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Prospects for the Management of Human T-cell Lymphotropic Virus Type 1-Associated Myelopathy

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Abstract

Over the twenty-five years since the association of human T-cell lymphotropic virus type 1 infection with tropical spastic paraparesis, little progress has been made in the treatment of this chronic debilitating condition. The purpose of this review is to highlight the most informative results and to identify the most promising candidates for further study. Although many small observational studies have been reported, only twice have the positive data been tested in randomized controlled studies. In the first study, interferon-alpha 3 MU was found to be better than 0.3 or 1 MU over four weeks, whilst zidovudine plus lamivudine performed no better than placebo after 24-48 weeks of therapy in the second study. Preliminary data from studies of immunomodulatory therapy including cyclosporine and monoclonal antibodies to CD25 and interleukin-15 are encouraging and further comparative studies are indicated with the combination of antiretroviral therapy with histone deacetylation inhibition, which has been shown to reduce simian T-lymphotropic virus type 1 proviral load in baboons, unless this proves unsuccessful in human T-cell lymphotropic virus type 1 infection. **(AIDS Rev. 2011;13:161-70)**

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Key words

HTLV-1-associated myelopathy. Treatment. Monoclonal antibodies. Antiretroviral therapy. Histone deacetylation inhibitors.

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus infecting up to 20 million persons worldwide. Infection, which is lifelong, may lead to neoplastic or inflammatory disease and increased susceptibility to other infections. Infection with HTLV-1 is endemic in Japan, South America, the Caribbean, West and Southern Africa, Melanesia and amongst the indigenous populations of North America and Australia. The highest prevalence of HTLV-1 amongst native Europeans is in Romania. The majority of HTLV-1-positive patients living in Europe are of Afro Caribbean origin, but transmission to the native population is occurring. In North America, in addition to American Indians, HTLV-1 is most commonly detected in African Americans.

Although HTLV-1[1] was discovered before HIV type 1 and the associations between the virus and adult T-cell leukemia/lymphoma (ATLL)[2] and tropical spastic paraparesis[3]/HTLV-1-associated myelopathy[4] (HAM/TSP) were made in the 1980s, there is still no widely accepted and applied treatment for HAM/TSP, a chronic, progressing and painfully disabling condition.

There are many reasons for this: (i) most infections occur in developing countries where access to healthcare is poor and surveillance data therefore incomplete; (ii) both ATLL and HAM/TSP are difficult to study due to their long latency from time of infection to symptom development and HAM/TSP often has an insidious and inconspicuous onset; (iii) patients present at different stages of their disease and recruitment of "same-stage" patients is a challenge; (iv) our understanding

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of the immunopathology of HTLV-1-associated conditions is still limited; (v) most treatments studied are expensive and thus not funded by the governments of developing countries; and (vi) both ATLL and HAM/TSP are rare diseases in industrialized nations, apart from Japan, and therefore attract little interest from the pharmaceutical industry and limited governmental funding for translational research. Conducting clinical studies has been particularly difficult and, with rare exceptions, such studies have mostly been small and observational, capturing patients at a variety of disease stages. Finally, unlike HIV where the aim of therapy is to inhibit viral replication leading to immune recovery, an interference with the host immune surveillance of HTLV-1 positive patients through immunomodulatory drugs could have severe consequences, risking HAM/TSP disease progression and/or the development of ATLL.

Thirty years on, the urgent need for different types of clinical trials as tools for understanding the disease and finding a cure has led to an international consensus regarding an efficacious and safe approach to conducting translational research in and for patients with HAM/TSP:

- Small, observational 'proof of concept' studies must be encouraged in order to understand pathogenesis, identify surrogate markers of treatment efficacy, and generate safety and outcome data which will direct.
- Larger, randomized, controlled, 'proof of efficacy' clinical trials.

