Hot News

News on Antiretroviral Therapy

The 2014 International Antiviral Society (IAS) Conference was held in Melbourne, Australia in July. This major HIV/AIDS scientific event was accompanied by the publication of several pivotal studies in the field in different medical journals. We discuss below some of the most important implications derived from these new releases.

As every two years, the IAS-USA panel released new guidelines for antiretroviral treatment of HIV-infected adults (Huldrych, et al. JAMA. 2014;312:410-25). Key messages are as follows:

- Antiretroviral therapy must be offered to every HIV-positive individual;
- Recommended regimens should include two NRTI plus a third agent (INI, NNRTI or PI/r);
- Triple nuc therapy or PI/r monotherapy is not recommended, but NRTI-sparing regimens may be considered;
- Monitoring every ≤ 6 months should be recommended for patients on stable antiretroviral therapy; and
- No rules for HIV-2 treatment.

Table 1 records the recommended antiretroviral agents in the new IAS guidelines.

Two switch studies funded by Gilead examined the performance of Stribild® replacement in HIV-infected individuals with undetectable viremia for longer than six months under either a NNRTI- or a PI/r-based regimen. In the STRATEGY studies, patients with prior virological failure or drug resistance were excluded. The main results of these phase III, non-inferiority trials are recorded in table 2. Compared to staying on the same regimen, switching to Stribild® was non-inferior to NNRTI (Pozniak, et al. Lancet Infect Dis. In press), or even superior to PI/r (Arribas, et al. Lancet Infect Dis. In press). In the NNRTI switch study, 80% were on efavirenz and 16% on nevirapine before replacement by Stribild®. In the PI switch study, 42% of patients were on atazanavir, 39% on darunavir, and 19% on lopinavir before replacement by Stribild®. It was unclear why a higher proportion of patients in the control group discontinued therapy due to non-virological reasons.

The GARDEL study, funded by AbbVie, the company that markets lopinavir/r (Kaletra®), was conducted in 19 clinics in South America and Spain (Cahn, et al. Lancet Infect Dis. 2014;14:572-80). Up to 44% of the 426 antiretroviral-naive patients recruited in the study had baseline viral load > 100,000 copies/ml. Patients were randomized to receive Kaletra® plus either lamivudine or a fixed dose nuc co-formulation. Of note, this was Combivir® in 54%. Table 3 records the main results. Although dual combination therapy did not underperform standard triple regimens at 48 weeks, hyperlipidemia was more common with dual therapy. Cost savings could be greater with dual therapy using generic lamivudine, but lopinavir is no longer a preferred protease inhibitor.

The D:A:D consortium has updated the figures for mortality in their large cohort of 49,731 HIV-infected persons followed from 1999 until 2011 in 211 clinics in the USA, Europe, and Australia (Smith, et al. Lancet. 2014;384:241-8). There has been a recent fall in AIDS-related deaths due to improved CD4 counts on antiretroviral therapy. Likewise, mortality due to liver disease or cardiovascular events have both recently declined as more attention and improved management of these conditions has been set up. In contrast, non-AIDS cancers have become the major cause of death (Fig. 1),

Table 1. New IAS antiretroviral treatment guidelines

NRTI backbone	INI	NNRTI	PI
Tenofovir/ emtricitabine (Truvada)	Dolutegravir	Efavirenz	Darunavir
Abacavir/ lamivudine (Kivexa)	Elvitegravir Raltegravir	Rilpivirine	Atazanavir

INI: integrase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Table 2. Main results in the STRATEGY studies

STRATEGY-NNRTI	Stribild (switch) n = 291	NNRTI + TVD n = 143	p
HIV RNA < 50 cop/ml at w48	271 (93%)	126 (88%)	0.066
Discontinuation due to AEs	6 (2%)	1 (1%)	
Virological failure	2	2	
Selection of drug resistance	0	0	
STRATEGY-PI	**Stribild (switch) n = 290**	**PI/r + TVD n = 139**	**p**
HIV RNA < 50 cop/ml at w48	272 (93.8%)	121 (87.1%)	0.025
Discontinuation due to AEs	6 (2%)	4 (3%)	
Virological failure	2	2	
Selection of drug resistance	0	0	

AE: adverse events; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI/r: ritonavir boosted protease inhibitor; TVD: Truvada.

