HTLV European Research Network 2023: the silent pandemic of HTLV-1 infection

The 2023 encounter of the HTLV European Research Network (HERN 2023) was held at the College of Physicians of Madrid on September 15 and 16. Clinicians and researchers from all over the world participated in this medical meeting. Abstracts presented at the conference are available online in a supplement of AIDS Reviews. Antoine Gessain, from the Pasteur Institute in Paris, addressed the origin of this retrovirus in humans from natural infection in African primates. Thus, it is a zoonosis-like infections caused by HIV (AIDS), monkeypox, or Ebola. There are an estimated 10 million people infected with HTLV-1 worldwide, half of them in equatorial Africa *(Gessain et al. Front Immunol 2023; 14: 1043600)*. Gabon and the Democratic Republic of Congo are the countries with the highest infection rate. Women in these regions exhibit increasing prevalence rates with age, reaching up to 10-25% in elderly women.

Most people infected with HTLV-1 are asymptomatic for many years or their entire lives. Only 10% develop clinical manifestations, typically subacute myelopathy or T-cell leukemia. However, both conditions are serious and have no treatment. Indeed, most patients with neurological disease end up in a wheelchair and very few patients with leukemia/lymphoma live longer than a year.

Many subjects infected with HTLV-1 are diagnosed late, after developing clinical manifestations. Diagnoses are late because HTLV-1 screening is rarely performed in populations at high risk of infection, such as migrants from endemic areas *(Mendoza et al. Int J Infect Dis 2022; 122: 970-5).* Many physicians and the general population have little knowledge about HTLV-1, in contrast with HIV, the AIDS virus, for which information is widely available.

HTLV-1 associated myelopathy (HAM)

Several series of patients with HAM were presented at the meeting. In the Spanish registry, there are 58 cases of HAM. Of note, 60% of them have Latin American origin and 76% are women. The prognosis is poor: up to 75% ended up in a wheelchair and/or with urinary/fecal sphincter incontinence.

In another series of ten HAM patients diagnosed in Sweden, almost all had a poor clinical outcome, dying one as a result of associated complications. Interestingly, many of these HAM patients are originally from Iraq, because of a political migrant agreement that took place after the Gulf War in 1990. During the following years, a massive arrival of people from Iraq and Iran was seen in Sweden. Precisely in the north-east of Iran, the region of Mashhad is highly endemic for HTLV-1.

In a Brazilian cohort of 74 asymptomatic individuals infected with HTLV-1, nine developed HAM after 12 years of follow-up. Reduced serum interleukin (IL)-10 levels at baseline predicted the development of myelopathy. In contrast, high proviral load or older age did not predict the incidence of HAM. The predictive value of IL-10 as a biomarker of HAM needs to be further confirmed.

An English cohort examined mortality associated with HTLV-1 infection, comparing 112 patients with HAM and a control group of asymptomatic HTLV-1 carriers. Many of the patients were of Caribbean origin living in London. Mortality was 2.4 times higher in patients with HAM compared to the rest. The role of chronic inflammation and persistent immune activation as driver of premature death in HTLV carriers has been highlighted in previous studies *(Ramos y cols. Lancet Infect Dis 2020; 20: 407-8).*

HTLV-1 leukemia/lymphoma

There are four clinical forms of presentation of HTLV-1-associated leukemia/lymphoma (ATL, adult T-cell lymphoma). The acute and lymphomatous forms are aggressive and the prognosis is very poor. Several chemotherapy modalities have been used with poor results. The other two forms (chronic and "smoldering") are indolent and have a better prognosis, although blast transformation may occur in a subgroup of patients.

During the meeting was presented the Spanish series of 35 cases of ATL registered to date *(de Mendoza et al. J Clin Virol 2023; 167: 105578).* Survival was <1 year in almost all cases. More than half were women, mostly Latin American or sub-Saharan African. The median age at diagnosis was 47 years.

Juan Carlos Ramos, from the University of Miami, referred to the combination of interferon, AZT and belinostat. The latter is a methylation inhibitor, which increases the immune response against infected tumor cells. It is administered orally and has little toxicity. A clinical trial has begun in the United States to examine this treatment.

Ambroise Marçais, of the Necker Hospital in Paris, described the efficacy of allogeneic bone marrow transplantation in 23 patients with ATL after a course of chemotherapy with complete response *(de Masson*

et al. Lancet 2023; 401: 1941-50). In some patients, the monoclonal antibody mogamulizumab (anti-CCR4) was used after the first 2 months after transplantation *(Cook et al. Blood 2021; 137: 459-70).* At 2 years, 75% were free of oncological disease. In addition, several had eliminated the HTLV-1 provirus from their body and had developed a specific immune response. In other words, similar to the so-called "Berlin patient," originally infected with HIV and then cured after a bone marrow transplant *(Hutter et al. N Engl J Med 2009; 360: 692-8),* the patients with ATL described not only cured their leukemia but also eradicated HTLV-1 infection after bone marrow transplantation.