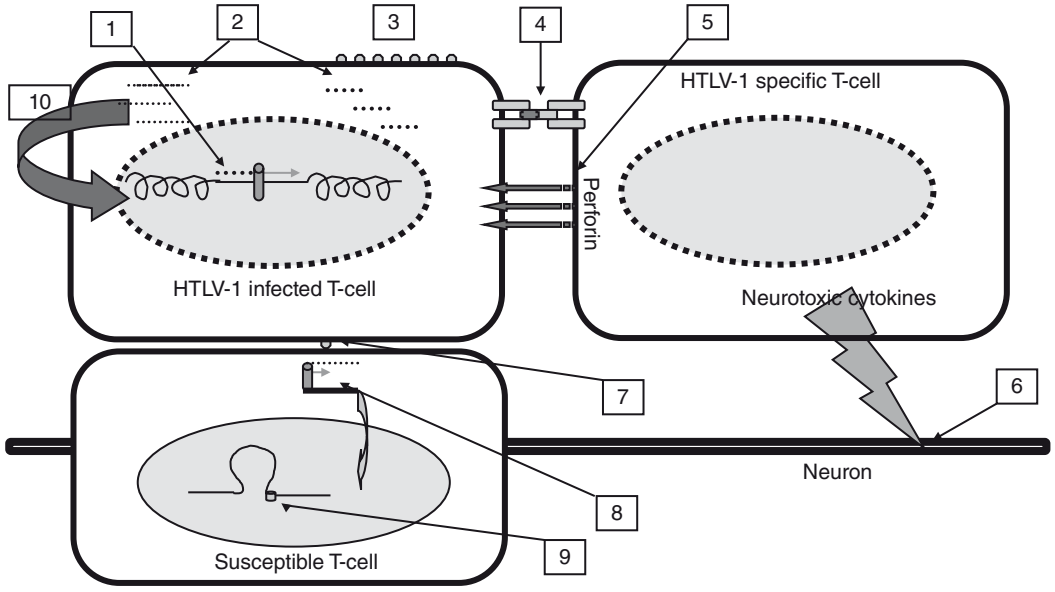
The former are usually best conducted in single centers, well supported by high-cost, intensive laboratory investigation, and the latter in endemic countries with access to large cohorts supervised by medically trained specialists in HTLV-1-associated conditions. For the purpose of this review, we have concentrated on the development of treatment strategies in patients with HAM/TSP.

Pathogenesis of Human T-cell Lymphotropic Virus Type 1-associated inflammation

Immune surveillance

Compared to the limited progress with therapy, our understanding of the pathogenesis of HAM/TSP has advanced and provides useful direction for new therapeutic interventions. There is a predilection of HTLV-1-associated neuro-inflammation for the thoracic cord, perhaps due to slower blood flow with more opportunity for cells expressing adhesion molecules to transmigrate. However, other watershed areas of the central nervous system (CNS) remain clinically silent. Histopathology reveals perivascular lymphocytic infiltration with both $CD4^+$ and $CD8^+$ T lymphocytes in earlier lesions, predominantly $CD8^+$ T lymphocytes in later lesions, and subsequent progression to a relatively acellular, atrophic picture with axonal and myelin degeneration[5-8]. HTLV-1-specific $CD8^+$ T lymphocytes that secrete neurotoxic cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), have been isolated from cerebrospinal fluid (CSF)[9,10]. HTLV-1-infected lymphocytes are found in the spinal cord or brain, but there is no *in vivo* evidence of HTLV-1 infection of neurons or astrocytes in patients with HAM/TSP. Today the 'bystander damage' theory of HAM/TSP pathogenesis caused by overactive immune surveillance[11,12] is preferred to the 'molecular antigen mimicry' theory, although both lead to autoimmune-type diseases[13] and form the basis on which proof-of-concept studies are designed. In the bystander damage theory, circulating HTLV-1-infected T lymphocytes will periodically make contact with an HTLV-1-specific $CD4^+$ or $CD8^+$ T lymphocyte whilst expressing HTLV-1 protein(s). In an efficient response, the infected cell is lysed with no pathological consequence. Contact with failure to lyse the cell efficiently results in a more complex response with secretion of multiple cytokines and further recruitment of inflammatory cells to the lesion. It is envisaged that both HTLV-1-infected and HTLV-1-specific cells migrate, leading to the inflammatory infiltration of tissue described above. This may and perhaps does occur in many tissue types, but when the interaction occurs in the central nervous system, secretion of TNF-α and IFN-γ damages neurons (Fig. 1). It is important to point out that a dynamic laboratory, histological or imaging marker in the blood, CSF or CNS of an asymptomatic carrier showing the preclinical onset of HAM/TSP development has not been discovered yet, although high HTLV-1 viral load is considered the best predictor of risk.

