppression was variable, with CD4 counts ranging from 2 to 618 cells/mm<sup>3</sup> (56% had less than 350 cells/mm<sup>3</sup>), and viral load ranged from undetectable to 7.8×10<sup>4</sup> RNA copies/ml. All HALS patients who improved or stabilized (52% of all HALS), were treated with ART except for one case which occurred before the ART era. The response to ART coincided with reduction in viral load and normalization of CD4 count. However, despite continued ART, normal CD4 count and undetectable viral load, three patients had clinical relapse after a period of initial improvement (15 months in one and 24 months in two).

One report found HIV subgroup B in homosexual male partners; one developed a benign fasciculation syndrome while the other developed “classical” ALS syndrome (Von Giesen et al, 2002). Three of the 29 reported HALS cases have been tested for HIV subgroups, two group B and one group C (Von Giesen et al, 2002; Pearl et al, 2003; Sinha et al, 2004). Prognosis of HALS was not related to age at onset, initial CD4 cell count or viral load, or duration of known HIV seropositivity. Five pathological reports of HALS have been described. Two looked typical of sALS suggesting the possibility of a mere coincidence between ALS and HIV infection (Casado et al, 1997; Simpson et al, 1994). Those patients did not respond to ART, one died four years later and the other lost follow up. The other three pathology reports were supportive of a HIV disease, one patient showed some improvement while the other two patients followed a typical sALS progressive course.

**3.1.1. Comments**—Sporadic ALS occurring in HIV-infected patients can be secondary to HIV infection or a mere coincidence. Although the pathogenesis of neither is understood, the likelihood of shared pathogenesis is suggested by the identical presentation in many cases. A retrovirus, likely HIV, as a cause of a subset of sALS cases is supported by the response to ART seen in 52% of HALS cases. This, however, has notable controversy. HIV does not infect neurons, but emerges predominantly in microglia/macrophages in the CNS (Cosenza et al, 2002). Thus, selective damage to motor neuron may occur by neurotoxic viral proteins or cytokines, and chemokines produced as a consequence of the viral infection (Jubelt et al, 2001). Autopsy studies have failed to connect HIV, or any virus, directly to motor neuron and muscle fiber loss (Galassi et al, 1998; Hoffman et al, 1985; Simpson et al, 1994) although the possibility exists that in these rare cases of HALS, HIV may mutate to infect motor neurons which would explain the dramatic response to ART in these patients. Clinically, HALS differs from sALS in several aspects, including: younger age at onset, rapid progression, almost always high protein in CSF, and partial clinical recovery in response to ART. In contrast to the invariable progression of sALS, outcome in HALS ranges from rapid deterioration and death to complete recovery with ART. Corticosteroids and IVIg have been used in HALS with no benefit. ART is the only class of drugs that improved, stabilized or even cured ALS cases. In fact, because of the potential reversibility of ALS in HIV infected patients, testing for concomitant HIV infection in every sALS case is warranted in any individual with risk for HIV infection, especially due to difficulty in separating sALS from HALS on clinical grounds alone. Trials in HIV-negative sALS cases with zidovudine (Westarp et al, 1993c) and indinavir (Scelsa et al, 2005) were unsuccessful.

It's important to note that ART, specifically stavudine, has been associated with a rare but life-threatening disorder called HIV-associated neuromuscular weakness syndrome (HANWS). It presents with rapidly progressive limb weakness that may sometimes be associated with bulbar and respiratory muscles weakness (Simpson et al, 2004).

