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REVIEW ARTICLE

Human endogenous retroviruses in neurologic disease

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Endogenous retroviruses are pathogenic – in other species than the human. Disease associations for Human Endogenous RetroViruses (HERVs) are emerging, but so far an unequivocal pathogenetic cause-effect relationship has not been established. A role for HERVs has been proposed in neurological and neuropsychiatric diseases as diverse as multiple sclerosis (MS) and schizophrenia (SCZ). Particularly for MS, many aspects of the activation and involvement of specific HERV families (HERV-H/F and HERV-W/MSRV) have been reported, both for cells in the circulation and in the central nervous system. Notably envelope genes and their gene products (Envs) appear strongly associated with the disease. For SCZ, for ALS, and for HIV-associated dementia (HAD), indications are accumulating for involvement of the HERV-K family, and also HERV-H/F and/or HERV-W. Activation is reasonably a prerequisite for causality as most HERV sequences remain quiescent in non-pathological conditions, so the importance of regulatory pathways and epigenetics involved in regulating HERV activation, derepression, and also involvement of retroviral restriction factors, is emerging. HERV-directed antiretrovirals have potential as novel therapeutic paradigms in neurologic disease, particularly in MS. The possible protective or ameliorative effects of antiretroviral therapy in MS are substantiated by reports that treatment of HIV infection may be associated with a significantly decreased risk of MS. Further studies of HERVs, their role in neurologic diseases, and their potential as therapeutic targets are essential.

Key words: Human endogenous retroviruses; multiple sclerosis; schizophrenia; neurologic; epigenetic; human immunodeficiency viruses; antiretroviral.

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We are the sum total of our component parts; both on the abstract and the biological level. In recent years, it has become clear that our component parts can be conceptualized as "the human superorganism" – our own cells plus the billions of microorganisms co-evolving with us and colonizing us: our skin and inner mucosal surfaces, and cells. Until recently, the focus on the microorganisms/microbiota contributing to the host microbiome has almost exclusively been on bacteria and their phages (bacteria-specific viruses) (1). In the virological context it is now emerging, that viruses also play potentially significant roles in the human microbiome, for example in our gut (2), and oropharynx (3). Furthermore, the genomes in all our cells also contain sequences of viral (specifically retroviral) origin. Indeed up to 8% of our genomic DNA sequences are retroviral, acquired from ancestral retroviral infections, fixed in our germline and inherited in the classical Mendelian fashion (4–6). Such sequences are known as human endogenous retroviruses (HERVs). Endogenous retroviral sequences (ERVs) are not, however, unique to the human genome – retroviral elements contribute to the genomes of more or less all vertebrates and at least some invertebrates (7, 8).

To summarize, retroviruses exist in two forms, as exogenous or endogenous entities. In humans, the isolation and characterization of both the exogenous and the endogenous retroviruses are relatively new, dating back to the 1980s. Human T-cell lymphotropic virus 1 (HTLV-1) was the first human pathogenic retrovirus characterized (9), followed by the other three human exogenous retroviruses HTLV-2 (10), and human immunodeficiency viruses HIV-1 (11, 12), and HIV-2 (13)). Human endogenous retroviruses (HERVs) were initially discovered in 1981 (14). Many HERV families and a large number of solitary long terminal repeats (LTRs) are now known, but interestingly, endogenous forms of HTLV and HIV are not known as yet, with the putative exception of the locus HRES-1 (HTLV-1-Related Endogenous Sequence), which encodes a short Gag-like polypeptide with similarities to

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HTLV-I Gag (15). However, HTLVs do share some common characteristics with certain HERVs; and these HERVs also exhibit splicing patterns comparable to the splicing in the more complex exogenous retroviruses. The concept of endogenization of retroviruses has recently been reviewed (16, 17), and furthermore, it has recently been proposed that HIV may have potential for endogenization (18).

In numerous other species, from mice (8, 19) to cats (20) to koalas (21), (some) endogenous retroviruses are demonstrably pathogenic, whereas in humans a role for HERVs in the etiology of a number of diseases have been suggested (5, 6, 22–24), but an unequivocal pathogenetic cause-effect relationship is as yet unknown.

Human endogenous retroviruses have pathogenic potential both as genes/gene products, and as (more or less active) retroviruses. Negative selection would disfavor pathogenicity; so most HERVs must be "innocent" as they are ubiquitous, and their possible pathogenicity tempered by numerous hereditary and environmental factors.

"Innocence" or commensality could be assumed to be based on functional gene products; an obvious example of this is that expression of the HERV-W Env gene product syncytin-1 is essential in human placental biology for establishment of the placental syncytiotrophoblast layer (25) and in immunotolerance of the mother to the paternal antigens of the fetus (26). Also at the gene promotor level, HERV sequences have been recruited in the tissue-specific expression of pleiotropin (placenta), apolipoprotein C1 (liver), and β-amylase (salivary glands) (4). Therefore, it is not unreasonable to assume that pathogenic potential necessitate functional gene products. Functional gene products require proviral coding capacity for sufficiently large open reading frames (ORFs). Table 1 presents a brief overview of HERV-encoded ORFs.

HERVS AS PATHOGENS

Human endogenous retroviruses could be considered as emerging pathogens, with disease associations proposed in certain types of cancer (22, 23, 27–30), in neurological and neuropsychiatric diseases as diverse as multiple sclerosis (MS) and schizophrenia (SCZ), and in certain (other) immune-mediated/autoimmune diseases (23, 31–33).

HERVs in neurology: pathogenesis of MS

Multiple sclerosis is a disease of the central nervous system. MS epidemiology suggests both genetic and environmental elements contributing to MS pathogenesis, with environmental factors operating on a background of genetic susceptibility. Two HERV families in particular, HERV-H/F and HERV-W/MSRV, are specifically associated with MS and

Table 1. HERV encoded ORFs

HERV	ORFs	Comment
HERV-K (HML)	Gag, Pol, Env, Rev	HERV-K(113,HML2) has full-length ORFs for all proteins at one locus Insertionally polymorphic
HERV-H/F*	Gag, Pol, Env	HERV-Fc1 most complete
HERV-W	Env	ERVW-1 locus *env* encodes syncytin-1
HERV-W/MSRV**	Gag, Env	MSRV Gag, MSRV Env
HERV-W/FRD	Env	HERV-FRD *env* encodes syncytin-2
HERV-R	Env	
HERV-P	Env	
HERV-T	Env	
HRES-1	Gag	28kD Gag-similar product

This table comprise a brief overview of the essential retroviral ORFs (annotated as Gag, Pol, and Env); without details on each distinct HERV locus. Env is by far the most common HERV ORF. It should be noted that few among the thousands of HERV loci in the human genome comprise the intact minimal structure for a provirus: 5′LTR-*gag-pro/pol-env*-LTR3′, and that much fewer encode intact ORFs. Apart from HERV-K (113,HML-2), the ORFs noted for each HERV are dispersed at individual loci throughout the genome; several of the Gag, Pol, or Env ORFs are represented at more than one locus. The MMTV-like HERVs are classified in various ways, now usually according to both or either tRNA primer and/or HML (human MMTV-like) subgroup, for example, HERV-K(HML-2) or HERV-K(HML-3). To unify various nomenclatures, specific members are most commonly named HERV-X (clone or sequence name, group) where X denotes the tRNA primer.