Considerable debate has centered on the role of HTLV-1-specific cytotoxic T lymphocytes (CTL) in HAM/TSP pathogenesis. Initially, HTLV-1-specific CTL were identified in the peripheral blood of patients with HAM/TSP[14] and, even though difficult to detect in patients with ATLL[15], the evidence for their presence in all patients with HTLV-1 infection is convincing[16-20]. Surprisingly, the frequency of HTLV-1-specific $CD8^+$ CTL is similar in patients with and without HAM/TSP, and although there seems to be a positive correlation between HTLV-1-specific CTL frequency and peripheral blood HTLV-1 viral load, it does not predict CTL response efficacy[18].



1. Transcription of HTLV-1 provirus. **2.** Production of genomic and messenger HTLV-1 RNA. **3 and 7.** Production of HTLV-1 virions. **4.** Expression of immunogenic HTLV-1 proteins recognized by HTLV-1-specific T-cells. **5.** Efficient HTLV-1-specific T-cells secrete perforin leading to lysis of 'unmasked' HTLV-1-infected cells and control of HTLV-1 viral load. **6.** Inefficient HTLV-1-specific T-cells secrete neurotoxic cytokines leading to increased neuronal damage (and recruitment of CD4 and CD8 cells leads to increased inflammation and a local increase in HTLV-1-infected cells). **7.** HTLV-1-infected cells not lysed will on contact with uninfected susceptible T-cells release HTLV-1 virions at the virologic synapse. **8.** HTLV-1 genomic RNA and enzymes released into cytoplasm – reverse transcription of HTLV-1 RNA to HTLV-1 DNA. **9.** HTLV-1 pre-integration complex shuttles to nucleus where HTLV-1 integrase integrates HTLV-1 DNA into host chromosome forming HTLV-1 proviral DNA. **10.** HTLV-1 proteins drive cell proliferation with mitotic increase in HTLV-1 proviral load.

Figure 1. *Mechanisms of viral replication and disease. HTLV: human T-cell lymphotropic virus.*

HTLV-1-specific $CD4^+$ T lymphocytes are commonly detected in HTLV-1-infected patients and seem to contribute to pathogenesis as well as immune surveillance[18,21]. In contrast to HTLV-1-specific $CD8^+$ cells, HTLV-1-specific $CD4^+$ cells are 10-25 times more frequent in patients with HAM/TSP than in asymptomatic carriers with similar viral load[22]. Recently, the prediction that human leukocyte antigen (HLA) class A responses to a novel HTLV-1 protein, HTLV-1 leucine B zipper (HBZ), determine HTLV infection outcome[23] have been corroborated in an observational study associating CD8 HBZ-specific responses with low viral load[24].

Human T-cell lymphotropic virus type 1 viral load threshold determines disease risk

An association between viral burden and HTLV-1-associated inflammatory disease, first noted in Southern blot analyses of patients with HAM/TSP[25], has been confirmed by limiting dilution polymerase chain reaction (PCR)[26] and by real-time PCR[27], in patients with HAM/TSP and uveitis[28]. The range of viral load in different patients with HTLV-1 infection is large, from < 1 HTLV-1 DNA copy per 100,000 peripheral blood mononuclear cells (PBMC) to 1 copy per PBMC[26]. HTLV-1 viral load remains relatively stable over time, which is different from HIV-1 RNA viral load where an increase in viral load in asymptomatic carriers over time is associated with disease progression.

High HTLV-1 viral loads are mostly seen in patients with ATLL, but have been found in patients with HTLV-1-associated inflammation, especially in rapid, progressive HAM/TSP. The median HTLV-1 viral load is 10-fold higher in patients with HAM/TSP than in asymptomatic carriers[25,27,29], but the ranges overlap[26]. Patients with HAM/TSP rarely have a HTLV-1 DNA copy/100 PBMC

Table 1. Summary of therapeutic studies in patients with human T-cell lymphotropic virus-associated myelopathy/tropical spastic paraparesis