### 3.2. Human T cell Leukemia Virus-1

It is estimated that HTLV-1 infects 15 to 20 million individuals throughout the world. The HTLV-1 antibody prevalence rate varies from 0.2 to 10% among adults, depending on the geographical area. It increases with age, in some places eventually reaching 20 to 50% of the female population aged 60 and above (Mueller, 1991). The two major diseases associated with HTLV-1, adult T-cell leukemia/lymphoma (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), are described in all endemic areas. HAM/TSP is a slowly progressive disorder with 50% of patients becoming wheelchair bound after 10 years. A case of HAM/TSP can fulfill all inclusion criteria for ALS, having both UMN and LMN signs. However, more findings that are atypical of ALS are found in HAM/TSP including bladder dysfunction, sensory symptoms, and generally multi-organ involvement (Castro et al, 2007). Compared to younger age groups, people in their 60s are at higher risk of developing ALS as well as seropositive for HTLV-1. This increased incidence of both entities can lead to a bias in over-estimating the proportion of ALS patient who are HTLV-1 seropositive. Since the description of HAM/TSP in mid-1980s, at least 35 cases of ALS-like syndrome have been reported (Table 5). Eleven of these cases fulfilled the El Escorial criteria for clinically definite ALS. All cases are HTLV-1 seropositive and, in addition to ALS-like symptoms, have atypical symptoms of ALS, namely autonomic and/or sensory symptoms. Two pathological reports of autopsy were available; both cases were suggestive of HAM/TSP and not ALS. The final diagnosis by authors of all reported cases was HAM/TSP with exception of one report (10 cases). Cases of HAM/TSP with ALS-like finding differed from classical ALS by the presence of atypical symptoms of ALS, sensory and autonomic, the long survival of 10.6 years on average, and the response to steroids in some cases. One report (Martin et al, 1995) suggested ALS to be secondary to HTLV-1 by showing that 25 out of 50 ALS patients are seropositive by immunoblot. The same group showed further evidence with detecting HTLV-1 tax-rbx sequences in PBMC of 40% of patients with ALS. Another group was unable to detect similar findings in any of 43 patients with ALS (Andrews et al, 1997).

**3.2.1. Comments**—The variability in clinical findings early in the course of ALS and the lack of any biological diagnostic marker make absolute diagnosis difficult and compromise the certainty of diagnosis in clinical practice, therapeutic trials and classification for research purposes. If ALS diagnosis was made by inclusion clinical criteria alone can overlap with other neurological syndrome. This can be seen in Table 5 where all HAM/TSP patients fulfilled the inclusion criteria for ALS diagnosis. However, the final diagnosis made was HAM/TSP due to the presence of other symptoms that are atypical of ALS. However, the World Federation of Neurology had recognized that sometimes classical ALS is present in association with laboratory-defined abnormalities that are of uncertain significance to the pathogenesis of ALS (Brooks et al, 2000). If and when antiviral therapy for HTLV-1 becomes available, it may be possible to determine if HTLV-1 can play a causative role in ALS in some of these patients.

### 3.3. Human Foamy Virus

Spuma- or foamy viruses (FV), enzootic in most non-human primates, cats, cattle and horses, comprise a special type of retrovirus that has developed a replication strategy combining features of both retroviruses and hepadnaviruses. Man is not a natural host for FVs but can become infected through contact with animals. A hallmark of FVs is their



apparent apathogenicity in natural hosts as well as in infected humans (Delelis et al, 2004). This is in stark contrast to their highly cytopathic nature *in vitro*, where infection ultimately results in the death of most target cells due to syncytia formation and vacuolization. In the early 1990s, HFV antibodies were reported to be prevalent in sera of sALS patients and an etiological linkage was suggested (Westarp et al., 1992, 1993a, 1993b, 1993d, 1994). Another group applied the same methodology but could not show the seropositivity of HFV in eight sALS patients' serum and CSF samples (Rosener et al, 1996).

**3.3.1. Comments**—The reports of HFV seropositivity in sALS sera (25% – 45%) came from the same group (Westarp et al., 1992, 1993a, 1993b, 1993d, 1994), while another group was not able to replicate these findings despite using the same methodology (Rosener et al, 1996). The association between HFV and sALS was refuted on the basis of autopsy studies that showed no evidence for the HFV nor the classical syncytia formation and vacuolization, typical of FV. To our knowledge no further studies have looked at this association since 1996.

#### 4. Detection of HERV expression in patients with ALS

The source of increased RT activity detected in more than half the sALS cases has not been found yet. Many speculated that the responsible virus is likely to be a human endogenous retrovirus (HERV). HERV are retroviral-like sequences that make up 8.2% of the human genome (Lander et al, 2000). A large number of pathologies especially autoimmune disorders and malignancies have been linked to HERVs (Urnovitz et al, 1996). They have been classified into 3 major classes according to similarities to known viruses & further subdivided into families according to tRNA primer binding site. Of all the HERV families, HERV-K and HERV-W have gained the most attention due to the presence of complete open reading frame (cORF) and the ability to form virus-like particles.