HERV-H/F* a.k.a. HERV–F/H is considered an expanded family.

HERV-W/MSRV**: there are uncertainties about the origins of MSRV (multiple sclerosis associated retrovirus) sequences. Orginally identified as a novel retrovirus (123), MSRV is reported to be similar to, but distinct from HERV-W (58, 113). No MSRV genomic locus (or loci) is known. A recent analysis of transcribed MSRV *env* sequences revealed that all could originate from genomic HERV-W *env* loci or recombinations among them (124).

HRES-1: HTLV-1 Related Endogenous Sequence. The table was compiled from (5–7, 15, 23, 24, 34, 125).

proposed to be involved in both the risk and the course of the disease. With respect to genetic risk, an analysis of DNA for associations between multiple sclerosis and polymorphisms near HERV loci with one or more (almost) intact genes has been performed in four cohorts of patients with MS and controls. The study found that SNPs (single-nucleotide polymorphisms) around the HERV-Fc1 on chromosome X were significantly associated with disease (34). For HERV-K, a small study of homozygous carriers of the HERV-K18 env (K18.3) allelle indicated a threefold increased risk of MS (35). On the other hand, a genomic DNA study of another representative of the HERV-K family, the insertionally polymorphic HERV-K113 (notable for open reading frames for all of its genes and found in 0–28% of humans with widespread geographic and racial variation) in a cohort of patients with MS tested for the presence of the HERV-K113 allele by PCR, with their unaffected parents as controls. The results from this study did not support an association between HERV-K113 and MS (36).

Cultured lymphocytes from MS patients produce reverse transcriptase (RT)-positive retrovirus-like particles containing HERV-H and/or HERV-W/MSRV sequences (37, 38), and such sequences in particle or virion-form can be found in the blood of most, but not all, MS patients and sporadically in controls (39, 40). On Sardinia, the population of patients with MS appears to have a number of distinct features; notably a strong association with HERV-W/MSRV (41, 42); for Sardinian patients with MS it has also been proposed that the presence of certain MSRV-related RNAs in the cerebrospinal fluid at MS debut can be regarded as a prognostic marker for a severe disease course (42).

As for the multifaceted immune response to activated HERVs – and the consequences of such immune responses, it has recently been demonstrated that antiviral/anti -HERV mechanisms in the innate immune response – the initiation of immune signaling pathways either via reverse transcribed HERV sequences generating single-stranded DNA or expressed HERV gene products producing viral signals, similar to the pathogen-associated molecular patterns (PAMPs) of exogenous retroviruses, enabling the innate immune detection. This context of pattern recognition receptor (PRR) activation has recently been reviewed, indicating implications for several inflammatory/immune-mediated diseases (43).

Furthermore, both arms of the adaptive immune response: the humoral and cell-mediated immune responses to certain HERVs are elevated/increased in MS, particularly in active MS (6, 44–48), and the target epitopes – HERV antigens – exhibit elevated expression levels on peripheral blood mononuclear cells from patients with MS in flow cytometric studies (49–51).

In analyses of HERVs in the brain and central nervous system (CNS) of patients with MS, it is interesting to bear in mind the reported directly induced neuronal cell death by Env encoded by the exogenous human retrovirus HIV (52). So far, it has been demonstrated that the HERV-W-encoded Env, syncytin 1 (*syncytin-1* is encoded by the ERVW1 locus on chromosome 7) – expressed as a construct in astrocytes – mediates oligodendrocyte cell death (53) and also that HERV-W-encoded Env can mediate a reduction of the oligodendroglial differentiation capacity (54). Accordingly, localized expression of HERV antigens may have direct pathogenic consequences in MS.

Studies on MS cerebrospinal fluid (CSF) have revealed some interesting HERV-related features in MS: Intrathecal synthesis of antibodies is one of the characteristics (increased IgG indices, CSF oligoclonal bands; OCB). This phenomenon is also found in viral infections in the CNS. In such infections, the antigenic target epitopes are the causal agent itself, whereas the OCBs in MS CSF are polyclonal. Analysis of CSF antibody specificities has reported a number of viral antigens, including several herpesviruses (55) and HERVs. A reported phage display library screen indicated MS CSF reactivity to HERV-W Env (56), and HERV-H Env epitopes (5).

At the transcriptional level, it has been reported that HERV-H, HERV-K, and HERV-W RNA levels are increased in MS brains (57), while a study which distinguished between MSRV and syncytin-1, showed increased expression of ERVWE1 RNA, but not MSRV RNA in MS brain samples (58). It has also been reported that immunohistochemical screening of brain samples with anti-HERV-W Gag (capsid) antibodies revealed expression of reactive HERV-W Gag epitopes in both normal and MS brain (neurons), with accumulation in axonal structures in demyelinated white matter and endothelial cells in active lesions from patients with MS, while anti-HERV-W Env antibodies exhibited reactivity toward microglia in normal brain, and to macrophages in early MS lesions (22, 59). A different study found HERV-W-encoded Env (ERVWE1, syncytin-1) up-regulated in glial cells in active lesions (53).

