Hot News

News from the 2011 Coinfection Workshop

In early June 2011, the latest Coinfection Workshop took place in Milan, Italy. Among others, two topics attracted particular attention: non-cirrhotic portal hypertension (NCPH) in HIV individua ls and new antivirals against hepatitis C in HIV/HCV-coinfected patients.

In 2006, the first reports of NCPH in HIV-infected subjects attracted special attention. Typically, HIV individuals, while unaware of any underlying liver illness, presented with variceal bleeding, which was occasionally fatal. Interestingly, severe portal hypertension occurred in the absence of liver function impairment in most cases (Maida, et al. J Acquir Immune Defic Syndr. 2006;42:177-82). Since then, many authors have reported similar cases in the western world. Liver biopsy reveals a distinctive histological feature characterized by massive absence of portal veins along with focal obliteration of small portal veins (Vispo, et al. AIDS. 2010;24:1171-6). After extensive ruling out of other etiologies, the role of antiretroviral toxicity, particularly didanosine exposure, has emerged as the major contributor to this condition (Kovari, et al. Clin Infect Dis. 2009;49:626-35). In order to identify why only a subset of HIV patients exposed to didanosine are susceptible to developing NCPH, a collaborative research project has started as part of the European Network Trial (NEAT) initiatives funded by the European Commission to unveil if there are any genetic determinants of this condition (Fig. 1).

The approval in May 2011 of the first direct-acting antivirals as therapy for chronic hepatitis C has revolutionized the field. Given that HCV-related liver disease is worsened in the HIV setting, the new antivirals are eagerly awaited for the coinfected population. However, drug interactions with antiretrovirals, increased and overlapping toxicities, and rapid selection of drug-resistant HCV mutants will be some of the most challenging issues when using direct-acting antivirals in HIV/HCV-coinfected patients.

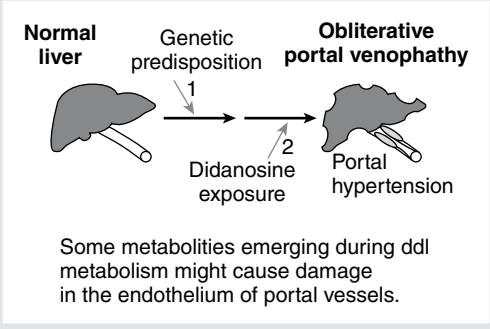

Figure 1. *Hypothesis "Two-hit" model for unexplained non-cirrhotic portal hypertension in HIV+ patients.*

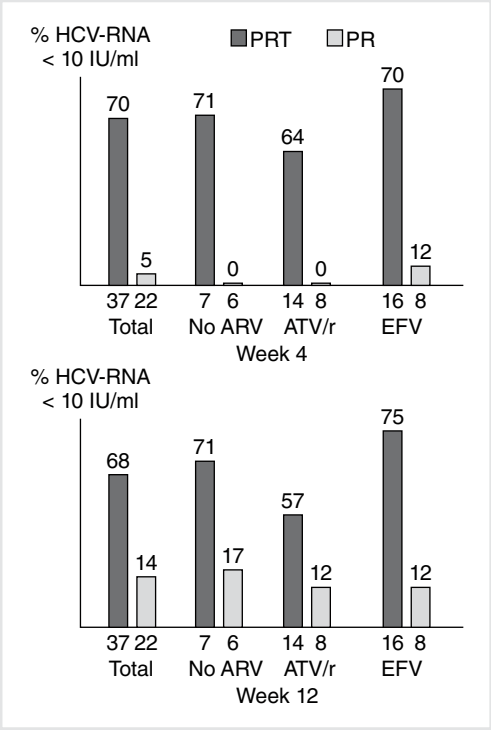

Figure 2. *Study 110, Telaprevir in HIV-HCV coinfected patients. PR: pegylated interferon-α/ribavirin; PRT: telaprevir plus pegylated interferon-α/ribavirin ARV: antiretroviral; ATV/r: ritonavir-boosted atazanavir; EFV: efavirenz* (adapted from Sulkowski, et al. CROI 2011, LB146).

Clinical trials evaluating the safety and efficacy of HCV protease inhibitors in coinfected patients are underway. The first data with telaprevir were released early this year at CROI (Sulkowski, et al. Abstract LB 146). Study 110 is an ongoing phase II trial that examines the safety and efficacy of telaprevir in combination with pegylated interferon-α/ribavirin in HIV/HCV-coinfected patients, most of whom were on antiretroviral therapy. Preliminary results at weeks four and 12 were recently released (Fig. 2), with responses similar to those seen in HCV-monoinfected patients. No serious adverse events were recorded, including rashes. Given the induction of telaprevir metabolism by efavirenz, higher telaprevir dosing was used in subjects receiving efavirenz. Other antiretrovirals allowed in the trial were tenofovir, emtricitabine, lamivudine, and ritonavir-boosted atazanavir, for all of which information on drug interactions is available.

A phase II trial with boceprevir is currently ongoing in HIV/HCV-coinfected patients and results are expected to be released early next year. The use of a lead-in phase of four weeks with pegylated interferon-α/ribavirin alone

before adding boceprevir and the prohibition for using efavirenz concomitantly has complicated this trial.