Three different groups have looked at the HERV expression in ALS patients; each studied different tissue samples: serum, muscle biopsy, and brain at autopsy. First evidence of HERV involvement in ALS came in 2004 when Hadlock et al. showed increased immune response to HML-2 gag protein in serum samples from ALS patients with IgG reactivity in 57% compared to 11% in control, and IgM reactivity of 11% in ALS compared to no reactivity in controls. Furthermore, they showed one-log reduction in HML-2 RNA in PBMC from ALS patients who are anti-HML-2 gag antibody positive. Other HERV families tested did not have an antibody response to their gag proteins, namely HML-1, HML-4, HML-5, HML-6, and HERV-W. The authors suggested an immune response against HERV-K may play a causal role in ALS.

Another group published two studies looking at HERV-W env and gag expression levels in muscle biopsies from ALS patients (M1), and compared them to muscle biopsies from unaffected muscle from ALS patients (M2) and from healthy controls (M3). Although the expression levels were slightly different with  $M1 < M2 < M3$ , the authors concluded from their first study (Oluwole et al, 2004) that ALS starts in the muscles with secondary degeneration of anterior horn cells. However, their second paper (Oluwole et al, 2007) conflicted with first by showing increased HERV-W env and gag expression in M1 compared to M2 and M3. For determining the source of the HERV-W in muscle biopsies, they measured the expression of some inflammatory markers, including: CD14, beta-2-microglobulin, and MDH1, all of which were elevated. They concluded that the increased HERV-W expression in muscle biopsies more likely reflect a macrophage response in the muscles undergoing neurogenic atrophy than a primary pathogenetic event in ALS.

Evidence for a direct role of HERV-K expression in ALS was found in 2011, when Douville et al. showed increased HERV-K expression directly in brain tissue from ALS cases. Brain tissue from patients with ALS exhibited increased HERV-K pol RNA expression, particularly from loci 7q34 and 7q36.1, compared to brain tissues from systemic disease, accidental death, and Parkinson's disease. Given that ALS is primarily a disease of motor neurons, expression of HERV-K pol in ALS was stratified by brain regions, namely: prefrontal, sensory, motor, and occipital. The result was substantially higher expression in prefrontal cortex and sensory cortex compared to motor cortex ( $p = 0.05$  and  $p < 0.05$  respectively) from patients with ALS. Regional differences in HERV expression were not seen in the control patient groups, suggesting that the patients with ALS had a unique pattern of HERV expression in the brain.

To assess the relationship between RT and TDP-43, the dominant component of inclusion bodies in sporadic ALS, prefrontal cortex brain tissue from ALS and control was immunostained for both HERV-K RT and TDP-43 proteins. They were found to co-localize in cortical neurons of patients with ALS. Importantly, HERV-K immunostaining was present in clusters of neurons but not in other cell types in the brain. Another study showed that there was extensive binding of transposable elements to TDP-43 and this association was reduced in patients with frontotemporal lobar degeneration. Further there was over expression of transposable elements in mouse models of TDP-43 dysfunction (Li et al., PLoS One 2012)

#### 4.1. Comments

A comprehensive study of the expression or reactivation of endogenous retroviral elements in ALS has not yet been undertaken. The literature on HERV-W involvement in ALS is difficult to interpret. Two independent reports; however, have shown increased HERV-K expression in both serum and brain tissue in ALS patients. It remains unknown if HERV-K expression is an epiphenomenon or plays a pathophysiological role in the disease. Increased expression of HERV has been associated with several other disorders such as schizophrenia (Karlsson et al. 2004), autoimmune disorders (Balada et al, 2010) and malignancies (Romanish et al, 2010). However there are several subtypes of HERV-K that are located in different chromosomes. In addition, there are polymorphisms in the human population. Hence, these endogenous retroviruses could potentially play a role in these diseases. It is also possible that there may be a broader dysregulation of retrotransposable elements in ALS similar to that reported in frontotemporal lobar degeneration. Since these elements have reverse transcriptase activity and endonuclease activity, one way to establish their role might be to develop interventions to suppress their expression and determine if it alters the course of the illness.

