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Hot News

HTLV-1 Infection is Rising Up in Spain Whereas HTLV-2 is Vanishing

Infection with human retroviruses is responsible for global epidemics and significant morbidity and mortality worldwide. The current global estimates of infected people are 38 million for HIV-1, 1-2 million for HIV-2, 10 million for human T-cell leukemia virus type 1 (HTLV-1), and 3 million for HTLV-2. Although HTLV-1 and HTLV-2 do not cause AIDS, infection with HTLV-1 has been associated with the development of subacute myelopathy and T-cell lymphomas in nearly 10% of carriers lifelong (Pasquier et al., Front Microbiol 2018; 9: 278). In contrast, HTLV-2 infection is generally asymptomatic although occasionally, it may cause neurological syndromes resembling HTLV-1-associated myelopathy (HAM)/tropical spastic paraparesis (TSP) (Roucoux et al., AIDS Rev. 2004; 6: 144-54).

HTLV-1 was the first identified human retrovirus. Interestingly, it is present globally with hot spots at distinct highly endemic regions in Japan, the Caribbean, Latin America, Iran, Romania, Sub-Saharan Africa, and Australia. The virus is mostly transmitted through sexual contact, being nowadays less frequently acquired following breastfeeding or transfusions.

HTLV-2 was first identified in 1982. It is noteworthy that high prevalence was first seen among intravenous drug users in North America and Western Europe, although endemic infections are also recognized in some Amerindian and African pygmy tribes. Herein, we analyze yearly rates of HTLV-1 and HTLV-2 new diagnoses in Spain during the past 30 years.

A nationwide HTLV register exists in Spain since 1989. A total of 369 persons with HTLV-1 and 803 with HTLV-2 infection had been reported up to the end of 2018. For HTLV-1, the median age at diagnosis was 41 years old, with predominance of women (62%). More than three-quarters were foreigners, mostly from Latin America (65%) and less frequently from Africa (11%). In contrast, HTLV-2 diagnoses were made at younger age (median, 35 years old), mostly in men (76%) and at least 73% were native Spaniards. HIV coinfection was recognized in up to 83% of HTLV-2 carriers, whereas it was only found in 3% of HTLV-1-infected persons.

Clinical manifestations associated with HTLV-1 infection were recognized in 22% of carriers, being HAM/TSP diagnosed in 47 patients and adult T-cell leukemia/lymphoma (ATL) in 28. Six patients had *Strongyloides stercoralis* infestation. In contrast, only three HTLV-2 carriers developed clinical manifestations potentially linked to the virus: a condition resembling HAM/TSP, a unique myopathy, and *S. stercoralis* infestation.

Yearly diagnoses of HTLV-1 and HTLV-2 infections are graphically summarized in figure 1. It is noteworthy that HTLV-2 diagnoses predominated until 2002, rapidly declining thereafter. In contrast, annual HTLV-1 diagnoses were in the range of 5-10 until 2008, and since then, figures above 20/year begun to be reported. Most new diagnoses of HTLV-1 infection among native Spaniards acknowledged sexual partners coming from HTLV-1 highly endemic regions, mostly in Latin America. Furthermore, nearly half of them had a prior history of sexually transmitted infections, for example, gonorrhea or syphilis.

The first cases of HTLV-1 infection in Spain were reported in the late 80s (Soriano et al., Lancet. 1990; 336: 627-8). They were found in persons with symptomatic infection, either TSP/HAM or ATL, or among immigrants from HTLV-1 endemic regions tested as part of exploratory epidemiological surveys. A total of 369 cases had been reported nationwide until December 2018. Although heterosexual contact is the most likely route of HTLV-1 acquisition in the Spanish register, at least 27 subjects (7.7%) had been infected with HTLV-1 perinatally, 10 after blood transfusion, and 5 following the transplantation of solid organs from unaware infected donors. Interestingly, four of the transplant recipients developed HAM shortly after surgery (Toro et al., Transplantation; 2003; 75: 102-4; Roc et al., Ther Adv Infect Dis. 2019; 6:2049936119868028). Although most HTLV-1 cases at the Spanish register are asymptomatic, 47 (13%) had developed HAM/TSP and 28 (7.4%) ATL.