Year	Country	Authors	Study design	Drug	Regime	Duration follow-up	(n)	Duration of HAM	Motor improvement*	Note
1990	UK	Duncan, et al.[42]	Case series	Methyl-prednisolone iv	500 mg (once daily / 5 days)		9	Not stated	Transient (6/9)	
1991	France	Gout, et al.[55]	Case series	Zidovudine	500 mg – 1 g/day	6 months	5	Chronic	None	
1991	USA	Harrington, et al.[44]	Case series	Zidovudine	200 mg tds - qds	2-15 weeks	6	< 1 to 15 years	5/6	Bladder improvement
1992	Brazil	Melo, et al.[45]	Case series	Danazol	200 mg tds	> 1 month	8	0.5-3 years	7/8	Bladder improvement
1993	Japan	Nagasato, et al.[46]	Case series	Heparin	5-10,000 U/day	9-93 days	10	1-45 years; median 11 years	7/10	
1993	USA	Sheremata, et al.[56]	Open label phase 1	Zidovudine	2 g/day 4 weeks 1 g/day 20 weeks	24 weeks	10	Not stated	50% improvement in timed gait in 7/7 ambulant patients	
1996	Japan	Nakagawa, et al.[41]	Non randomized, open label, prospective clinical trial sequential recruitment	Prednisolone po	1-2 mg/kg daily	6-12 months	131	15.7 ±12.7 years (1-60 years)	> 1 grade 91/131	Treated for 1-2 months then tapered
				Interferon-α im	3 MIU/day	30 days	32		> 1 grade 10/43	
				High-dose vitamin C	1.5-3 g	3-4 days	20		> 1 grade 4/20	
				Erythromycin	600 mg/day	1-3 months	25		> 1 grade 4/25	
				Azathioprine	50-100 mg/day	1-3 months	9		> 1 grade* 2/9	
				Salazosulfapyridine	1-1.5 g/day	1-3 months	24		> 1 grade 3/24	
1996	Japan	Izumo, et al.[49]	Multicentre double blind, RCT 3 doses	Interferon-α im	0.3 MU or 1 MU or 3 MU	8 weeks	48	≤ 5 or > 5 years	Transient improvement at 3 MU dose	No placebo
1997	Japan	Yamasaki, et al.[50]	Case series	Interferon-α	6 MU daily then tiw for 24 weeks	+ 24 wks posttreatment	7		5/7	2 discontinued
1997	Japan	Shirabe, et al.[47]	Open label proof-of-concept	Pentoxifylline	300 mg po	4 weeks	15	2-24 years	Improvement at 4 weeks in 14/15 and in 4 at 48 weeks	
1998	USA	Lehky, et al.[59]	Open label proof-of-concept	Anti-CD25 monoclonal antibody	1 mg/kg x 5 iv	14 weeks	9	3-15 years	3/9 improved gait	
1999	UK	Taylor, et al.[57]	Open label proof-of-concept	Lamivudine	150 mg twice daily	10.2 months	5	7 months to 17 years	Temporary significant 1/5	
2004	Japan	Saito, et al.[51]	Cohort	Interferon-α	3 MU daily	4 weeks	25	2-25 years	"Good" 10/25	

(*continue*)

Table 1. Summary of therapeutic studies in patients with human T-cell lymphotropic virus-associated myelopathy/tropical spastic paraparesis *(continued)*

Year	Country	Authors	Study design	Drug	Regime	Duration follow-up	(n)	Duration of HAM	Motor improvement*	Note
2005	USA	Oh, et al.[53]	Open label proof-of-concept	Interferon-β1a	30 mcg weekly < 60 mcg twice weekly	24 weeks treatment 12 weeks follow-up	12	2-20 years	No deterioration	
2006	UK	Taylor, et al.[36]	Placebo RCT	Zidovudine plus lamivudine	250 mg + 150 mg (twice daily)	48 weeks	16	9	No improvement	
2007	Japan	Arimuri, et al.[52]	Phase IV	Interferon-α	3 MU daily	Median 30 days	167		67% improved at 4 weeks 'mild' to 'marked'	Concomitant medications
2007	Martinique	Lezin, et al.[78]	Pilot study	Sodium valproate	20 mg/kg/day	3 months	16	> 2 years	Transient worsening	Significant, transient reduction in HTLV-1 proviral load
2008	Brazil	Croda, et al.[43]	Prospective observational cohort	Methyl prednisolone iv	3 days every 3-4 months	2.2 years	39	8	Transient improvement with initial treatment	

*Grade relates to 10 point motor disability scale described in the paper.
RCT: randomized controlled trial; im: intramuscular; iv: intravenous; MIU: million international units; po: oral; qds: four times daily; tiw: three times weekly.

of < 1, and in a Japanese population, above this threshold the incidence of HAM/TSP rises exponentially[27]. Thus, viral load is an important but not exclusive determinant of disease risk.