The next edition of the Coinfection Workshop will be held in Madrid, Spain, next spring (May 30th to June 2nd, 2012). At that time, data from several ongoing studies testing the efficacy and safety of distinct direct-acting antivirals in HIV/HCV-coinfected patients will be available and no doubt will be the focus of major attention at the meeting.

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Highlights from the last International Drug Resistance Workshop (June 2011)

A new edition of the International Workshop on HIV & Hepatitis Drug Resistance and Curative Strategies was held in Los Cabos, Mexico on June 7-11, 2011. New insights regarding HIV resistance to novel antiretroviral agents, such as rilpivirine, and distinct agents belonging to the integrase inhibitor class, as well as new resistance technologies were presented.

The resistance profile to rilpivirine (formerly TMC-278), the most recently approved nonnucleoside analogue inhibitor, was focus of particular attention during the meeting. The genotypic and phenotypic characterization of HIV-1 variants from patients failing to rilpivirine in the phase III studies ECHO and THRIVE (rilpivirine vs. efavirenz both along with co-formulated tenofovir/emtricitabine) were reported (Rimsky, et al. Antivir Ther. 2011;16[Suppl 1]:A17; Kulkarni, et al. Antivir Ther. 2011;16[Suppl 1]:A21). In these trials, E138K (45%) and the combination E138K/M184I (34%) were the most commonly found mutations in rilpivirine failures: provided fold-changes of 2.8 and 6.7, respectively, determined by Antivirogram® (biological cutoff of 3.7). Similarly, site-directed mutants harboring K101E/M184I exhibited on average a rilpivirine fold-change of 5.8. By contrast, the combination E138K/M184V only displayed a minor impact on rilpivirine susceptibility (fold-change of 3.1). These findings suggest a specific role for mutation M184I in rilpivirine resistance.

The replication capacity and reverse transcriptase activity were evaluated in recombinant HIV-1 viruses containing E138K and M184I/V mutations alone and in combination. The double mutant E138K/M184I results in increased reverse transcriptase activity and confers a relative replication advantage as compared with the E138K/M184V mutant (Hu, et al. Antivir Ther. 2011;16[Suppl 1]:A20). Moreover, mutation E138K seems to restores the enzymatic processivity and viral replication capacity of HIV-1 variants harboring M184I/V (Xu, et al. Antivir Ther. 2011;16[Suppl 1]:A19). However, the dynamics of appearance of these mutations and their specific role in rilpivirine resistance is still unclear.

With respect to HIV-1 integrase inhibitors, the molecular basis for resistance to a novel class named non-catalytic integrase inhibitors (NCINI) was reported (Fenwick, et al. Antivir Ther. 2011;16[Suppl 1]:A9). These compounds bind to a conserved allosteric pocket on the viral integrase. The resistance profile to this new drug class is in striking contrast to that for raltegravir, elvitegravir, or dolutegravir, which belong to the group of integrase strand transfer inhibitors (INSTI). Mutations that confer resistance to NCINI encode substitutions in the vicinity of the allosteric pocket targeted by NCINI (Y99H, L102F and H171T). Thus, there is no overlapping resistance with INSTI. This information is of special interest since the last results from the VIKING cohort I trial, which evaluated the antiviral activity of dolutegravir in patients who experienced virologic failure to raltegravir, suggest that partial cross-resistance between both drugs exists (Underwood, et al. Antivir Ther. 2011;16[Suppl 1]:A10). In this regard, NCINI might represent a unique rescue intervention for HIV-1 patients who fail INSTI.

New data from the ANRS HIV-2 cohort concluded that CCR5 inhibitors, such as maraviroc, may provide a feasible therapeutic option for HIV-2 individuals (Visseaux, et al. Antivir Ther. 2011;16[Suppl 1]:A48). The authors demonstrated a strong association between HIV-2 phenotypic tropism and V3 loop genotypic determinants, reinforcing what these authors had previously reported at CROI 2011 (Visseaux, et al. CROI 2011; Boston, USA, Abstract 671). Four major genotypic determinants at the V3 loop of the gp105 HIV-2 envelope were associated with CXCR4-coreceptor use in HIV-2: any substitution at position 18, V19K/R, insertion of 1 amino acid at position 24, and V3 global net change > 6. None of the HIV-2 isolates phenotypically classified as R5 and fully susceptible to maraviroc harbored any of these genotypic determinants. Conversely, isolates phenotypically identified as DM/X4 and resistant to maraviroc showed at least three of the genotypic determinants associated with CXCR4-coreceptor usage. This new genotypic tool might allow a rapid and easy identification of HIV-2-infected patients who could benefit from CCR5 inhibitors.

Finally, the relevance of using ultra-deep sequencing to determine the presence of minority HIV drug resistance variants and their impact on the clinical response to several drugs were extensively discussed (Lataillade, et al. Antivir Ther. 2011;16[Suppl 1]:A34; Kozal, et al. Antivir Ther. 2011;16[Suppl 1]:A98); Metzner, et al. Antivir Ther. 2011;16[Suppl 1]:A107). At this time, the clinical role of ultra-deep sequencing in the field of HIV drug resistance is uncertain, given that conflicting data exist. In certain situations, however, detection of minority variants could predict virologic failure, as in poor drug adherent patients using drugs with a low barrier for resistance, such as nonnucleoside analogues (Li, et al. Antivir Ther. 2011;16[Suppl 1]:A16). In any case, technical issues preclude examining accurately the value of minority variants present in less than 1% of the viral quasispecies population in most cases.

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