#### 5. Future Directions

As reviewed above, several lines of evidence suggest a possible role for retroviral elements in the pathophysiology of ALS. Since these elements have unique enzymes associated with them, they could potentially be exploited for drug development. Silencing these host genes would not be expected to have any detrimental effects, since in normal adults these genes are thought to be silenced. Since most current neuroprotective and neuroregenerative approaches have had little success in treatment of ALS and other neurodegenerative diseases, targeting retroviral elements would represent a novel therapeutic approach. Certainly, in selected patients with HIV infection and an ALS-like syndrome, antiretroviral therapy resulted in resolution of symptoms, which suggests that stabilization or reversal of symptoms in ALS patients may not be an unrealistic goal.

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### Highlights

- A small percentage of HIV-1 or HTLV-1 patients develop ALS-like syndromes.
- HTLV-1 associated ALS syndrome has autonomic and sensory features, atypical of ALS.
- HIV-associated ALS (HALS) can mimic classical ALS.
- HALS occurs at a younger age and may improve with antiretroviral therapy.
- Recent studies have revealed significantly increased expression of HERV-K in ALS cases.

**Table 1**

Revised El Escorial criteria for clinical diagnosis of ALS (Brooks et al, 2000).

<b>Clinical Grade</b>	<b>Description</b>
Clinically Definite ALS	Clinical evidence of UMN, as well as LMN signs, in three regions.
Clinically Probable ALS	Clinical evidence of UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
Clinically Probable - Laboratory-Supported ALS	Clinical signs of UMN and LMN dysfunction in only one region, or UMN signs in one region, and LMN signs defined by EMG criteria in at least two limbs, with neuroimaging and clinical laboratory investigations to exclude other causes.
Clinically Possible ALS	Clinical signs of both UMN and LMN dysfunction in only one region or UMN signs alone in two or more regions; or LMN signs rostral to UMN signs and the diagnosis of Clinically Probable - Laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must be excluded to accept a diagnosis of Clinically possible ALS.
Clinically Suspected ALS	Is a pure LMN syndrome, where the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study.

\*The body is divided into four regions: cranial, cervical, thoracic and lumbosacral.



**Table 2**

Summary of demographics and RT activity in sALS

Author Reference	Subjects (number)	Age (years)	Duration of ALS	RT in Brain tissue	RT in serum	RT in CSF	Assay used	RV tests negative for
Viola et al, 1975	ALS (2)	NR	NR	2/2	ND	ND	RT assay	ND
Andrews et al, 20001	Control (0/2)	NR	NR	0/2	ND	ND	RT assay	ND
	ALS (56)	26–80	7–56 mo (20.6mo)		59%	ND	PERT	HILV1/2, HTLV1/2, HFV, HRV5
Steele et al, 2005	Control (58)	NR			5%	ND	PERT	HIV1/2, HTLV1/2, HFV, HRV5
	ALS (30)	NR	6.9mo-10.2yrs (3.05yrs)		47%	ND	PERT	NR
MacGowen et al, 2007	Control							
	Unrelated (44)		NR		18%	ND	PERT	NR
	Relatives (14)		NR		43%	ND	PERT	NR
McCormick et al, 2008	ALS(23)	32–75	11.8mo-6.1yrs (2.85yrs)		56%	39%	RT assay	HIV
	Control (21)	24–72			19%	19%	RT assay	HIV
McCormick et al, 2008	ALS serum(22) + CSF (25)	NR	NR		50%	4%	PERT	HIV HTLV
	Control (14)	NR	NR		7%	ND	PERT	HIV HTLV

NR = Not reported; ND = Not detected; RT = Reverse transcriptase; PERT = Product enhanced RT; mo = months; HFV = Human foamy virus.

Table 3

Clinical manifestations of cases of ALS-like syndrome associated with HIV infection.