Up to 265 cases of HTLV-1 infection (72% of total) had been identified during the past decade, mostly reflecting the steadily introduction of HTLV antibody screening in a growing number of blood banks in Spain. Indeed, 129 HTLV-1 diagnoses during this period were made in blood donors, of whom 108 were

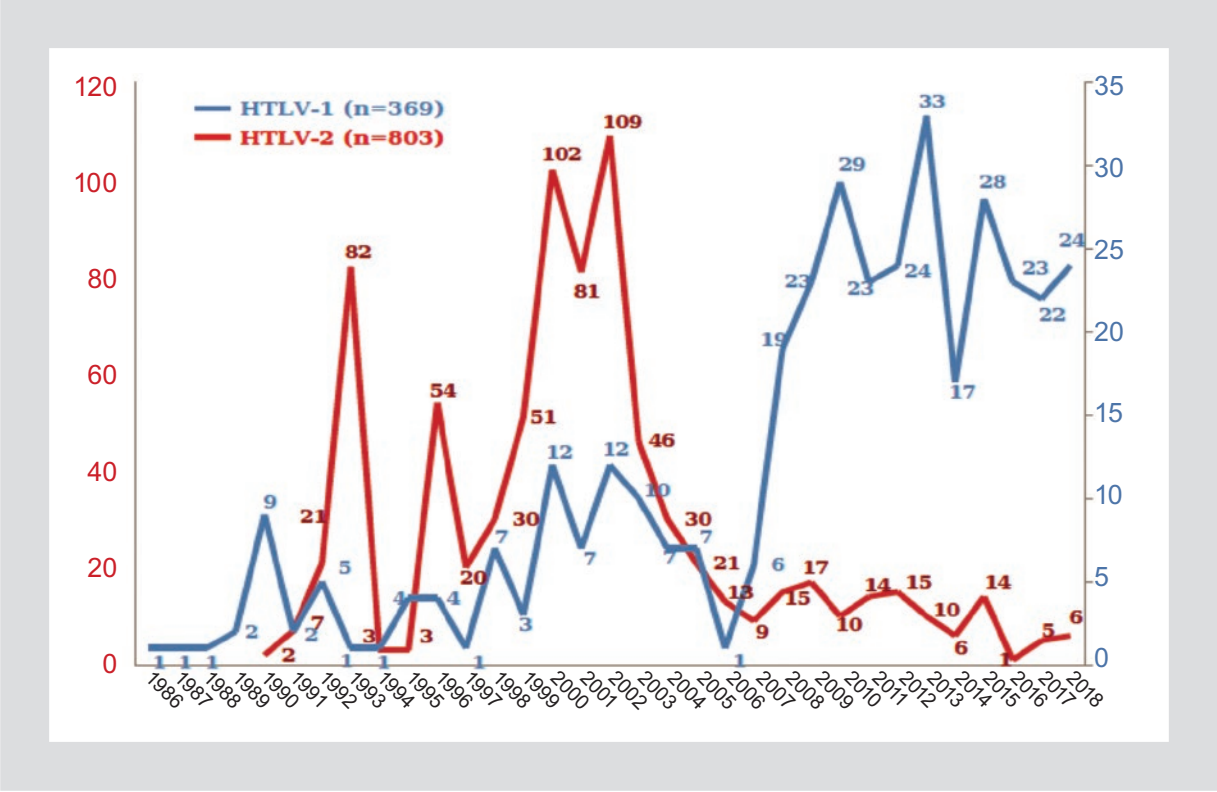

Figure 1. *Yearly incidence of new HTLV diagnoses in Spain.*

individuals coming from Latin America. Most native Spaniards newly diagnosed with HTLV-1 infection acknowledged sexual partners coming from HTLV-1 highly endemic regions, mostly in Latin America.

The first cases of HTLV-2 infection in Spain were found in the early 90s, following testing for anti-HTLV of distinct risk group populations. Relatively high rates of anti-HTLV-2 were found among injection drug users, many of them coinfected with HIV and hepatitis C. Although the cumulative number of HTLV-2 cases achieved 803 up to December 2018, new diagnoses had fell since 2002, accompanying nationwide drastic declines in injection drug use (Pérez-Cachafeiro et al., Clin Infect Dis. 2009; 48: 1467-70). Indeed, only six cases of HTLV-2 infection were diagnosed in Spain during the year 2018. All but one were native Spaniards and positive for HIV-1. Only anecdotal reports of conditions potentially caused by HTLV-2 had been found in our population, including a case of myopathy (Soriano et al., Clin Infect Dis 1994; 19: 350-1), being asymptomatic carriers the rest or mostly developing symptoms associated with HIV or hepatitis C virus that were frequent coinfections.

Given the greater pathogenicity of HTLV-1 compared to HTLV-2 and the fact that transmission can effectively be halted avoiding breastfeeding of newborns from infected mothers and excluding contaminated blood transfusions, HTLV antibody screening should be recommended as part of antenatal testing and in all organ and blood donors in Spain. Furthermore, HTLV testing should be considered as part of the screening for sexually transmitted infections (Caswell et al., Sex Transm Infect. 2019; 95: 24).

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Why Not an Opioid Epidemic in Europe Like in the USA?

