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HIV-HCV co-infection: epidemiology, pathogenesis and therapeutic implications

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Abstract. – Hepatitis C virus (HCV) is the cause of more than three-quarters of liver-related deaths in HIV-seropositive individuals and it is remarkable that today approximately one-quarter of HIV-infected individuals in Europe and the USA have a HCV coinfection. HIV/HCV coinfected patients were more likely to develop cirrhosis, had an increased risk of developing AIDS, of HIV-related disease and of overall mortality. How HCV may affect the course of HIV infection is not well known even if it was suggested that HCV co-infection is able to increase immune activation and to sensitize CD4+ T-cells towards apoptosis in the absence of HIV therapy. There are many evidences that the simultaneous presence of HIV infection accelerates the liver damage from HCV favouring the evolution to cirrhosis in co-infected patients. HIV increasing of TNF alpha liver production and of HCV replication in peripheral blood lymphomonocytes are the mechanisms at the basis of this phenomenon. HAART had a positive effect on HIV/HCV co-infection, otherwise it does not appear to fully correct the adverse effect of HIV infection on HCV-related outcomes. Traditional treatment with pegilated Interferon plus ribavirin have low rates of sustained virological response in co-infected patients especially if infected with HCV genotype 1, and better results were often obtained in patients in which the use of antiretroviral treatment was avoided to reduce the occurrence of adverse effects. The recent preliminary results on the use of anti-HCV protease inhibitor drugs, boceprevir and telapravir, in co-infected people seems to demonstrate an enhanced antiviral efficacy in the HIV/HCV co-infected population of triple anti-HCV treatment even is some important limitation as interactions with antiretroviral agents and selection of HCV drug resistance, lead to consider the need for further studies designed to assess the best therapeutic strategies.

Key Words:
HIV, HCV, Co-infection, Boceprevir, Telapravir, HAART.

Introduction

Approximately 15% to 30% of people with HIV are estimated to be co-infected with hepatitis C virus (HCV), and up to 90% of those with HIV secondary to injection drug use are co-infected. Chronic liver disease from co-infection, including cirrhosis and hepatocellular carcinoma, leads to significant morbidity and mortality. Data collected from study cohorts demonstrate that HIV/HCV co-infected patients visit the emergency department more frequently, are hospitalized more often, and have longer hospital stays than HIV mono-infected patients. Other studies have established HCV-related end-stage liver disease as a leading cause of in-hospital mortality among HIV-infected patients. Therapy for HCV has become increasingly successful. However, anti-HCV therapy is complex, particularly in the presence of HIV, and requires many treatment considerations, as well as careful monitoring.

The purpose of this review is to provide an update on the latest literature data concerning epidemiology, pathogenesis and therapeutic indications of HIV/HCV co-infection with particular regard to toxicity issues and latest treatment strategies about the two infections.

Burden of HIV and HCV Virus Coinfection

Hepatitis C virus (HCV) is the cause of more than three-quarters of liver-related deaths in HIV-seropositive individuals and it is remarkable that today approximately one-quarter of HIV-infected individuals in Europe and the USA have a hepatitis C coinfection[1]. Overall, available data suggest that the prevalence of HCV infection is about 2.2-3.0% worldwide (130-170 million people), while HIV infection accounts for an estimated 33.3 million chronic infections[2,3].

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HIV and HCV share common routes of transmission, but they differ in efficiency by which certain types of exposures transmit them. In the past, illicit drug use has been the major route of transmission for infections due to these viruses and in '80 and '90 injecting drug users have been the largest transmission group for new HIV infections in many European Countries, resulting in a high impact on individual health and costly consequences on healthcare systems[4].

