Perspective

Highlights of the 2014 International AIDS Conference: Update From Down Under

The 20th International AIDS Conference held in Melbourne, Australia, from July 20 through July 25, 2014, provided much new data on nucleoside analogue reverse transcriptase inhibitor–sparing antiretroviral therapy, potential consequences of switching suppressive antiretroviral regimen, antiretroviral treatment with integrase strand transfer inhibitors, effects of antiretroviral therapy on HIV-associated neurocognitive impairment, and hepatitis C virus (HCV) treatment in HIV/HCV-coinfected individuals. This article summarizes an IAS–USA continuing education webinar presented by Paul A. Volberding, MD, in August 2014, in which he focused on a few select highlights from the Conference.

Keywords: HIV, 20th International AIDS Conference, AIDS 2014, dual antiretroviral therapy, integrase inhibitors, cognitive impairment, hepatitis C virus, HCV, coinfection

The following represents the presenter's selection of highlights from the 20th International AIDS Conference, held in Melbourne, Australia, from July 20 through July 25, 2014.

Dual Antiretroviral Therapy and Nucleoside Analogue Reverse Transcriptase Inhibitor–Sparing Regimens

The MODERN (Maraviroc Once-daily With Darunavir Enhanced by Ritonavir in a New Regimen) study compared the nucleoside analogue reverse transcriptase inhibitor (nRTI)-sparing regimen of ritonavir-boosted (/r) darunavir plus once-daily maraviroc with tenofovir, emtricitabine, and darunavir/r among treatment-naive, HIV-infected patients.[1] Virologic response (plasma HIV RNA level reduced to < 50 copies/mL) occurred in 86.8% of patients taking triple therapy compared with 77.3% of patients taking dual therapy at 48 weeks (adjusted difference, -9.5%; 95% confidence interval, -14.8% to -4.2%). One analysis in the MODERN study showed no substantial difference in prediction of virologic response with genotype testing or use of a coreceptor tropism assay in either the dual- or triple-therapy groups. The triple-therapy regimen did not show noninferiority. As that was the aim of the study, the nRTI-sparing arm failed to achieve the study goals.

The GARDEL (Global Antiretroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r-Based Standard Therapy) trial of HIV-infected, treatment-naive patients showed no statistically significant difference in rates of virologic response (HIV RNA level reduced to < 40 copies/mL) at 48 weeks between lamivudine plus lopinavir/r or standard triple therapy, among all patients (88.3% vs 83.7%, respectively; $P = .171$) or among those with baseline HIV RNA levels greater than 100,000 copies/mL (87.2% vs 77.9%, respectively; $P = .145$).[2] This dual regimen offers the potential advantages of reducing cost (lamivudine is now available in generic form) and reducing the need to monitor for kidney disease.

The European AIDS Treatment Network (NEAT) 001 trial also showed that dual therapy with raltegravir plus darunavir/r was noninferior to triple therapy with tenofovir, emtricitabine, and darunavir/r.[3] Virologic failure rates at 96 weeks were 17.4% with dual therapy and 13.7% with triple therapy. Failure rates were 7% and 7%, respectively, among patients with baseline HIV RNA levels of less than 100,000 copies/mL and were 36% and 27%, respectively, among those with baseline HIV RNA levels of 100,000 copies/mL or greater ($P = .09$). However, virologic failure was statistically significantly more common with dual therapy among patients with baseline CD4+ cell counts less than 200/µL (39.0% vs 21.3%, respectively; $P = .02$); this finding, together with the higher failure rate of dual therapy among patients with higher baseline viral load, suggests that the dual regimen of raltegravir plus darunavir/r has somewhat weaker antiretroviral activity than the triple regimen of tenofovir, emtricitabine, and darunavir/r.

Hazards of Switching Antiretroviral Therapy

A study from the Canadian Observational Cohort indicated that switching from a suppressive antiretroviral regimen for any reason was associated with increased risk of virologic failure (adjusted odds ratio [aOR], 1.35; $P < .001$).[4] Increased risk of virologic failure after switching was observed among women (aOR, 0.35; $P < .001$, for men vs women) and injection drug users (aOR, 2.85; $P < .001$). No statistically significant associations between virologic failure and older age, baseline CD4+ cell count, province, or year of antiretroviral therapy initiation were observed.