HERVs in neuropsychiatry: pathogenesis of schizophrenia

The etiologies of schizophrenia (SCZ) and bipolar disorder are uncertain; they are complex neuropsychiatric diseases and both genetic and environmental factors, and gene-environment interactions are

involved. A study designed to identify HERV loci, potentially active in the brain by exploring the possible implication of DNA methylation, identified a single HERV-K locus (HERV-K102 on chromosome 1), and possibly a HERV-H/F locus on chromosome 22 (60). A recent, whole-genome analysis of enhancer activity of human-specific endogenous retroviral inserts (hsERVs), identfied a HERV-K-related insert serving as an enhancer for the schizophrenia-linked gene PRODH. PRODH is one of the candidate genes for susceptibility to schizophrenia and other neurological disorders (61). With respect to genetic risk factors, a number of recent studies have suggested several genes involved in disease risk, but results have been ambiguous. Recent results indicate that a high number of common susceptibility variants of comparatively small effect are involved in SCZ (62). Further in SCZ, Indications of immune dysregulation are emerging, and a recent study evaluated pleiotropy in SNPs associated with SCZ and MS. As SCZ and bipolar disorder (BD) have clinical and genetic overlap pleiotropy between BD and MS was also investigated. Significant genetic overlap between SCZ and MS was identified at several independent loci, driven by the major histocompatibility complex but with opposite directionality. No genetic overlap between BD and MS was found (63).

Both the HERV-W and the HERV-K families have been linked with SCZ, mostly in PCR-based studies of HERV-W and/or HERV-K *pol* transcripts in CSF or post-mortem brains (64–66). In the circulation, on the other hand, a study on plasma samples found up-regulation of HERV-W *env* transcripts in 36% of SCZ samples (67), while a study of serum samples, using anti-HERV-W Gag and Env antibodies for capture of reactive antigens, showed an increased frequency of positive samples from patients with schizophrenia (47–49%) relative to controls (3–4%) (68). At the protein level, the expression of HERV-W Gag epitopes has been studied in post-mortem brain tissue of controls and of patients with SCZ, BD, and major depression. Immunohistochemical screening found expression of reactive HERV-W Gag epitopes in both neurons and astroglial cells in control samples, with a significant reduction in expression in patient samples (69).

Interestingly, an *in vitro* study indicated that overexpression of HERV-W env in glial cells induced the SCZ-associated brain-derived neurotrophic factor (BDNF) (67).

HERVs in neurodegenerative disease: association with amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis is a progressive and ultimately fatal neurodegenerative disease leading to the loss of upper and lower motor neurons, involving multiple systems and neuronal groups in the brain (70). The cause(s) of ALS is uncertain, but a possible retroviral implication has been hypothesized as it is known that retroviruses can cause similar neurodegeneration. Product-enhanced RT assay studies of serum samples from patients with ALS, but seronegative for HIV or HTLV-1, demonstrated reverse transcriptase (RT) activity in 50–60% of the ALS samples, and sporadically in controls (RT is encoded by the *pol* gene) (71, 72). Analysis of RT activity as such does not identify the origin of the enzyme, but the involvement of HERV-encoded elements has been proposed for HERV-W (ALS muscle biopsies) (73), or HERV-K (ALS post-mortem brain) (74). See also (24) and (75, 76).

HERVs and HIV neuropathogenesis

HIV access the CNS very early in the infection; even during the primary viremia, HIV-1-encoded proteins, and virions are present in the CSF; HIV RNA is detectable in the CSF of (almost) all viremic patients with HIV, implying that infection of the CNS is a consistent element (reviewed (77, 78)). However, HIV infection is usually neurologically asymptomatic, but can for some patients develop to HIV-associated dementia (HAD), an encephalopathy with severe motor and cognitive dysfunction.

Some similarities between MS and HAD can be found, for example in the involvement of astrocytes and monocytes/macrophages in eliciting and promoting the neurodegenerative process and in the comparability of the signaling processes, exemplified by up-regulation vs down-regulation of certain cytokines/chemokines (6, 79). HIV infection apparently leads to activation of HERVs; this has been shown in reports of induction of cross-reactive HIV/HERV-K epitope cytotoxic T lymphocyte (CTL) responses to HIV (80, 81), and of activation of HERV transcription (HERV-K, HERV-W, and HERV-H/F) in post-mortem brain samples from patients with HIV (57).

Table 2 outlines neurologic and neuropsychiatric diseases for which HERV associations have been reported.

MECHANISMS FOR REGULATION OF HERV ACTIVATION/EXPRESSION

Although the links or associations of HERVs with neurological disease are well-established, the questions of which pathways are involved in regulating the HERV activation in these diseases are in the

Table 2. Neurologic and neuropsychiatric diseases with reported HERV associations

Neurologic disease	Associated HERV families
Multiple sclerosis (MS)	HERV-H/F
	HERV-W/MSRV
	(HERV-K?)
Schizophrenia (SCZ)	HERV-K
	HERV-W
Amyotrophic lateral sclerosis (ALS)	HERV-K
	HERV-W
HIV-associated dementia (HAD)	HERV-K
	HERV-H/F
	HERV-W

Additionally, there are sporadic reports of increased HERV-W RNA levels in post-mortem brain from patients with Alzheimer's dementia (57), cross-reactivity of HERV K peptides (126) and HRES-1 peptides (15) with HTLV-1 in HTLV-1 myelopathia, and of RNA sequences encoded at several different HERV loci in the CSF of patients with sporadic Creutzfeldt–Jacob disease (127). Table 2 is compiled from references in the text.

early phases of clarification. Activation at some level is reasonably a prerequisite for causality as most HERV sequences remain quiescent in non-pathological conditions.

HERV activation, derepression, restriction, epigenetics

Virus infection, particularly by human herpesviruses, and notably Epstein–Barr virus (EBV) (5, 82–85), human herpesvirus 6 (HHV 6A/HHV 6B) (83, 86, 87), varicella zostervirus (VZV), and herpes simplex virus type 1 (HSV 1) (82, 88, 89); have often been suggested as environmental triggers or contributing etiologic factors in MS. Notably, cross-talk and mutual interactivation between herpesviruses and retroviruses, both exogenous retroviruses (90, 91), and HERVs (92–94), are well-documented.

An integral element in the host cell defenses against retroviral infection is the retroviral restriction system, comprising a multitude of cellular factors that actively target distinct steps in retrovirus replication and so protects the cell (95).

An example of such retroviral restriction factors are members of the tripartite motif (TRIM) protein family (96).

One of the first members of this family to be characterized was TRIM-28, which mediates post-integration transcriptional silencing of murine leukemia virus and other retroviruses (97, 98). Notably, it was recently reported, so far in mice only, that endogenous retroviruses are controlled by TRIM28-mediated histone modifications in neural progenitor cells, suggesting that these elements control specialized transcription patterns in the brain. This de-repression of ERV sequences may also impact transcriptional dynamics of nearby genes and the expression of long non-coding RNAs (99). It is also becoming clear that the brain constitutes a unique environment for DNA-methylation patterns and epigenetic regulation (100).