On the other hand, although sexual transmission of HCV is known to be rather inefficient in discordant heterosexual couples, recent observations suggest that this is the most likely mode of HCV acquisition among HIV-infected men who have sex with men (MSM). In fact, since 2000, the prevalence and incidence of HCV infections have increased in HIV-infected MSM in large cities in the Netherlands, United Kingdom, France, USA, and Australia[5-10]. In an attempt to find an explanation for this phenomenon, several Authors have diagnosed a high prevalence of ulcerative sexually transmitted infections, mainly syphilis and lymphogranuloma venereum, in HIV/HCV co-infected MSM, suggesting that HCV infections among MSM epidemiologically follow the epidemics of syphilis[11,12]. Recently, use of recreational drugs, in particular gamma hydroxyl butyrate (GHB), have been identified as independent risk factors for HCV transmission in MSM, beside intravenous drug use and HIV infection[9,13].

Finally, recent phylogenetic analysis revealed a large international network of HCV transmission among HIV-positive MSM in Europe. The rapid spread of HCV among neighboring Countries is supported by the large proportion (74%) of European MSM infected with an HCV strain co-circulating in multiple European Countries, the low evolutionary distances among HCV isolates from different Countries, and the trend toward increased country mixing with increasing cluster size[14].

With regard to the specific situation in Italy, the detection of acute HCV infections may provide informations about the mode of transmission and the main risk groups. In 2010, the incidence of acute infections by HCV reported by SEIEVA was 0.2 per 100,000 (0.0, 0.4, 0.2, respectively, for ages 0-14, 15-24, and ≥ 25 years). Today, individuals who develop acute hepatitis C are mostly male. The age group most affected is 15-24 years. Major risk factors include promiscuous sexual activity, percutaneous exposure in the course of beauty treatments, intravenous drug use and surgery[2,15].

Is HCV a Cofactor for HIV Disease Progression? Has HIV Influence on HCV disease?

HIV infection, in the absence of therapy, is almost invariably fatal. However, following the advent of HAART (Highly Active Antiretroviral Therapy), a dramatic decline in morbidity and mortality has deeply changed the natural course of HIV infection. Chronic HCV infection can cause a wide spectrum of liver disease, potentially leading to severe liver damage, including cirrhosis, organ failure and hepatocellular carcinoma[16]. The large amount of investigations performed over the last 15 years on the interaction between the two viruses and the mutual influence on disease progression was reviewed[17-24].

Does HCV Affect HIV Disease Progression?

The influence of HCV on HIV disease progression and the extent of the relationship has been a matter of debate for long and it is still an unresolved issue. In post-HAART era, the HOPS (HIV Outpatient Study) cohort[25] investigated the influence of coinfection on HIV disease progression in 267 HIV/HCV coinfected patients and 556 HIV monoinfected subjects. Coinfected persons had no a greater risk of AIDS, of renal or cardiovascular disease, but they were more likely to develop cirrhosis and transaminase elevations. Factors associated with survival were age [HR: 1.73, 95% CI from 01.19 to 2.53), $p < 0.0042$], baseline CD4+ cell count [HR: 0.12, 95% CI from 0.06 to 1.51), $p < 0.0001$] and duration of HAART [HR: 0.17, 95% CI from 0.10 to 1.29) $p < 0.0001$], but not HCV infection [HR: 0.91, 95% CI from 0.55 to 1.51), $p = 0.71$]. Data from EUROSIDA cohort[22] suggest that HCV serostatus did increase the risk of liver disease-related deaths in coinfected patients (IRR, 11.71 [95% CI, 6.42-21.34]), without affecting the viro-immunological response to HAART and HIV disease progression. Data from ICONA cohort[26] reported that HCV coinfection was associated with increased risk of developing AIDS (RR: 2.61; 95% CI: 1.88-3.61), bacterial infection (RR: 3.15; 95% CI, 1.76-5.67), HIV-related disease (RR: 2.68; 95% CI, 1.03-6.97), and mycotic disease (RR: 3.87; 95% CI, 2.28-6.59), but it was not associated to non-Hodgkin lymphoma (RR: 0.88; 95% CI, 0.22-3.48). A recent meta-analysis[27] including 30 studies (over 100.000 patients) showed that, after the advent of HAART, HCV coinfection increased the risk of overall mortality, but not of AIDS progression. Another

study[28] in HIV infected women (813 HIV monoinfected, 494 HIV/HCV coinfected women, of whom 87 HCV were nonviremic, while 407 were HCV viremic) showed a twofold increased AIDS risk among coinfected women with high level of T-cell activation.