Progress With Integrase Strand Transfer Inhibitors

The 48-week analysis of the SAILING (A Study of GSK1349572 Versus Raltegravir [RAL] With Investigator Selected Background Regimen in Antiretroviral-Experienced, Integrase Inhibitor-Naive Adults) study, which compared the integrase strand transfer inhibitors (InSTIs)

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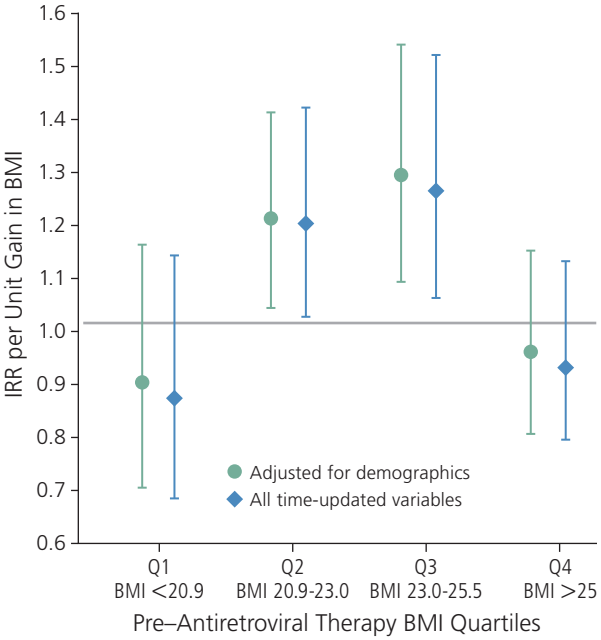

Figure 1. Effect of increase in body mass index (BMI) during antiretroviral therapy on cardiovascular disease risk in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study cohort ($P = .11$, for effect modification in adjusted models). IRR indicates incidence rate ratio. Adapted with permission from Achhra et al.[9]

dolutegravir and raltegravir combined with investigator-selected background therapy in HIV-infected, treatment-experienced, InSTI-naive patients was presented. Virologic failure occurred in 0 of 32 patients who received dolutegravir and 7 of 32 patients who received raltegravir, which suggested that dolutegravir may have greater potency. Virologic failure occurred in 0 of 19 patients who received dolutegravir with 2 nRTIs, 3 of 19 patients who received raltegravir with 2 nRTIs, 0 of 12 patients who received dolutegravir with 1 nRTI, and 4 of 13 patients who received raltegravir with 1 nRTI. In 1 patient taking dolutegravir without nRTIs and 3 patients with missing phenotype, virologic failure was not observed.[5] In studies of treatment-naive patients, resistance to dolutegravir or background drugs was not observed through 96 weeks in the SPRING-2 (A Trial Comparing GSK1349572 50mg Once Daily to Raltegravir 400mg Twice Daily) trial, 96 weeks in the SINGLE (A Trial Comparing GSK1349572 50mg Plus Abacavir/Lamivudine Once Daily to Efavirenz/Emtricitabine/Tenofovir) trial, and 48 weeks in the FLAMINGO (Dolutegravir Compared to Darunavir/Ritonavir, Each in Combination With Dual Nucleoside Reverse Transcriptase Inhibitors [NRTIs] in ART-naive Subjects) trial.

Antiretroviral Therapy and Neurocognitive Impairment

Neurocognitive impairment is common in HIV disease. The CHARTER (Central Nervous System [CNS] HIV Anti-Retroviral Therapy Effects Research) study has shown that improvement in neurocognitive function is possible for some patients taking antiretroviral therapy. Of more than 400 patients, a decline in neurocognitive function was observed in 22.7%, stable neurocognitive function in 60.8%, and improvement in neurocognitive function in 16.5%.[6] Sustained viremia was associated with neurocognitive decline, with neuropsychiatric test scores clearly worsening among patients with consistently detectable HIV RNA levels ($P = .005$) compared with patients who had sometimes detectable or never detectable HIV RNA levels. Stopping antiretroviral therapy was also associated with neurocognitive decline (relative risk [RR], 1.9). Other predictors of neurocognitive decline included lower serum albumin level (RR, 1.6 per 1 unit), lower hematocrit level (RR, 1.1 per 1 unit), severe neurocognitive comorbidity (RR, 2.1 vs minimal comorbidity), history of methamphetamine use (RR, 2.1), and depression (RR, 1.02 per 1 unit on the Beck Depression Inventory). Predictors of neurocognitive improvement included higher baseline intelligence quotient, lower total protein level in cerebrospinal fluid, lower aspartate aminotransferase level, and no history of depression.