Recently an *in silico* statistical study of certain post-translational modifications to histones, including H3K4me3, and identifying chromatin features predicting exogenous gamma-retrovirus integration site selection was utilized in an attempt to determine whether cell type-specific chromatin markers were enriched in the vicinity of HERV loci in embryonic stem cells. The study showed the developmental regulation of HERV-H/F expression, the association of HERV-H/F with binding sites for pluripotency transcription factors, and extremely high levels of HERV-H RNA in human embryonic stem cells, suggesting that HERV-H/F contributes to pluripotency in human cells (101).

The TRIM-family members, TRIM5 (34, 102) and TRIM22 (102), have been demonstrated to be statistically associated with the genetic risk of MS.

Further, a direct link between multiple sclerosis, altered epigenetic regulation, and HERVs has been reported. It was demonstrated that increased expression of a series of pro-inflammatory cytokines in PBMCs from patients with MS was correlated with decreased promoter-recruitment of the HP1 epigenetic regulator. In a subset of the patients, this defective silencing could be attributed to increased activity of the peptidylarginine deiminase PADI4 that destroys the HP1-binding site on histone H3 (PADI4 converts histone arginine 8 (H3R8) into a citrulline, thereby destroying the HP1-binding site formed by methylated H3K9. Consistent with this, approximately one-third of the patients in the cohort had increased PADI4 activity. A similar reduction in recruitment was also observed at the promoter of several HERVs (103).

HERV-DIRECTED THERAPY – ANTIRETROVIRALS AS CANDIDATES FOR NOVEL THERAPEUTICS IN NEUROLOGIC DISEASE

Targeting HERVs in MS

It tends to be overlooked that the original underlying rationale for testing a possible therapeutic efficacy of the widely used IFN-β in MS were its antiviral effects. Further, the antiretroviral activity of IFN-β has been established: for example, IFN-β1a therapy reduces the HTLV-I tax messenger RNA load and the frequency of potentially pathogenic HTLV-I-specific CD8(+) cells in patients with HAM/TSP (104), and IFN-β mediates suppression

of HIV replication *in vitro* (105). For HERVs, it has been reported that IFN-β therapy in MS reduces the circulating HERV-W/MSRV *env* RNA load (106), and that circulating anti-HERV-H Env and anti-HERV-W Env antibody reactivities are significantly decreased as a consequence of IFN-β therapy, coupled to efficacy of therapy (107).

In 2011, a case report was published of a patient diagnosed with MS, for whom the disease was suggested to be triggered by an acute HIV infection some months previously. The patient's MS symptoms resolved completely after starting combination antiretroviral therapy and remained so for more than 12 years. The authors proposed that the antiretroviral therapy for HIV could affect the progression of MS via a possible effect on HERVs (108). Since this case report, two studies have substantiated that treatment of HIV infection is associated with a significantly decreased risk of developing MS (109, 110); the larger UK-based study showing that the rate ratio of developing MS in people with (most probably) treated HIV infection, relative to those without HIV, was 0.38 (110). There are several possible mechanisms for this protective association, including the immunosuppression inherent in chronic HIV infection, or the highly active antiretroviral therapy (HAART) now widely used. An interesting case in point is the recent report of another of the rare HIV patients with MS. In this case a woman from Uganda with non-progressive HIV-1 infection was newly diagnosed with relapsing-remitting MS. This patient had stable normal CD4 + cell counts and a low viral load (a "HIV-controller") and was not receiving antiretroviral treatment (111).

The possible protective or ameliorative effect of antiretroviral therapy in MS certainly merits further investigations. Currently, a clinical study of the antiretroviral Raltegravir in patients with MS in the UK is ongoing (Raltegravir (Isentress) Pilot Study in Relapsing Multiple Sclerosis (INSPIRE https://clinicaltrials.gov/show/NCT01767701 (accessed 20. April 2015). Early clinical trials of a neutralizing antibody (GNbAC1), specifically targetting HERV-W Env/MSRV Env are also ongoing (112, 113).

Antiretrovirals in SCZ, ALS, and HAD

Work on possible effects of antiretrovirals in SCZ is sparse and no conclusive results on a possible effect of antiretrovirals have emerged. Indeed limited work has been published on treatment of patients with comorbidity of severe mental illness and HIV infection; as reviewed in (114).

An association of ALS (or motor neuron disease) with HIV infection has been described 30 years ago (115), but more recent reports are scarce and it appears that HIV-associated ALS syndrome may differ from the classical ALS (116). However, a few case reports indicate at least partial clinical recovery following combination antiretroviral therapy (cART), HAART, whereas such therapy had no effect in other cases (117).

For HIV-associated dementia (HAD), the incidence of the severe manifestations of HAD has dramatically decreased following the introduction of antiretroviral therapy, whereas the milder forms of HAD appear to have increased (78, 118, 119). The proposed explanations for this are varied and as yet unresolved (118, 119). From a HERV perspective, interestingly, a recent deep sequencing study of HERV RNAs from HIV^+ vs HIV^- autopsied brain material revealed RNA-tags from HERV-K, HERV-H/F, and HERV-W; with HERV-K tags clearly most abundant in HIV^+ brain material. HERV-K(II) Env was highly expressed in human neurons, especially during HIV/AIDS, but was shown to additionally exert neuroprotective effects *in vitro* and in a mouse model (120).

This could indicate that expression of distinct HERVs in specific cells during certain pathogenetic conditions could play complex adverse roles, which should also be considered in future therapeutic strategies.

Certainly, further studies of HERVs and their role in human diseases are merited.

CONCLUDING REMARKS

Human endogenous retrovirus activation is associated with different neurological diseases. It is also established that HERV-encoded gene products, notably Envs, mediate immunosuppression and have direct or indirect pathogenic effects on immune cells in the periphery and cells in the CNS. The multitude of potential pathogenic mechanisms affected by this HERV activation/expression is beyond the scope of the present review.

As noted above, the questions of actual causal relationship of HERVs with neurological diseases remain unanswered, and further studies are necessary to clarify the questions of causality, for example, in the context of Bradford-Hill's criteria for causation (121, 122). HERV-directed therapeutics could contribute to this clarification.

Perhaps the concept of strict associations of one specific HERV family or even a specific HERV locus with a given disease also somewhat restricts the empirical exploration of the contributions of HERVs to causation, and the currently expanding field of investigations of meta-data; for example,

genetic risk analyses, pathways in (retro)viral restriction, and the contributions of epigenetic regulatory mechanisms will be valuable contributions to our understanding of the role of HERVs in human disease.