So data are conflicting. How HCV may affect the course of HIV infection is also unclear. A proposed mechanism suggests that the HCV effect may be mediated by increased immune activation and CD4+ T cells apoptosis in untreated subjects[29]. In fact, it was demonstrated that although HCV alone did not increase CD4+ T-cell apoptosis, HCV/HIV co-infection disproportionately increased the rates of apoptosis in CD4+ T-cells, compared to HIV mono-infected controls. HCV co-infection seems to be able to sensitize CD4+ T-cells towards apoptosis in the absence of HIV therapy, as this effect is rapidly lost under HAART[29]).

Does HIV Affect HCV-Related Liver Disease?

There are many and consistent studies confirming that HIV can adversely affect the progression of HCV liver disease. In order to investigate the possible role of HIV infection in the natural history of chronic parenterally-acquired hepatitis C, a multicenter cross-sectional study[20] was performed in 116 patients with and 431 without HIV infection. Results showed that, in the first 10 years, 14.9% (13/87) of HIV subjects developed cirrhosis, compared to 2.6% (7/272) in the HIV-uninfected controls ($p < 0.01$). In addition, mean interval from estimated time of HCV infection to cirrhosis was significantly longer in HIV-negative than HIV-positive patients (23.2 vs. 6.9 years; $p < 0.001$). HCV RNA levels were lower in HIV patients with a more preserved immune function (i.e. CD4+ cell counts > 500 cells/ml) than those with a more advanced disease ($p < 0.05$). According to a meta-analysis (17 studies), the prevalence of cirrhosis after 20 and 30 years of HCV infection in HIV population was 21% (16-28%) and 49% (40-59%), respectively[21]. Liver-biopsy studies[22], in pre-HAART era, demonstrated higher rates of cirrhosis and more-advanced fibrosis stages in the livers of HIV/HCV-coinfected patients than of HCV-monoinfected patients, after comparable infection times. A retrospective study[18] in 135 HIV/HCV coinfected patients, who underwent liver-biopsy (2 procedures, at least 1 year apart), showed that liver fibrosis progressed with high frequency over a 3 year period (13% had cirrhosis in the second biopsy) and that factors associated to a slower progression included undetectable HIV RNA, successful response to anti-HCV treatment and absent-to-mild lobular necroinflammation at baseline. A case control study[17] in 122 coinfected *versus* 122 monoinfected patients reported a higher prevalence of extensive liver fibrosis and of moderate/severe activity in HIV patients (60% *vs* 54%, respectively) than in monoinfected subjects (47% *vs* 30%, respectively; $p < .05$ and $p < .001$, respectively). The median fibrosis progression rate (FPR) was 0.153 (95% CI, 0.117-0.181) and 0.106 (95% CI, 0.084-0.125) fibrosis units per year, ($p < .0001$), respectively. Factors associated to an increased FPR were: HIV infection ($p < .0001$), alcohol consumption, age at HCV infection (< 25 years old, $p < .0001$), and severe immunosuppression (CD4 count below 200 cells/ml, $p < .0001$).

The protective effect of HAART on FPR (defined as Ishak fibrosis score 0-6) in the setting of HIV/HCV coinfection was confirmed in 274 HIV individuals (95.2% on HAART, 51.2% of whom with HIV RNA < 400 copies/ml) compared to 382 HCV monoinfected subjects[30]. HIV/HCV-coinfected patients with any detectable HIV viral load (> 400 copies/ml) had a faster FPR (0.151) than HCV-monoinfected patients (0.128, $p = 0.015$). Alternatively, coinfected subjects with undetectable HIV RNA (0.122, $p = 0.013$) had the same FPR as HCV-monoinfected subjects (0.128, $p = 0.52$). FPR was accelerated in HIV viremic patients, when CD4+ cells were below 500 cells/mm (0.162 vs. 0.123 when HIV RNA was undetectable, $p = 0.005$), but not with higher CD4+ cells (0.118 vs. 0.121, $p = 0.89$). In multivariable linear regression analysis, HIV RNA levels, necroinflammation and age at HCV infection were independently correlated to FPR, but not alcohol use or CD4+ cell count.