Another analysis indicated that efavirenz use is not associated with increased risk of neurocognitive impairment. In 2 large study populations, aORs for neurocognitive impairment among patients who did or did not receive efavirenz were 1.02 ($P = .89$) and 0.98 ($P = .90$), respectively.[7] These findings may provide some reassurance about efavirenz use, given recent concerns that it may be associated with an elevated risk—albeit a low absolute risk—of suicidal ideation. Efavirenz is now recommended by the World Health Organization for use as a third drug in antiretroviral regimens for use in countries with developing economies[8]; thus, many millions of people are being treated with this drug.

HIV and Metabolism

A study in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study cohort showed that patients in the second quartile (20.9 kg/m^2-23.0 kg/m^2) and third quartile (23.0 kg/m^2-25.5 kg/m^2) of pretreatment body mass index (BMI) were at substantially

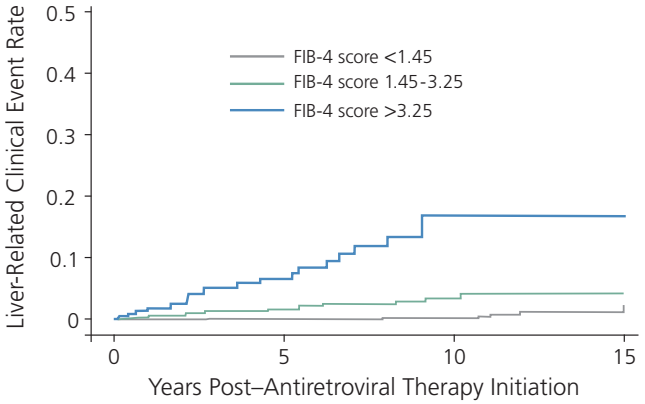

Figure 2. Association between baseline Fibrosis-4 (FIB-4) score and risk of liver-related events in HIV/hepatitis C virus (HCV)–coinfected patients in the ICONA (Italian Cohort of Antiretroviral Naive Patients) cohort. Adapted with permission from Mussini et al.[10]

increased risk for cardiovascular disease per unit gain in BMI while taking antiretroviral therapy (Figure 1).[9] Diabetes risk was also substantially increased per unit gain in BMI among patients with a pretreatment BMI of 18.5 kg/m^2 to 25 kg/m^2 or 25 kg/m^2 to 30 kg/m^2.

HIV and Hepatitis C Virus Coinfection

A study in the ICONA (Italian Cohort of Antiretroviral Naive Patients) cohort indicated that higher Fibrosis-4 (FIB-4) score at the start of antiretroviral therapy was associated with increased risk for major liver-related adverse events or death ($P < .001$ for FIB-4 score > 3.25) among patients with HIV/hepatitis C virus (HCV) coinfection (Figure 2); major liver-related adverse events were decompensated cirrhosis, hepatic encephalopathy, gastrointestinal bleeding, hepatocellular carcinoma, and hepatorenal syndrome.[10] These findings support the importance of assessment of liver fibrosis in HIV/HCV-coinfected patients. Analysis from another study suggested that higher FIB-4 score at the start of antiretroviral therapy also predicted an increased risk for liver-related adverse events among HIV-monoinfected patients.[11]