Most recently, the frequency of expression of the HTLV-1 regulatory protein Tax by unstimulated PBMC was shown to be ~ 3-fold higher in patients with HAM/TSP compared to asymptomatic carriers with equivalent HTLV-1 DNA load[30]. The protective effect of HLA-A2, HLA-CW08 and the cytokine polymorphisms SDF-1+801A 3'UTR and IL-15 191C against the development of HAM/TSP is through association with lower HTLV-1 viral load, whereas the converse is seen with HLA-B5401[31,32]. These genetic factors were detected in a Japanese population and the findings could not be completely replicated in Peru where proviral load alone successfully predicted disease, with gender, age, and HLA-A2 status contributing to an optimized predictive model[33].

In HTLV-1-infected patients, there is now substantial evidence that viral load is mainly maintained through cell division and not viral replication and new infection[34]. In patients with ATLL, the viral load may exceed 100%, i.e. at least one copy of HTLV-1 DNA per cell due a to mono- or oligoclonal expansion of HTLV-1-infected cells with one or more integration sites[35]. Despite vigorous immune surveillance, HTLV-1 is able to persist without the need for constant reverse transcription. Therefore, the impact of mono or dual therapy with viral reverse transcriptase inhibitors with the aim of reducing the HTLV-1 viral load *in vivo* has been minimal[36]. The 'mitotic maintenance and increase' in viral load is likely to account for the slower rate of evolution of HTLV-1 compared with other RNA viruses[37]. The duration of infectious spread in primary HTLV-1 infection and the contribution of infectious spread to maintenance of viral load in established infection remains unquantified. High throughput sequencing with identification of the number and frequency of individual viral integration sites provides an opportunity to finally address this fundamental question[38].

Therapy

The variety of interventions tried in HAM/TSP (summarized in Table 1) is testimony to the lack of efficacy demonstrated to date. Early observational studies with corticosteroids reported variable and usually short-term benefit[39-42]. A recent survey of potential participants in a HAM/TSP International Trials Network revealed that corticosteroids are the most widely prescribed therapy, especially at initial presentation, based on the anecdotal

experience of the physicians (unpublished data). Clinical improvement with pulsed methylprednisolone has been reported from a Brazilian cohort with decreasing benefit with repeated courses[43], and whilst this is also our own experience, short-term improvement, particularly in pain, can significantly improve quality of life and be targeted to coincide with important life events (Martin, et al. 2011 submitted).

Two open studies of a total of 15 patients have reported improvement in mobility and particularly in bladder function with danazol, a synthetic derivative of 17-α ethinyl testosterone, albeit with abnormal liver function at higher doses[44,45]. Alternative approaches have been to interfere with the migration of $CD4^+$ T lymphocytes using heparin[46] and to downregulate T helper-1 (Th1) activity with pentoxifylline[47,48], with some clinical response reported in both observational studies.

In a blinded study, 3 MU IFN-α given daily for 28 days showed better clinical benefits than 0.3 and 1 MU IFN-α given daily, but there was no placebo arm and the follow-up was short[49]. Improvement following six months of therapy with IFN-α has been reported, but only seven patients were studied[50]. Saito, et al. reported a reduction in HTLV-1 proviral load and in $CD8^+$ memory cells ($CD45RA^-CD27^+$) after four weeks of therapy with IFN-α, and associated a reduction in perforin expression with clinical improvement[51]. Post-marketing surveillance of IFN-α in Japan indicates both a high response rate at four weeks (66%) and a high adverse event rate (536 events reported in 146 patients, 46 classified as severe)[52]. Twelve patients given IFN-β1A for six months in an open study did not deteriorate, but the documented reduction in CTL frequency was not specific for HTLV-1 antigens[53].

The inhibitory activity of the nucleoside reverse transcriptase inhibitors (NRTI) zidovudine and dideoxycytidine against HTLV-1 reverse transcriptase was first documented *in vitro* in 1987[54]. No clinical response was seen in five patients treated with zidovudine in France[55], whereas a 50% improvement in timed walk was noted in patients with less advanced disease in a study from Miami[56]. A reduction in viral load and clinical improvement in one patient with early disease and a reduction in HTLV-1 proviral load without clinical improvement in a further four patients with chronic stable disease was seen with the cytosine analogue reverse transcriptase inhibitor, lamivudine[57]. However in a randomized, double-blind, placebo-controlled study of 16 patients no clinical, viral or immunological response with the combination of zidovudine 250 mg plus lamivudine 150 mg twice daily was observed[36].