Source	Age/ Gender	Duration of HIV infection (months)	CD4 cell/mm <sup>3</sup>	HIV load	MND deficit: UMN LMN	EI Escorial diagnostic grade	Treatment	Survival (months)	ALS course Remarks
Hoffman et al., 1985	26/M	Newly discovered	Not reported	Not reported	LMN + UMN	Definite	Not reported	>12	Progressive
Sher et al., 1988	30/M	Unknown	Not reported	Not reported	LMN	Probable/possible		3, died	Progressive
Verma et al., 1990	32/M	Newly discovered	CD4/CD8: 0.72	Not reported	LMN + UMN	Probable/possible	Not reported	24, died	Improved, died of infection
Huang et al., 1993	45/M	Newly discovered	397	Not reported	LMN	Suspected	Zidovudine	Unknown	Progressive
Casado et al., 1997	30/M	18	CD4/CD8: 0.76	Not reported	LMN + UMN	"Classical"	Not reported	>16	Progressive
Simpson et al., 1994	45/M	Unknown	560	Not reported	LMN + UMN	Definite	Zidovudine, IVIg, Prednisone	48, died	No improvement
Galassi et al.*	22/W	Unknown	438, CD4/CD8: 0.39	Not reported	LMN	Probable/possible	Zidovudine, Methyl- Prednisolone, IVIg	Not available	Deterioration, relapse, improvement
Galassi et al., 1998	30/M	Unknown	340	Not reported	LMN	Suspected	Zidovudine, Zalcitabine, Steroid	3, died	Rapidly Progressive
Sastre-garriga et al., 2000	39/W	Newly discovered	540	22000	LMN	Suspected	Not reported	4, alive	Progressive
MacGowan et al., 2001	32/W	Newly discovered	44	77.9 × 10 <sup>3</sup> (serum) 61.6 × 10 <sup>3</sup> (CSF)	LMN + UMN	Definite	Zidovudine, Lamivudine, Nelfinavir	>48, alive	Recovered
Moulligner et al., 2001									
Patient #1	27/M	Newly discovered	84	Not detected	LMN + UMN	Definite	Zidovudine	6, died	Transiently stabilized
Patient #2	61/M	72	44	Not detected	LMN + UMN	Probable/possible	Zidovudine	26, died	Total recovery
Patient #3	29/M	54	2	Not detected	LMN + UMN	Probable/possible	Zidovudine	14	Subtotal recovery
Patient #4	22/M	6	123	3.7 log10	LMN + UMN	Zidovudine, Didanosine	Probable/possible	35, died	Partial recovery
Patient #5	25/M	28	37	4.9 log10	LMN + UMN	Zidovudine, Lamivudine	Probable/possible	52, alive	Subtotal recovery
Patient #6	40/W	19	227	3.3 log10	LMN + UMN	Zidovudine, Zalcitabine, Indinavir	Probable/possible	>40, alive	Total recovery
Nishio et al., 2001	42/W	108	107	44.5 × 10 <sup>3</sup>	LMN	Suspected	Stavudine, Lamivudine, Nelfinavir	>7, alive	Recovered; minimal residual deficit
Zoccollella et al., 2002	44/M	Newly discovered	360	34 × 10 <sup>3</sup>	LMN + UMN	"Classical"	Zidovudine, Lamivudine, Nevirapine, Riluzole	36, died	Progressive
Von Giesen et al., 2002	?/M	1	447	21.9 × 10 <sup>3</sup>	Not provided	"Classical"	Zidovudine, Lamivudine, Nevirapine	Not available	Deteriorated
Pearl et al., 2003	33/M	192	110	56 × 10 <sup>3</sup>	LMN	Suspected	Not reported	1, died	Progressive, died of infection
Sinha et al., 2004	37/M	discovered	170	Not reported	UMN	Probable	Zidovudine, Lamivudine, Nevirapine	>1, alive	Slight improvement
Verma et al., 2006									
Patient #1	60/M	132	430	Not detected	LMN + UMN	Definite	Zidovudine, Lamivudine, Saquinavir	13, died	Progressive
Patient #2	59/M	36	394	Not detected	LMN + UMN	Definite	Zidovudine, Lamivudine, Trizivir	76, died	Progressive
Berger et al., 2005	35/M	Newly discovered	244	8.3 × 10 <sup>3</sup>	LMN	Suspected	Zidovudine, Lamivudine, Abacavir, IVIg	46, alive	Stable
Verma A & Mishra SK, 2006									
Patient #1	57/M	37	618	Not detected	UMN	Definite	Zidovudine, Lamivudine Lopinavir, Ritonavir, Tenofovir Zidovudine,	36, alive	Stable
Patient #2	42/M	146	219	32.2 × 10 <sup>3</sup>	UMN	Definite	Lamivudine, Intaviride, Ritonavir, Tenofovir Lamivudine,	42, alive	Stable
Orsini et al., 2012	56/M	Newly discovered	300	698	LMN	Suspected	Stavudine, Nevirapine, IVIg,	48, alive	Progressive

