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Hot News

New insights from IeDEA and COHERE on global trends in CD4 counts at ART initiation

In 2000, the inextricable link between HIV/AIDS, poverty, and the development of whole nations was recognized in the Millennium Development Goals. Since then, the international community has invested considerable efforts and resources into combating the global HIV/AIDS epidemic, resulting in the reduction of new HIV infections by an estimated 40% by 2013. Underwriting this enormous progress was the scale-up of HIV services and the global roll-out of combination antiretroviral therapy (ART). To capitalize on the gains made in the previous years, the Joint United Nations Programme on HIV/AIDS unveiled its 90-90-90 strategic plan in 2014. The aim of this ambitious global agenda was for 90% of all HIV-infected people to know their HIV status, 90% of those infected to be on effective ART, and 90% of those on treatment to achieve virologic suppression by the year 2020. With the year 2020 fast approaching, how far have we come toward realistically achieving the targets?

In the most comprehensive study to date on global trends in CD4 cell count at ART initiation, the International Epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) recently pooled data on nearly 1 million HIV-infected individuals from North America, Latin America and the Caribbean, Asia-Pacific, Sub-Saharan Africa, and Europe who were initiated on ART between 2002 and 2015 (*Andereg et al., 2018*). A total of 46 countries were included, which were further categorized by income into 16 low-income (LICs), 11 lower-middle-income (LMICs), 9 upper-middle-income (UMICs), and 19 high-income (HICs) countries. The analysis showed that there were substantial increases in the median CD4 cell count at ART initiation across all country categories from 2002 to 2015; i.e. 78-287/μL in LICs, 99-234/μL in LMICs, 71-311/μL in UMICs, and 161-327/μL in HICs.

The median CD4 cell count at ART initiation remained the highest in the HICs, rising to 435/μL in North America in 2014. However, the increases were most pronounced in the LICs (all of them in Sub-Saharan Africa except Haiti) and UMICs. Interestingly, the improvements in CD4 counts at ART initiation seemed to coincide with the timing of the adoption of the 2009 WHO treatment guidelines, which recommended early treatment, raising the CD4 threshold from ≤200/ to ≤ -350/μL. Thus, in the HICs where national treatment guidelines had already adopted higher CD4 cutoffs at ART initiation, the improvements occur before 2008; whereas in Sub-Saharan African and other resource-limited countries, progress is observed later on after 2010. It is expected that the trend toward higher CD4 cell count will continue, following START trial and widespread adoption of the 2016 WHO guidelines that recommend universal ART initiation regardless of CD4 cell count.

Perhaps the most sobering observation from this landmark study was that despite the increases in CD4 cell count at ART initiation, they have generally remained below 350/μL across all country income categories, including in the HICs. Taking all the findings together, a string of common themes emerges that has already been described before. Late-stage HIV diagnosis remains a widespread global challenge, which leads to poor clinical outcomes, early mortality, and increased health-care costs in an already overburdened health-care system. Moreover as the IeDEA and COHERE study now reveals, there is also a substantial delay in ART initiation after HIV diagnosis, further compounding the problem of late-stage HIV diagnosis.

Clearly, tremendous strides have been made in the fight against the global HIV/AIDS epidemic in the past two decades, with many HICs close to achieving the targets. However, there are still many obstacles to overcome, especially in the LICs and LMICs where progress has been slow and unequal across the individual components of the 90-90-90 strategic plan. These countries continue to disproportionately bear the brunt of the epidemic, in large measure due to inadequate resources in the face of a multitude of other competing developmental priorities. As HIV infection has become an increasingly

more treatable condition, the international community must renew and redouble efforts to assist the hardest-hit countries in addressing the disparities that currently exist in HIV care to achieve more equitable outcomes.

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HTLV-1 Infection Still A Neglected Disease

Infection with Human T-lymphotropic virus (HTLV)-1, the first discovered human retrovirus, affects 10-15 million people worldwide. Hot spots of endemic infection are recognized in Japan, Iran, the Caribbean basin, western and northern Latin America, West and South Africa, Central Australia, Romania, and Papua-New Guinea. To update information on the epidemiology and therapeutic management of HTLV-1 infection, nearly 100 international researchers met in Beirut, Lebanon, at the end of June 2018. Ali Bazarbachi was the chair.

Lifelong 10% of chronic carriers may develop severe and life-threatening illnesses such as adult T-cell leukemia (ATL) and a subacute myelopathy, known as HTLV-associated myelopathy or tropical spastic paraparesis (HAM/TSP). Although the incidence of clinical manifestations increases with age, the proviral load is a good predictor of prompt disease development. Carriers with the virus infecting more than 4% of their peripheral blood mononuclear cells exhibit the greater risk. They should be checked periodically. Recently, a team from the NIH reported that inhibition of acting nanotubes using cytarabine could interfere with intercellular HTLV-1 transmission (*Omsland et al., Sci Rep 2018;8:11118*), opening a new path for halting intrahost viral expansion. In patients with overt HTLV-1 diseases, mogamulizumab, a monoclonal anti-CCR4 antibody, has shown to be effective in some ATL and HAM/TSP patients (*Sato et al., N Engl J Med. 2018;378:529-38*).

Although HTLV-1 is a blood-borne pathogen, most new infections occur horizontally through sexual contact and vertically through breastfeeding. In newborns, the rate of infection is <5%, 20%, or 40% for breastfeeding <6, 6-12, and >12 months, respectively. In Japan, universal prenatal HTLV testing since 2011 has allowed to halt most infections of newborns from infected mothers. Dr. Watanabe, from Tokyo, highlighted that most current incident HTLV-1 infections in Japan (roughly 4200 per year) are sexually acquired, contributing to a total estimated number of 800,000 HTLV-1 carriers, which represents 0.8% of the Japanese population. Every year, around 100 cases of HAM/TSP and 1000 cases of ATL are diagnosed in Japan.

Eduardo Gotuzzo, from Lima, Peru, reported his experience in Latin America, where infestation with *Strongyloides stercoralis* is frequently recognized in otherwise asymptomatic HTLV-1 carriers. In contrast with Japan, HAM/TSP is more frequent than ATL among infected persons in Latin America. Moreover, a wide spectrum of inflammatory conditions, including uveitis, arthritis, alveolitis, dermatitis, and thyroiditis, may appear in infected persons. Gotuzzo took the opportunity to announce that the 19 h International Conference on Human Retrovirology will be held in Lima on April 24-26, 2019 (www.htlvperu2019.com) and that he will chair this important HTLV event.

The rising diagnoses of HTLV-1 in non-endemic countries must increase clinical suspicion. This is the case for Spain, with a large immigration flow from Latin America (*de Mendoza et al., AIDS. 2017;31:1653-63*), and the United Kingdom or France, with an important immigrant population from both the Caribbean and Sub-Saharan Africa (*Taylor et al., J Acquir Immune Defic Syndr. 2005;38:104-9; Gessain et al., Front Microbiol. 2012;3:388*).

The prospects for new therapeutic strategies for controlling the HTLV-1 epidemic are limited. In the absence of a prophylactic vaccine, some antiretrovirals developed against HIV-1 have been tested against HTLV-1, generally with poor results. Despite limited efficacy, zidovudine plus interferon-alpha is a first-line regimen for treating ATL. The recent advent of dolutegravir, a potent integrase inhibitor, has renewed the interest for antivirals against HTLV-1.

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