Steroid-sparing agents have been tried in a few patients and always in open studies. A Japanese study reported improvement in 6/9 patients taking azathioprine and in 12/24 patients on sulphasalazine, but similar improvement was also reported with erythromycin and vitamin C[41]. So far all patients recruited were included without staging their HAM/TSP as early progressive or late chronic. A cyclosporine study was the first proof-of-concept study that targeted recruitment of patients with 'early progressive' HAM/TSP. Early progressive disease was defined in the study as disease of less than two years duration from first symptom, excluding bladder symptoms (early) or documented 30% deterioration in ambulation during the preceding three months (progressive). A reduction in viral load, especially in the CSF, was correlated with an improvement in inflammatory markers and clinical improvement in 5/7 patients[58] (full manuscript in preparation).

Monoclonal antibody therapy is another attractive treatment strategy. In 1998, clinical improvement in 3/9 patients with HAM/TSP treated with an anti-CD25 humanized monoclonal antibody (daclizumab) was reported along with a significant reduction in $CD4^+CD25^+$ lymphocytes and a related reduction in HTLV-1 proviral load[59]. More recently, the same group have targeted interleukin (IL)-15, which is also upregulated by HTLV-1 Tax and contributes to immune activation in HAM/TSP, with the anti-CD122 (IL-15 receptor-β) antibody, Hu MiK β1 (see NCT00076843, clinicaltrials.gov), although preliminary data suggest higher doses than initially infused will be required to saturate the receptor[60]. Based on the pathogenesis studies implicating TNF-α, we are currently investigating the specific blockade of TNF-α with infliximab (NCT00823641, clinicaltrials.gov). However, due to a lack of an exact understanding of HAM/TSP pathogenesis and the aforementioned potential risk of ATLL development with immunosuppressive therapy, such interventions require intensive and long-term monitoring and, without a stronger and more persistent clinical response, might not be a fundable, lifelong, monotherapy option at the moment.

In summary, diverse therapies have been used in HAM/TSP, but only 86 patients have taken therapy within randomized controlled trials. Two of these studies, enrolling a total of 40 patients, have found the enticing approach of reducing the HTLV-1 viral burden by inhibiting HTLV-1 reverse transcriptase to be disappointing. With the exception of cyclosporine in early progressive disease and transient benefit with IFN-α in chronic disease, no therapy has been proven or tested long enough to alter the course of HAM/TSP.

The rationale for a trial of sodium valproate with antiretroviral therapy

Most therapies aim to reduce the HTLV-1 viral load in patients with HAM/TSP. Persistent proviral integration of resting CD4+ T lymphocytes prevents the eradication of HIV-1 and HTLV-1 infection by the host immune surveillance. There is evidence that the presence of HAM/TSP is associated independently with a high rate of HTLV-1 Tax expression ($p = 0.03$), whilst HTLV-1 viral load correlates with high Tax expression ($p = 0.005$) and low cytotoxic CD8+ T-cell efficiency ($p = 0.003$)[30]. High HTLV-1 proviral load has been associated with progression of HAM/TSP[61] and HTLV-1 viral load in CSF also discriminates patients with HAM/TSP from asymptomatic carriers[62]. There are also, as described above, limited data associating reductions in HTLV proviral load with clinical improvement[58,59]. However, the great majority of HTLV-1-infected CD4+ T lymphocytes do not at any one time express any viral protein in the peripheral blood[30,63]. It is likely that an inhibitory mechanism restricts viral gene expression while infected cells divide and proliferate, maintaining the proviral load. Also, HTLV-1 viral infection correlates with inhibition of apoptotic processes, which helps to preserve the reservoir of latent HTLV-1-infected cells[64,65].

A recent approach to decreasing the HTLV-1 viral load has been to increase viral expression in order to make infected cells more visible to CTL, leading to a targeted eradication of infected CD4 T lymphocytes. Sodium valproate has been licensed for the treatment of epilepsy, mania, neuropathic pain[66], and mood disorders[67] for decades and is known to be safe, with low toxicity when used in adults. It has been shown to be neuro-protective in rats with spinal cord injury[68] or experimental neuritis[69]. Most importantly, sodium valproate acts as a histone deacetylase inhibitor (HDI), increasing retroviral (HTLV-1/BLV/STLV) expression in humans, sheep, and baboons and thereby increases cellular and viral gene transcription[70], making infected T-cells more accessible to CD8+ cytotoxic T-cells and, for reasons still unknown, reinstates the apoptotic ability of the infected cells[71]. Interestingly, sodium valproate also has microtubular inhibition and proapoptotic activity, and is considered as a chemotherapeutic adjuvant in humans.