Findings thus far in the TURQUOISE-I study suggest that HCV treatment outcomes with current regimens are not impaired by HIV/HCV coinfection. Among patients receiving 12 weeks (n = 31) or 24 weeks (n = 32) of the investigational nonstructural protein 5A inhibitor ombitasvir (formerly ABT-267) plus the investigational protease inhibitor paritaprevir/r (formerly ABT-450/r) combined with the investigational nonnucleoside polymerase inhibitor dasabuvir (formerly ABT-333) and ribavirin, HCV virologic response rates were 100% and 100%, respectively, at 4 weeks of treatment (rapid virologic response); 97% and 97%, respectively, at end of treatment;93.5% and 97%, respectively, at 4 weeks after end of treatment (sustained virologic response 4 weeks after end of treatment [SVR4]); and 93.5% in the 12-week group at 12 weeks after end of treatment (SVR12).[12] In another study of 38 patients with history of injection drug use who received methadone or buprenorphine, the same regimen produced end-of-treatment, SVR4, SVR12, and SVR24 rates of 97% each.[13]

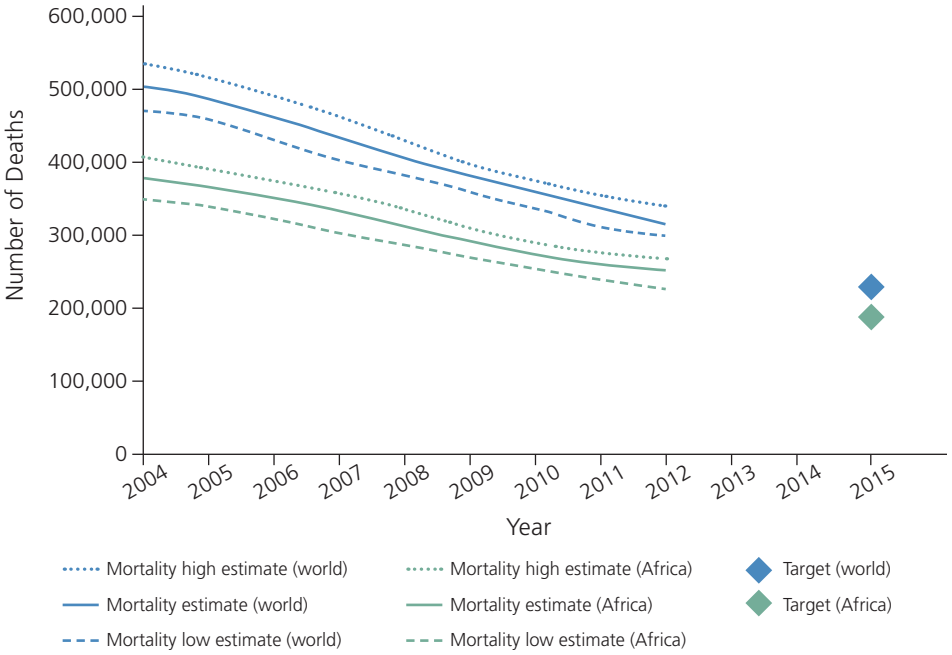

Figure 3. Policy, advocacy, and implementation of HIV and tuberculosis (TB) diagnosis and treatment programs reduced the number of HIV/TB coinfection–related deaths between 2004 and 2012. Adapted with permission from Havlir.[14]

Tuberculosis

Considerable progress has been made in battling the overlapping HIV and tuberculosis (TB) epidemics, resulting in a greater than 40% decline in HIV/TB coinfection–related deaths and more than 1.3 million lives saved between 2004 and 2012 (Figure 3).[14] However, much work remains to be done. Globally, HIV serostatus was known for only 40% of patients with TB infection as of 2011; although efforts have increased this percentage to approximately 70% in Africa, the percentage remains low in other resource-limited regions around the world, at approximately 30%.[14] Improvements in diagnosis of TB and HIV infections, timeliness of TB and HIV treatment initiation, completion of TB treatment courses, and transitioning TB-infected patients to HIV care are needed.

In Closing

Of course, the 20th International AIDS Conference was clouded by the tragic loss of life on Malaysia Airways Flight 17, including that of the former President of the International AIDS Society, Dr Joep Lange. An amazing leader in the field of HIV/AIDS medicine, a mentor to many, and a close friend and colleague, Dr Lange was remembered, along with his partner Jacqueline van Tongeren and others on the flight, throughout the Conference. In the end, the hope represented by the scientific progress evident at the Conference was the best response to the senseless tragedy that affected all.

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Financial affiliations in the past 12 months: Dr Volberding has served on scientific advisory boards for Bristol-Myers Squibb and Gilead Sciences, Inc.

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