HTLV-1 transmission from pregnant women

About 15% of mothers carrying HTLV-1 can transmit the virus to their babies. Most occur through breastfeeding, although there are also cases of intrauterine infection and at the time of vaginal delivery. If breastfeeding is eliminated and cesarean section is performed, there is hardly any vertical transmission of HTLV-1 *(Vieira et al. Sci Rep 2021; 11: 15367).*

The meeting presented the results of a Spanish study that examined the presence of antibodies against HTLV-1 in more than 7000 pregnant women. Four positives were identified, all from Latin America. Three were primigravida under the age of 23. They were told to avoid breastfeeding and to date, no children have been infected. On the contrary, several cases of HTLV-1-infected children have already been reported in Spain after making late diagnosis in their mothers.

Considering the Latin American population residing in Spain and its high birth rate, it has been estimated that around 30 new HTLV-1 infections could occur each year by vertical transmission in Spain. This figure exceeds those of congenital syphilis, HIV, or hepatitis B, all diseases for which there is a recommendation for antenatal screening. Given that prenatal screening for Chagas disease is already performed in pregnant women in Latin America, it would be convenient to add HTLV screening to the same population. An international study has concluded that this measure could be cost-effective in many European countries and much more in endemic regions *(Rosadas et al. Lancet Glob Health 2023; 11: E781-E790).*

Sexual transmission of HTLV-1

Globally, sexual transmission, especially male-to-female, accounts for the majority of new HTLV-1 infections. In places with high endemicity, transmission of the virus to newborns of infected mothers is also an important source of contagion.

Data from sexually transmitted infection (STI) clinics were presented at the meeting. In Spain, a recent study identified five subjects infected with HTLV-1 testing nearly 2000 who attended STI clinics. Three were homosexual Latin American males. These results reinforce the convenience of including HTLV-1 screening within the list of STI tests, especially if subjects come from highly endemic regions.

Are antiretrovirals active against HTLV-1?

Since HTLV-1 is a retrovirus like HIV, the AIDS agent, and many of the proteins are similar in both viruses, including polymerase, integrase, and protease, it has been investigated whether antiretrovirals are effective in treating HTLV-1 infection. The results to date have been negative.

Once HTLV-1 infection is established in a new subject, the persistence of infection occurs without viral replication. There is expansion by viral spread from cell to cell through synapses; and proliferation of cells infected by division with the integrated provirus. This explains why there is no plasma viremia, that is, extracellular viral particles in the blood. Thus, viral replication inhibitors do not block HTLV-1 replication in vivo. However, they do so in experimental *in vitro* models, with inhibitory concentrations similar to those observed against HIV. The integrase inhibitors bictegravir, cabotegravir, and dolutegravir are the most potent inhibitors of HTLV-1 replication.

There has been speculation about the activity of these antiretrovirals to prevent HTLV-1 infection in subjects with risk behaviors taking pre-exposure prophylaxis against HIV. The design and conduct of a study of this nature are complicated. So far, *in vivo* efficacy against HTLV-1 has not been recognized with the use of antiretrovirals.

HTLV-1 elite controllers

In HIV infection (AIDS), a subgroup of patients with persistently undetectable or very low plasma viral load is well documented. These individuals show little immune damage and their clinical prognosis is good. Many experts consider it unnecessary to prescribe antiretroviral medication. During the HERN 2023 workshop, an English team described a group of people with western blot HTLV-1 seroreactivity who, persistently, showed undetectable proviral load. The longitu-

dinal follow-up allowed to recognize occasionally HTLV-1 DNA positive values, although very low, in some of them. In others, the examination of multiple viral genome regions or the use of more sensitive molecular techniques unveiled the presence of the viral provirus. Most of these patients showed elevated HTLV-1 specific immune responses. However, in a few subjects, no molecular evidence of viral infection was found despite all efforts.

The significance of HTLV-1 positive serologies in the absence of genomic detection is uncertain. Hypothetically, it could be: (1) slow progressors, which control the infection to a large extent; (2) individuals who may have been exposed to the virus and have completely cleared the infection; and (3) serological false positives. In the case of being controllers of a true viral infection, one could speculate that it is a strong immune response in these individuals what explains it. Alternatively, they could be infected by a low-pathogenic variant. However, this option is highly unlikely, as genetic variability in HTLV-1 is very low.

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