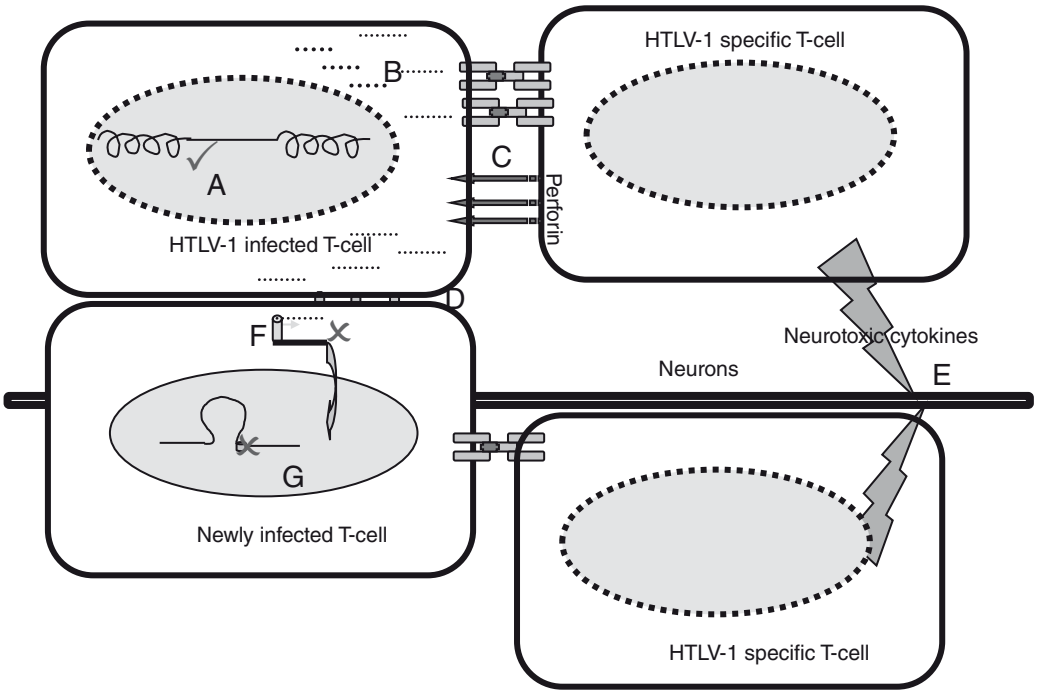
The safety of sodium valproate (valproic acid) as an HDI has been assessed in a study of HIV-associated cognitive impairment, a condition where treatment remains a challenge despite HAART. Valproic acid, which has been shown to protect mice from neuronal loss in a model of HIV encephalitis[72], was used as adjunctive therapy in a 10-week, double-blind, placebo-controlled study: 22 HIV-positive patients with/without HAART and with/without undetectable serum HIV-1 RNA were given valproic acid 250 mg twice daily. The treatment was safe and well tolerated, with trends towards improved neuropsychological performance and brain metabolism in HIV patients with cognitive impairment. Although HIV was not eradicated, sodium valproate treatment did not lead to a persistent rise in plasma HIV-1 RNA concentration or HIV-1 proviral load, a decrease in CD4+ T lymphocyte counts, or clinical deterioration[73].

Following this study, high-dose valproic acid was found to be safe in a retrospective case-control study, even in patients with detectable HIV viral loads. No increase in HIV viral load in plasma or CSF or disease progression was detected when 15 HIV-positive individuals on antiretroviral therapy initiated valproic acid treatment for seizures, migraines, or mood disorder during follow-up for at least three months .The average daily dose was more than 1000 mg[74].

Sodium valproate has been shown to induce HIV expression *ex vivo* from the resting CD4+ T-cells of aviremic patients on HAART, but without upregulation of cell-surface markers of activation or increased susceptibility to *de novo* HIV infection[75]. In an *in vivo* proof-of-concept study in HIV patients on intensified HAART, an increased rate of decline in the frequency of infected resting CD4+ T-cells after the addition of valproic acid (500-750 mg twice daily) was seen in 3/4 patients at 18 weeks. None of the patients developed viremia or showed disease progression[70].