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REFERENCES

1. Ogilvie LA, Bowler LD, Caplin J, Dedi C, Diston D, Cheek E, et al. Genome signature-based dissection of human gut metagenomes to extract subliminal viral sequences. Nat Commun 2013;4:2420.
2. Kernbauer E, Ding Y, Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria. Nature 2014;516:94–8.
3. Yolken RH, Jones-Brando L, Dunigan DD, Kannan G, Dickerson F, Severance E, et al. Chlorovirus ATCV-1 is part of the human oropharyngeal virome and is associated with changes in cognitive functions in humans and mice. Proc Natl Acad Sci USA 2014;111:16106–11.
4. Griffiths DJ. Endogenous retroviruses in the human genome sequence. Genome Biol 2001;2: Reviews1017.
5. Christensen T. Association of human endogenous retroviruses with multiple sclerosis and possible interactions with herpes viruses. Rev Med Virol 2005;15:179–211.
6. Christensen T. HERVs in neuropathogenesis. J Neuroimmune Pharmacol 2010;5:326–35.
7. Villesen P, Aagaard L, Wiuf C, Pedersen FS. Identification of endogenous retroviral reading frames in the human genome. Retrovirology 2004;1:32.
8. Boeke JD, Stoye JP. Retrotransposons, endogenous retroviruses, and the evolution of retroelements. In: Coffin JM, Hughes SH, Varmus HE, editors. Retroviruses. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press, 1997:343–435.
9. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 1980;77:7415–9.
10. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, Miyoshi I, Golde D, Gallo RC. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 1982;218:571–3.
11. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983;220:868–71.
12. Gallo RC, Sarin PS, Gelmann EP, Robert-Guroff M, Richardson E, Kalyanaraman VS, et al. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science 1983;220:865–7.
13. Clavel F, Guetard D, Brun-Vezinet F, Chamaret S, Rey MA, Santos-Ferreira MO, et al. Isolation of a new human retrovirus from West African patients with AIDS. Science 1986;233:343–6.
14. Martin MA, Bryan T, Rasheed S, Khan AS. Identification and cloning of endogenous retroviral sequences present in human DNA. Proc Natl Acad Sci USA 1981;78:4892–6.
15. Perzova R, Graziano E, Sanghi S, Welch C, Benz P, Abbott L, et al. Increased seroreactivity to human T cell lymphoma/leukemia virus-related endogenous sequence-1 Gag peptides in patients with human T cell lymphoma/leukemia virus myelopathy. AIDS Res Hum Retroviruses 2015;31:242–9.
16. Weiss RA. On the concept and elucidation of endogenous retroviruses. Philos Trans R Soc Lond B Biol Sci 2013;368:20120494.
17. Weiss RA, Stoye JP. Virology. Our viral inheritance. Science 2013;340:820–1.
18. Denner J. HIV infection en route to endogenization: two cases. Clin Microbiol Infect 2014;21: e33–4.
19. Lavignon M, Evans L. A multistep process of leukemogenesis in Moloney murine leukemia virus-infected mice that is modulated by retroviral pseudotyping and interference. J Virol 1996;70:3852–62.
20. Roy-Burman P. Endogenous env elements: partners in generation of pathogenic feline leukemia viruses. Virus Genes 1995;11:147–61.
21. Denner J, Young PR. Koala retroviruses: characterization and impact on the life of koalas. Retrovirology 2013;10:108.
22. Hohn O, Hanke K, Bannert N. HERV-K(HML-2), the best preserved family of HERVs: endogenization, expression, and implications in health and disease. Frontiers Oncol 2013;3:246.
23. Magiorkinis G, Belshaw R, Katzourakis A. 'There and back again': revisiting the pathophysiological roles of human endogenous retroviruses in the post-genomic era. Philos Trans R Soc Lond B Biol Sci 2013;368:20120504.
24. Douville RN, Nath A. Human endogenous retroviruses and the nervous system. Handb Clin Neurol 2014;123:465–85.
25. Mi S, Lee X, Li X, Veldman GM, Finnerty H, Racie L, et al. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature 2000;403:785–9.
26. Mangeney M, Renard M, Schlecht-Louf G, Bouallaga I, Heidmann O, Letzelter C, et al. Placental syncytins: genetic disjunction between the fusogenic and immunosuppressive activity of retroviral envelope proteins. Proc Natl Acad Sci USA 2007;104:20534–9.
27. Kassiotis G. Endogenous retroviruses and the development of cancer. J Immunol 2014;192:1343–9.
28. Romanish MT, Cohen CJ, Mager DL. Potential mechanisms of endogenous retroviral-mediated genomic instability in human cancer. Semin Cancer Biol 2010;20:246–53.
29. Stauffer Y, Theiler G, Sperisen P, Lebedev Y, Jongeneel CV. Digital expression profiles of human