The CDC reported 70,237 drug overdose deaths in the United States in 2017 (Scholl et al., MMWR 2018; 67: 1419-27). Sadly, this yearly rate has been increasing significantly during the past two decades. Opioids, mostly synthetic drugs other than methadone, and particularly fentanyl, are currently the major responsible of drug overdose deaths (Fig. 1). The US states with the highest fatality rates due to drug overdose are West Virginia, Ohio, Pennsylvania, the District of Columbia, and Kentucky. Being preferently

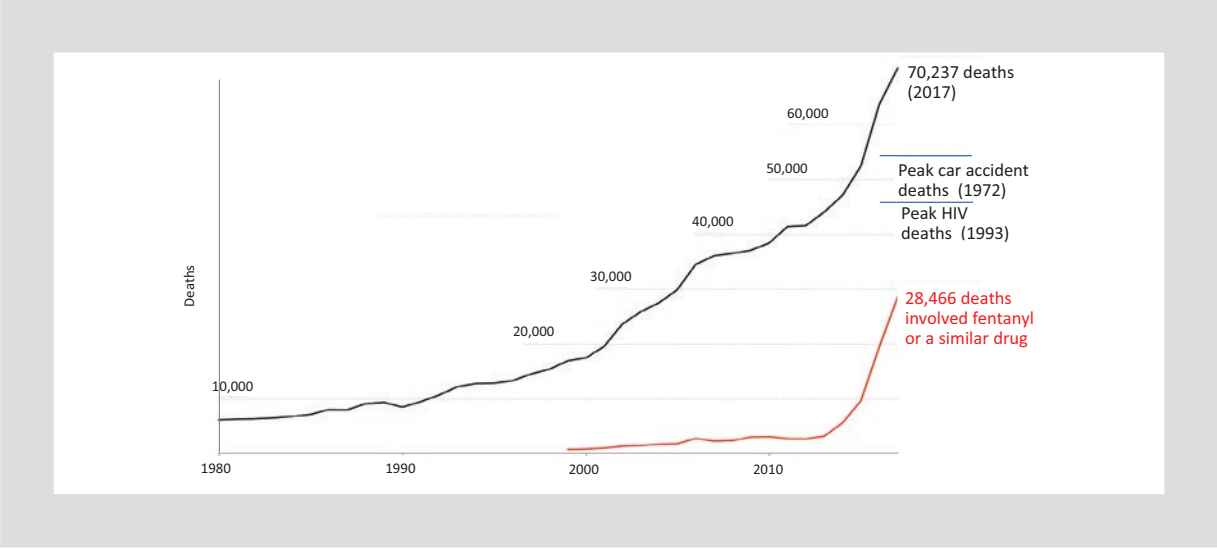

Figure 1. *Trends in the US drug overdose deaths.*

rural in the earliest times, most drug overdose fatalities nowadays occur in urban populations, affecting particularly young people, unemployed, and persons belonging to broken homes or dysfunctional families.

Drug overdose deaths, unintentionally or as suicide, have become the first cause of mortality in the US adults younger than 55 years old (Hedergaard et al., NVSR 2018; 67: 1-14). In a country of roughly 325 million people, the current figures for drug overdose deaths exceed those produced by traffic accidents or AIDS at its highest peak in 1995 (Fig. 1).

Authorities acknowledge that the increasing use and abuse of analgesics are at the root of the current US opioid crisis. As the population ages, prescription of chronic pain killers has increased, shifting from aspirin, paracetamol, and nonsteroidal anti-inflammatory drugs (ibuprofen, etc.) to opioids. In the latest group, prescriptions have steadily shifted from low-potency agents (codeine, tramadol) to high-potency meds, including morphine and especially synthetic opioids, such as oxycodone and fentanyl among others. The way the US prescription pharmacy market works has permitted abuse in an unprecedented manner. In other words, a large proportion of opioid analgesics medically prescribed has ended within the hands of consumers for illicit recreational use (Dowell et al., JAMA 2017).

Not surprisingly, the transfer to injection drug use in opioid consumers has been associated with a recrudescence in HIV and hepatitis C, often as local outbreaks (Lerner and Fauci. JAMA 2019). Furthermore, there is a resurgence of tricuspid endocarditis and candidemia syndromes (Barter et al., MMWR 2019; 68: 285-8), conditions almost forgotten since the 80s when intravenous heroin and cocaine where the illicit drugs mostly consumed by drug users.

The situation at the European Union so far is quite different. The control over opioid prescriptions has been greater in Europe than in the US, which has made difficult access to non-direct beneficiaries. However, other drugs with less regulatory control are increasingly been used as recreational agents, especially among young adults. Indeed, the current epidemic of sexually transmitted infections (Soriano and Del Romero. AIDS Rev 2018; 20: 187-204) is largely favored by chemsex, being psychostimulants such as cocaine, methamphetamine, or ecstasy the most common agents.

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