In sheep, treatment with sodium valproate 10 g intramuscular thrice weekly (equivalent to 80 mg/kg/day) prior to inoculation with bovine leukemic virus (BLV), a member of the HTLV-BLV viral family that induces B-cell leukemia/lymphoma in sheep, did not prevent disease, but after an initial rise at day 15, the B lymphocyte counts declined and continued to fall posttreatment for up to 265 days. Treatment of sheep that developed BLV-induced lymphoma with sodium valproate alone led to persistent tumor regression at 15 months[76].

An *in vitro* study showed that HDI doubled HTLV-1 Tax expression in naturally infected lymphocytes, while the rate of CD8+ cell-mediated lysis of Tax-expressing cells halved[77], raising the concern that *in vivo* viral load may rise and disease may progress. However, an open, nonrandomized study of 19 patients with chronic HAM/TSP treated with sodium valproate (20 mg/kg/day) for two years showed an initial rise of viral load at two



1. Sodium valproate inhibits histone deacetylation leading to transcriptionally active site. **2.** Increased production of HTLV-1 messenger RNA leads to. **3.** Unmasking of infected cell and increased cell lysis. **4.** Increased production of HTLV-1 messenger and genomic RNA leads to transient increase in virion production, new viral infection and increased HTLV-1 proviral load. **5.** Increased HTLV-1 viral replication due to HDI may increase inflammation. **6.** Zidovudine inhibits HTLV-1 reverse transcriptase preventing productive infection of target cell. **7.** Alternatively, raltegravir inhibits HTLV-1 integrase blocking provirus formation.

Figure 2. *Rationale for dual therapy and mechanism of potentially harmful and beneficial effects of sodium valproate alone. HTLV-1: human T-cell lymphotropic virus type 1; HDI: histone deacetylase inhibitor.*

weeks, followed by an average 24-fold reduction in viral load ($p = 0.001$) before a gradual return to baseline levels. There was no change in absolute $CD4^+$ and $CD8^+$ T-cell counts, but a significant reduction of Tax expression by $CD4^+$ T-cells was observed *ex vivo*[78]. No significant clinical improvement was observed, but this could be because the duration of disease in these patients prior to therapy was 7-19 years[79].

Most recently, an animal study has demonstrated significant simian T-lymphotropic virus (STLV) viral load reduction following treatment with the combination of zidovudine plus sodium valproate in human-equivalent doses. Twenty baboons *(Papio papio)* naturally infected with STLV-1, (STLV-1 is genetically identical to HTLV-1) with STLV viral loads similar to those seen in HTLV-1 asymptomatic carriers, were treated. Neither drug alone reduced the viral load, and an initial rise in viral load with sodium valproate alone was documented. The combination of sodium valproate with the proapoptotic, NRTI, zidovudine both prevented this initial increase in viral load and reduced the STLV-1 viral load compared with baseline up to eight weeks[80]. The observation, from this baboon model in which zidovudine was added to prevent new viral infection, that both zidovudine and HDI are required to reduce viral load raises the question as to whether zidovudine acts as an NRTI or whether, as in the treatment of ATLL, another property of zidovudine is important. Should the proposed human study confirm the efficacy of zidovudine with sodium valproate to reduce HTLV DNA viral load, the relevance of inhibition of reverse transcriptase can be tested by replacing zidovudine with raltegravir which inhibits HTLV-1 integrase[81]. Figure 2 illustrates the sites of activity of the proposed therapy.

Conclusions

Transient benefit may be obtained in some patients with HAM/TSP treated with high-dose methyl prednisolone. The best experience with IFN-α is from Japan where this treatment is commonly prescribed and continued long term in some patients. The benefits of immunosuppressive therapy have only been observed in small observational studies and may be most apparent in patients with early disease. Much larger studies are needed to confirm these findings and to gauge the risk/benefit balance. Whilst antiretroviral therapy alone does not reduce HTLV-1 viral load and there are conflicting reports relating to the effect of sodium valproate alone on viral load, data from baboons infected with STLV-1 lend strong support to the conducting of a randomized controlled study of the combination of antiretroviral therapy with sodium valproate in patients with HAM to confirm the reduction in viral load and to determine whether this is associated with clinical benefit. Given the chronicity of this condition, long-term (48-96 week) studies will be required, to confirm benefit and detect toxicity, whilst careful characterization of patients will be essential to determine whether all patients will benefit or whether there is a therapeutic window of opportunity in early disease.

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