Source	Age/ Gender	Duration of HIV infection (months)	CD4 cell/mm <sup>3</sup>	HIV load	MND deficit: UMN LMN	El Escorial diagnostic grade	Treatment	Survival (months)	ALS course Remarks
Almeida et al, 2010	59M	60	473	Not detected	UMN	Suspected	Not reported	36, alive	Progressive
Calza et al, 2004	60M	108	579	3100	UMN + LMN	Definite	Zidovudine, Didanosine, Nelfinavir, Riluzole	36, died	initial improvement then progressive

\* article not found, case of HALS in table from Verma et al, 2006.

**Table 4**

Summary of reports of ALS cases associated with HIV infection.

Category	Number (%)
<b>Number of cases</b>	29
<b>Age (average), years</b>	22–61 (40)
<b>Gender: Male/Female (M:F)</b>	24/5 (4.8 : 1)
<b>Duration of HIV prior to ALS, months</b>	
< 1	38%
Average (all)	40.7
Average (>1month only)	72.57
<b>CD4 count (average), cells/mm<sup>3</sup></b>	2–618 (291.5)
<200 [severe immunosuppression]	9 (36%)
200–350 [require HAART]	5 (20%)
>500 [Normal]	4 (16%)
<b>ALS grade (by El Escorial criteria)</b>	
Definite	12 (41.4%)
Probable/Possible	9 (31%)
Suspected	8 (28%)
<b>High CSF protein</b>	7 (88%)
<b>ALS course</b>	
Progressive	14 (48%)
AZT only	3
HAART	5
No treatment	6
Improved/Stabilized > 1year	15 (52%)
Definite	5 (33%)
Probable/Possible	8 (54%)
Suspected	2 (13%)
<b>Improved in Definite/Probable/Possible</b>	13 (87%)
AZT only	4 (31%)
HAART	8 (62%)
No treatment (pre AZT era)	1 (7%)
<b>Motor neuron deficit</b>	
UMN only	3 (11%)
LMN only	9 (32%)
Mixed	16 (57%)

**Table 5**  
Clinical manifestations of HTLV-1 positive cases that meet the E/Eschorial criteria for ALS

Author reference	Age/ Gender	Age at onset (years)	Disease duration (years)	E/Eschorial diagnostic grade	Remarks	HTLV-1 test used	Authors' final diagnosis
Silva et al 2005							
Patient# 1	49/M	33	16	Probable	Long survival	ELISA, WB	HAM/TSP
Patient# 2	62/F	52	10	Definite	Long survival	ELISA, WB	HAM/TSP
Patient# 3	51/M	44	7	Definite	Long survival	ELISA, WB	HAM/TSP
Patient# 4	38/F	29	9	Definite	Long survival	ELISA, wbc	HAM/TSP
Patient# 5	63/M	60	3	Probable	Died of PNA	ELISA, WB	HAM/TSP
Matsuzaki et al, 2000							
5 cases		52.2	-	3 Definite 1 Probable 1 Suspected	2/3 responded to prednisolone	ELISA, WB	HAM/TSP
10 cases		63.4	-	unknown	0/4 responded to prednisolone	ELISA, WB	ALS
Kuroda et al, 1991	57/M	52	4.5	Definite	-	ELISA, WB	HAM/TSP
Vernant et al, 1989	4 cases	-	-	3 Definite 1 Suspected	-	-	HAM/TSP
Arimura et al, 1989	67/?	-	-	Definite	-	-	HAM/TSP
Evance et al, 1989	75/?	-	-	Suspected	-	-	HAM/TSP
Sahashi et al, 1989	36/F	11	25	Definite	Improved with Prednisolone	ELISA, WB	HAM/TSP
					Young age of onset		
					Long survival		

HAM/TSP = HTLV-1 associated myelopathy/tropical spastic paraparesis; PNA = Pneumonia; WB = Western Blot.