endogenous retroviral families in normal and cancerous tissues. Cancer Immun 2004;4:2.
30. Tonjes RR, Lower R, Boller K, Denner J, Hasenmaier B, Kirsch H, et al. HERV-K: the biologically most active human endogenous retrovirus family. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13(Suppl 1):S261–7.
31. Volkman HE, Stetson DB. The enemy within: endogenous retroelements and autoimmune disease. Nat Immunol 2014;15:415–22.
32. Tugnet N, Rylance P, Roden D, Trela M, Nelson P. Human endogenous retroviruses (HERVs) and autoimmune rheumatic disease: is there a link? Open Rheumatol J 2013;7:13–21.
33. Lee-Kirsch MA, Wolf C, Gunther C. Aicardi-Goutieres syndrome: a model disease for systemic autoimmunity. Clin Exp Immunol 2014;175:17–24.
34. Nexo BA, Christensen T, Frederiksen J, Moller-Larsen A, Oturai AB, Villesen P, et al. The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. PLoS One 2011;6:e16652.
35. Antony JM, Deslauriers AM, Bhat RK, Ellestad KK, Power C. Human endogenous retroviruses and multiple sclerosis: innocent bystanders or disease determinants? Biochim Biophys Acta 2011;1812:162–76.
36. Moyes DL, Goris A, Ban M, Compston A, Griffiths DJ, Sawcer S, et al. HERV-K113 is not associated with multiple sclerosis in a large family-based study. AIDS Res Hum Retroviruses 2008;24:363–5.
37. Perron H, Firouzi R, Tuke P, Garson JA, Michel M, Beseme F, et al. Cell cultures and associated retroviruses in multiple sclerosis. Acta Neurol Scandinavica Suppl 1997;169:22–31.
38. Christensen T, Jensen AW, Munch M, Haahr S, Sorensen PD, Riemann H, et al. Characterization of retroviruses from patients with multiple sclerosis. Acta Neurol Scand Suppl 1997;169:49–58.
39. Christensen T, Dissing Sorensen P, Riemann H, Hansen HJ, Moller-Larsen A. Expression of sequence variants of endogenous retrovirus RGH in particle form in multiple sclerosis. Lancet 1998;352:1033.
40. Garson JA, Tuke PW, Giraud P, Paranhos-Baccala G, Perron H. Detection of virion-associated MSRV-RNA in serum of patients with multiple sclerosis. Lancet 1998;351:33.
41. Serra C, Sotgiu S, Mameli G, Pugliatti M, Rosati G, Dolei A. Multiple sclerosis and multiple sclerosis-associated retrovirus in Sardinia. Neurol Sci 2001;22:171–3.
42. Sotgiu S, Serra C, Mameli G, Pugliatti M, Rosati G, Arru G, et al. Multiple sclerosis-associated retrovirus and MS prognosis: an observational study. Neurology 2002;59:1071–3.
43. Hurst T, Magiorkinis G. Activation of the innate immune response by endogenous retroviruses. J General Virol 2014;96:1207–18.
44. Mameli G, Cossu D, Cocco E, Frau J, Marrosu MG, Niegowska M, et al. Epitopes of HERV-Wenv induce antigen-specific humoral immunity in multiple sclerosis patients. J Neuroimmunol 2015;280:66–8.
45. Brudek T, Christensen T, Hansen HJ, Bobecka J, Moller-Larsen A. Simultaneous presence of endogenous retrovirus and herpes virus antigens has profound effect on cell-mediated immune responses: implications for multiple sclerosis. AIDS Res Hum Retroviruses 2004;20:415–23.
46. Moller-Larsen A, Brudek T, Petersen T, Petersen EL, Aagaard M, Hansen DT, et al. Flow cytometric assay detecting cytotoxicity against human endogenous retrovirus antigens expressed on cultured multiple sclerosis cells. Clin Exp Immunol 2013;173:398–410.
47. Petersen T, Moller-Larsen A, Thiel S, Brudek T, Hansen TK, Christensen T. Effects of interferon-beta therapy on innate and adaptive immune responses to the human endogenous retroviruses HERV-H and HERV-W, cytokine production, and the lectin complement activation pathway in multiple sclerosis. J Neuroimmunol 2009;215:108–16.
48. Perron H, Jouvin-Marche E, Michel M, Ounanian-Paraz A, Camelo S, Dumon A, et al. Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. Virology 2001;287:321–32.
49. Brudek T, Christensen T, Aagaard L, Petersen T, Hansen HJ, Moller-Larsen A. B cells and monocytes from patients with active multiple sclerosis exhibit increased surface expression of both HERV-H Env and HERV-W Env, accompanied by increased seroreactivity. Retrovirology 2009;6:104.
50. Laska MJ, Brudek T, Nissen KK, Christensen T, Moller-Larsen A, Petersen T, et al. Expression of HERV-Fc1, a human endogenous retrovirus, is increased in patients with active multiple sclerosis. J Virol 2012;86:3713–22.
51. Mameli G, Poddighe L, Mei A, Uleri E, Sotgiu S, Serra C, et al. Expression and activation by Epstein Barr virus of human endogenous retroviruses-W in blood cells and astrocytes: inference for multiple sclerosis. PLoS One 2012;7:e44991.
52. Xu Y, Kulkosky J, Acheampong E, Nunnari G, Sullivan J, Pomerantz RJ. HIV-1-mediated apoptosis of neuronal cells: proximal molecular mechanisms of HIV-1-induced encephalopathy. Proc Natl Acad Sci USA 2004;101:7070–5.
53. Antony JM, van Marle G, Opii W, Butterfield DA, Mallet F, Yong VW, et al. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. Nat Neurosci 2004;7:1088–95.
54. Kremer D, Schichel T, Forster M, Tzekova N, Bernard C, van der Valk P, et al. Human endogenous retrovirus type W envelope protein inhibits oligodendroglial precursor cell differentiation. Ann Neurol 2013;74:721–32.
55. Reiber H, Ungefehr S, Jacobi C. The intrathecal, polyspecific and oligoclonal immune response in multiple sclerosis. Mult Scler 1998;4:111–7.
56. Jolivet-Reynaud C, Perron H, Ferrante P, Becquart L, Dalbon P, Mandrand B. Specificities of multiple sclerosis cerebrospinal fluid and serum antibodies against mimotopes. Clin Immunol 1999;93:283–93.
57. Johnston JB, Silva C, Holden J, Warren KG, Clark AW, Power C. Monocyte activation and differentiation augment human endogenous retrovirus expres-