Table 3. Main results in the GARDEL study

	LPV/r + 3TC BID n = 217	LPV/r + FDC n = 209	p
Completed planned length therapy	198	175	ns
HIV RNA < 50 cop/ml at w48	189 (88.5%)	169 (83.7%)	0.17
Response in VL > 100,000 cop/ml	87.2%	77.9%	ns
Discontinuation due to safety	1 (0.4%)	10 (4.9%)	0.01
Drug-related adverse events	65	88	0.007
Virological failure	10 (4.7%)	12 (5.9%)	ns
Selection of drug resistance	2	0	ns

3TC; lamivudine: BID: once daily; FDC: fixed dose combination; LPV/r: ritonavir boosted lopinavir; VL: viral load.

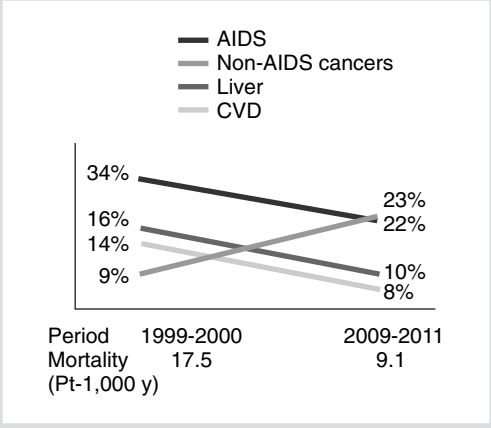

Figure 1. *Causes of death in HIV+ persons in the D:A:D study.*

the most common being lung cancer, anal cancer, neck and head cancers, and Hodgkin's lymphoma.

Pablo Labarga
Department of Internal Medicine
Clínica La Luz
Madrid, Spain

Controlling HIV Epidemics is Feasible but HIV Eradication Remains Elusive

When AIDS was first recognized in 1981 and HIV was discovered as its cause in 1983, we could never have imagined the rapid worldwide expansion of the pandemic. Neither could we have expected the great success of antiretroviral therapy. Nevertheless, in contrast with the hepatitis C virus (HCV), another RNA virus that affects large patient populations and for which new drugs promise a cure, HIV cannot be eradicated with only antiviral treatment.

However, the proof-of-concept for the possibility of HIV eradication comes from the widely publicized "Berlin" patient. To date this HIV-infected individual has remained without any evidence of the virus after more than seven years off antiretrovirals, following bone marrow transplantation of unique compatible homozygote CCR5 delta-32 donor stem cells (Hutter, et al. N Engl J Med. 2009;360:692-8).

Since then, HIV elimination has been claimed for another three patients, although in all this was transient as the virus rebounded after relatively long periods off antiretroviral therapy. However, the three patients –a child from Mississippi and two adults from Boston– experienced significant reductions in the amount of residual infectious virus and waning of HIV antibodies. The newborn from Mississippi initiated antiretroviral therapy within 30 hours of delivery from her HIV-positive mother and stayed on treatment for 18 months. She seemed to be cured, with undetectable plasma viremia and negative PCR for HIV proviral DNA on peripheral blood cells, even after discontinuing antiretroviral therapy (Persaud, et al. N Engl J Med. 2013;369:1828-35). However, eventually the baby experienced viral rebound after a remarkable 27 months off therapy. The two adults from Boston were infected with HIV and received stem-cell transplants for lymphoma (Henrich, et al. J Infect Dis. 2013;207:1694-702). The virus rebounded at 12 and 32 weeks, respectively, after discontinuing antiretroviral therapy.

In this path towards HIV elimination from infected persons, innovative strategies, including therapeutic vaccines or gene editing therapy, are being tested. In this regard, some success has recently been achieved in making cells resistant to HIV using gene therapy to eliminate the main receptor for HIV entry, CCR5, *ex vivo*. In a recent clinical trial of 12 patients with HIV infection on antiretroviral therapy, CCR5-negative gene-modified T lymphocytes were safely transferred and persisted in blood and tissue (Tebas, et al. N Engl J Med. 2014;370:901-10). Six of these individuals stopped antiretroviral therapy and virus rebounded in all six, although encouragingly the CCR5-negative gene-modified T-cells survived longer in the presence of active virus replication than non-modified CD4+ T-cells.

In summary, several different approaches are being tested to pursue HIV cure, including genetic, immune-based, and early antiretroviral treatment strategies. Ultimately, purging HIV from infected cells will probably require a combination of both activation of dormant infectious proviruses and blocking new infections by circulating virions, what is now referred to as a "kick and kill" strategy.

Carmen de Mendoza
Department of Internal Medicine
Puerta de Hierro Research Institute and University Hospital
Majadahonda, Spain