sion: implications for inflammatory brain diseases. Ann Neurol 2001;50:434–42.
58. Antony JM, Zhu Y, Izad M, Warren KG, Vodjgani M, Mallet F, et al. Comparative expression of human endogenous retrovirus-W genes in multiple sclerosis. AIDS Res Hum Retroviruses 2007;23:1251–6.
59. Perron H, Lazarini F, Ruprecht K, Pechoux-Longin C, Seilhean D, Sazdovitch V, et al. Human endogenous retrovirus (HERV)-W ENV and GAG proteins: physiological expression in human brain and pathophysiological modulation in multiple sclerosis lesions. J Neurovirol 2005;11:23–33.
60. Nakamura A, Okazaki Y, Sugimoto J, Oda T, Jinno Y. Human endogenous retroviruses with transcriptional potential in the brain. J Hum Genet 2003;48:575–81.
61. Suntsova M, Gogvadze EV, Salozhin S, Gaifullin N, Eroshkin F, Dmitriev SE, et al. Human-specific endogenous retroviral insert serves as an enhancer for the schizophrenia-linked gene PRODH. Proc Natl Acad Sci USA 2013;110:19472–7.
62. Borglum AD, Demontis D, Grove J, Pallesen J, Hollegaard MV, Pedersen CB, et al. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. Mol Psychiatry 2014;19:325–33.
63. Andreassen OA, Harbo HF, Wang Y, Thompson WK, Schork AJ, Mattingsdal M, et al. Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. Mol Psychiatry 2015;20:207–14.
64. Yolken RH, Karlsson H, Yee F, Johnston-Wilson NL, Torrey EF. Endogenous retroviruses and schizophrenia. Brain Res Brain Res Rev 2000;31:193–9.
65. Karlsson H, Bachmann S, Schroder J, McArthur J, Torrey EF, Yolken RH. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci USA 2001;98:4634–9.
66. Frank O, Giehl M, Zheng C, Hehlmann R, Leib-Mosch C, Seifarth W. Human endogenous retrovirus expression profiles in samples from brains of patients with schizophrenia and bipolar disorders. J Virol 2005;79:10890–901.
67. Huang W, Li S, Hu Y, Yu H, Luo F, Zhang Q, et al. Implication of the env gene of the human endogenous retrovirus W family in the expression of BDNF and DRD3 and development of recent-onset schizophrenia. Schizophr Bull 2011;37:988–1000.
68. Perron H, Mekaoui L, Bernard C, Veas F, Stefas I, Leboyer M. Endogenous retrovirus type W GAG and envelope protein antigenemia in serum of schizophrenic patients. Biol Psychiatry 2008;64:1019–23.
69. Weis S, Llenos IC, Sabunciyan S, Dulay JR, Isler L, Yolken R, et al. Reduced expression of human endogenous retrovirus (HERV)-W GAG protein in the cingulate gyrus and hippocampus in schizophrenia, bipolar disorder, and depression. J Neural Transm (Vienna) 2007;114:645–55.
70. Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, Shaw PJ. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. Nat Rev Neurol 2011;7:616–30.
71. Andrews WD, Tuke PW, Al-Chalabi A, Gaudin P, Ijaz S, Parton MJ, et al. Detection of reverse transcriptase activity in the serum of patients with motor neurone disease. J Med Virol 2000;61:527–32.
72. McCormick AL, Brown RH Jr, Cudkowicz ME, Al-Chalabi A, Garson JA. Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. Neurology 2008;70:278–83.
73. Oluwole SO, Yao Y, Conradi S, Kristensson K, Karlsson H. Elevated levels of transcripts encoding a human retroviral envelope protein (syncytin) in muscles from patients with motor neuron disease. Amyotroph Lateral Scler 2007;8:67–72.
74. Douville R, Liu J, Rothstein J, Nath A. Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis. Ann Neurol 2011;69:141–51.
75. Alfahad T, Nath A. Retroviruses and amyotrophic lateral sclerosis. Antiviral Res 2013;99:180–7.
76. Li W, Lee MH, Henderson L, Tyagi R, Bachani M, Steiner J, et al. Human endogenous retrovirus-K contributes to motor neuron disease. Sci Transl Med 2015;7:307ra153.
77. Michaels J, Sharer LR, Epstein LG. Human immunodeficiency virus type 1 (HIV-1) infection of the nervous system: a review. Immunodef Rev 1988;1:71–104.
78. Grill MF, Price RW. Central nervous system HIV-1 infection. Handb Clin Neurol 2014;123:487–505.
79. Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. J Neurol Sci 2002;202:13–23.
80. Garrison KE, Jones RB, Meiklejohn DA, Anwar N, Ndhlovu LC, Chapman JM, et al. T cell responses to human endogenous retroviruses in HIV-1 infection. PLoS Pathog 2007;3:e165.
81. Jones RB, Garrison KE, Mujib S, Mihajlovic V, Aidarus N, Hunter DV, et al. HERV-K-specific T cells eliminate diverse HIV-1/2 and SIV primary isolates. J Clin Investig 2012;122:4473–89.
82. Christensen T. Human herpesviruses in MS. Int MS J 2007;14:41–7.
83. Hollsberg P, Kusk M, Bech E, Hansen HJ, Jakobsen J, Haahr S. Presence of Epstein-Barr virus and human herpesvirus 6B DNA in multiple sclerosis patients: associations with disease activity. Acta Neurol Scand 2005;112:395–402.
84. Haahr S, Hollsberg P. Multiple sclerosis is linked to Epstein-Barr virus infection. Rev Med Virol 2006;16:297–310.
85. Farrell RA, Antony D, Wall GR, Clark DA, Fisniku L, Swanton J, et al. Humoral immune response to EBV in multiple sclerosis is associated with disease activity on MRI. Neurology 2009;73:32–8.
86. Fotheringham J, Jacobson S. Human herpesvirus 6 and multiple sclerosis: potential mechanisms for virus-induced disease. Herpes 2005;12:4–9.
87. Yao K, Gagnon S, Akhyani N, Williams E, Fotheringham J, Frohman E, et al. Reactivation of human

herpesvirus-6 in natalizumab treated multiple sclerosis patients. PLoS One 2008;3:e2028.
88. Bech E, Lycke J, Gadeberg P, Hansen HJ, Malmestrom C, Andersen O, et al. A randomized, double-blind, placebo-controlled MRI study of anti-herpes virus therapy in MS. Neurology 2002;58:31–6.
89. Carter CJ. Susceptibility genes are enriched in those of the herpes simplex virus 1/host interactome in psychiatric and neurological disorders. Pathog Dis 2013;69:240–61.
90. Csoma E, Bacsi A, Liu X, Szabo J, Ebbesen P, Beck Z, et al. Human herpesvirus 6 variant a infects human term syncytiotrophoblasts in vitro and induces replication of human immunodeficiency virus type 1 in dually infected cells. J Med Virol 2002;67:67–87.
91. Griffiths PD. Herpesviruses and AIDS. Scand J Infect Dis Suppl 1996;100:3–7.
92. Perron H, Suh M, Lalande B, Gratacap B, Laurent A, Stoebner P, et al. Herpes simplex virus ICP0 and ICP4 immediate early proteins strongly enhance expression of a retrovirus harboured by a leptomeningeal cell line from a patient with multiple sclerosis. J General Virol 1993;74:65–72.
93. Sutkowski N, Chen G, Calderon G, Huber BT. Epstein-Barr virus latent membrane protein LMP-2A is sufficient for transactivation of the human endogenous retrovirus HERV-K18 superantigen. J Virol 2004;78:7852–60.
94. Turcanova VL, Bundgaard B, Hollsberg P. Human herpesvirus-6B induces expression of the human endogenous retrovirus K18-encoded superantigen. J Clin Virol 2009;46:15–9.
95. Goff SP. Retrovirus restriction factors. Mol Cell 2004;16:849–59.
96. Nisole S, Stoye JP, Saib A. TRIM family proteins: retroviral restriction and antiviral defence. Nat Rev Microbiol 2005;3:799–808.
97. Teich NM, Weiss RA, Martin GR, Lowy DR. Virus infection of murine teratocarcinoma stem cell lines. Cell 1977;12:973–82.
98. Wolf D, Hug K, Goff SP. TRIM28 mediates primer binding site-targeted silencing of Lys 1,2 tRNA-utilizing retroviruses in embryonic cells. Proc Natl Acad Sci USA 2008;105:12521–6.
99. Fasching L, Kapopoulou A, Sachdeva R, Petri R, Jonsson ME, Manne C, et al. TRIM28 represses transcription of endogenous retroviruses in neural progenitor cells. Cell Rep 2015;10:20–8.
100. Sweatt JD. The emerging field of neuroepigenetics. Neuron 2013;80:624–32.
101. Santoni FA, Guerra J, Luban J. HERV-H RNA is abundant in human embryonic stem cells and a precise marker for pluripotency. Retrovirology 2012;9:111.
102. Nexo BA, Hansen B, Nissen KK, Gundestrup L, Terkelsen T, Villesen P, et al. Restriction genes for retroviruses influence the risk of multiple sclerosis. PLoS One 2013;8:e74063.
103. Sharma P, Azebi S, England P, Christensen T, Moller-Larsen A, Petersen T, et al. Citrullination of histone H3 interferes with HP1-mediated transcriptional repression. PLoS Genet 2012;8:e1002934.
104. Oh U, Yamano Y, Mora CA, Ohayon J, Bagnato F, Butman JA, et al. Interferon-beta1a therapy in human T-lymphotropic virus type I-associated neurologic disease. Ann Neurol 2005;57:526–34.
105. Brule F, Khatissian E, Benani A, Bodeux A, Montagnier L, Piette J, et al. Inhibition of HIV replication: a powerful antiviral strategy by IFN-beta gene delivery in CD4 + cells. Biochem Pharmacol 2007;74:898–910.
106. Mameli G, Serra C, Astone V, Castellazzi M, Poddighe L, Fainardi E, et al. Inhibition of multiple-sclerosis-associated retrovirus as biomarker of interferon therapy. J Neurovirol 2008;14:73–7.
107. Petersen T, Moller-Larsen A, Ellermann-Eriksen S, Thiel S, Christensen T. Effects of interferon-beta therapy on elements in the antiviral immune response towards the human herpesviruses EBV, HSV, and VZV, and to the human endogenous retroviruses HERV-H and HERV-W in multiple sclerosis. J Neuroimmunol 2012;249:105–8.
108. Maruszak H, Brew BJ, Giovannoni G, Gold J. Could antiretroviral drugs be effective in multiple sclerosis? A case report. Eur J Neurol 2011;18:e110–1.
109. Nexo BA, Pedersen L, Sorensen HT, Koch-Henriksen N. Treatment of HIV and risk of multiple sclerosis. Epidemiology 2013;24:331–2.
110. Gold J, Goldacre R, Maruszak H, Giovannoni G, Yeates D, Goldacre M. HIV and lower risk of multiple sclerosis: beginning to unravel a mystery using a record-linked database study. J Neurol Neurosurg Psychiatry 2015;86:9–12.
111. Chin JH. Multiple sclerosis and HIV-1 infection: case report of a HIV controller. J Neurovirol 2015;21:464–7.
112. Kremer D, Forster M, Schichel T, Gottle P, Hartung HP, Perron H, et al. The neutralizing antibody GNbAC1 abrogates HERV-W envelope protein-mediated oligodendroglial maturation blockade. Mult Scler 2014;21:1200–3.
113. Derfuss T, Curtin F, Guebelin C, Bridel C, Rasenack M, Matthey A, et al. A phase IIa randomised clinical study of GNbAC1, a humanised monoclonal antibody against the envelope protein of multiple sclerosis-associated endogenous retrovirus in multiple sclerosis patients. Mult Scler 2015;21:885–93.
114. Blank MB, Himelhoch S, Walkup J, Eisenberg MM. Treatment considerations for HIV-infected individuals with severe mental illness. Curr HIV/AIDS Rep 2013;10:371–9.
115. Hoffman PM, Festoff BW, Giron LT Jr, Hollenbeck LC, Garruto RM, Ruscetti FW. Isolation of LAV/HTLV-III from a patient with amyotrophic lateral sclerosis. New Engl J Med 1985;313:324–5.
116. Sinha S, Mathews T, Arunodaya GR, Siddappa NB, Ranga U, Desai A, et al. HIV-1 clade-C-associated "ALS"-like disorder: first report from India. J Neurol Sci 2004;224:97–100.
117. Verma A, Berger JR. ALS syndrome in patients with HIV-1 infection. J Neurol Sci 2006;240:59–64.
118. Silva K, Hope-Lucas C, White T, Hairston TK, Rameau T, Brown A. Cortical neurons are a prominent source of the proinflammatory cytokine osteo-

pontin in HIV-associated neurocognitive disorders. J Neurovirol 2015;21:174–85.
119. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol 2010;67:699–714.
120. Bhat RK, Rudnick W, Antony JM, Maingat F, Ellestad KK, Wheatley BM, et al. Human endogenous retrovirus-K(II) envelope induction protects neurons during HIV/AIDS. PLoS One 2014;9: e97984.
121. Giovannoni G, Cutter GR, Lunemann J, Martin R, Munz C, Sriram S, et al. Infectious causes of multiple sclerosis. Lancet Neurol 2006;5:887–94.
122. Christensen T, Giovannoni G. HERVs: have we been here before? Mult Scler 2013;19:827–9.
123. Perron H, Garson JA, Bedin F, Beseme F, Paranhos-Baccala G, Komurian-Pradel F, et al. Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. Proc Natl Acad Sci USA 1997;94:7583–8.
124. Laufer G, Mayer J, Mueller BF, Mueller-Lantzsch N, Ruprecht K. Analysis of transcribed human endogenous retrovirus W env loci clarifies the origin of multiple sclerosis-associated retrovirus env sequences. Retrovirology 2009;6:37.
125. Belshaw R, Katzourakis A, Paces J, Burt A, Tristem M. High copy number in human endogenous retrovirus families is associated with copying mechanisms in addition to reinfection. Mol Biol Evol 2005;22:814–7.
126. Perzova R, Graziano E, Sanghi S, Welch C, Benz P, Abbott L, et al. Increased seroreactivity to HERV-K10 peptides in patients with HTLV myelopathy. Virol J 2013;10:360.
127. Jeong BH, Lee YJ, Carp RI, Kim YS. The prevalence of human endogenous retroviruses in cerebrospinal fluids from patients with sporadic Creutzfeldt-Jakob disease. J Clin Virol 2010;47:136–42.