Similar data were reported in another retrospective study[31] comparing 296 HCV-monoinfected patients and 85 HIV-HCV-coinfected patients. Patients were divided in group 1 (HCV monoinfected subjects), group 2 (no HIV therapy or only NRTIs), group 3 (subjects treated with HAART) and group 4 (mono or dual therapy, then switched to HAART). The main finding was that patients in group 3 had similar necroinflammatory scores, fibrosis stages, rates of fibrosis progression, and prevalences of and mean times to cirrhosis development, compared with the group 1 (HCV-monoinfected population). This benefit was not observed in coinfected patients who receive no HAART or NRTIs.

Despite extensive data support the evidence that HIV/HCV infected individuals progress more rapidly to serious liver disease than HCV mono-infected subjects, the mechanisms by which HIV can accelerate the HCV liver damage has not been clarified yet. They may include direct viral effects or immunologic alterations such as immune activation and apoptosis. Immune activation may induce cytokines, which increase liver inflammation and fibrosis. Accumulation of HIV specific cytotoxic CD8+ T cells in the liver can produce TNF-α, which is associated with fibrosis[32]. In addition, HCV is not only hepatotropic, but can replicate in PBMCs (peripheral blood mononuclear cells)[33] and in native human macrophages *in vitro*[34]. After HIV infection, the replication of HCV from PBMC cultures of mono-infected subjects can increase by 1 to 2 logs, compared to HIV uninfected controls[35]. Most recent researches suggest the role of HIV-1 Tat in enhancing HCV replication in PBMCs, through the interferon gamma-inducible protein-10 (IP-10), as confirmed by the block of the effect in the presence of anti-IP10 monoclonal antibodies[36].

Antiretroviral Drugs and Liver Fibrosis in Coinfected Patients

Despite the protective effect of HIV therapy on immune system and liver function[30] in coinfected patients, HAART-related hepatotoxicity may occur and its frequency depends on type of drugs and regimens[37]. As the HIV therapy is a combination of agents given concomitantly, it's difficult to discriminate the role of single drugs as potential enhancer of liver fibrosis progression. Some authors[38] suggested a protective effect of protease inhibitors on fibrosis progression, while others[39] did not show any association between the use of NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) and the severity of liver fibrosis. Overall, study designs are often inadequate, confounders are numerous, results are sometimes conflicting and prospective studies are lacking[37]. Indeed, the benefit of HIV treatment largely outweighs the risk of pharmacological toxicity and potential enhancement of fibrosis in coinfected individuals. A recently published study[40] investigated mortality from HCV among patients diagnosed with AIDS. This is a cohort study of 2026 participants (21% had evidence of past or current HCV infection, 79% HCV RNA positive) enrolled in the Longitudinal Studies of the Ocular Complications of AIDS (LSOCA). These participants (all with previous AIDS diagnosis) were followed up prospectively for a median of more than 6 years. The proportion of deaths related to cardiovascular disease, AIDS, and non-AIDS-related cancer was similar between patients with and without HCV infection. Despite competing risks, current HCV coinfection resulted to be independently associated with a 50% increase in mortality among these patients. In fact, the relative risk of dying during follow-up was higher in patients with chronic HCV infection (RR: 1.5, 95% CI, 1.2-1.9; p = 0.001). For coinfected individuals, 20.4% of deaths were liver-related vs 3.8% in HCV uninfected patients. Mortality risk was not increased in patients with cleared HCV infection. All that suggests that effective HCV treatment may benefit patients with AIDS who are co-infected with HCV. For all these reasons, HIV/HCV coinfected individuals should be treated more aggressively than HIV monoinfected patients and current guidelines suggest, in the presence of coinfection, to start HAART (regardless of CD4 counts) and consider HCV eradication as well[24].

Treatment of Chronic HCV Infection in Coinfected Patients

Actually liver diseases represents the second leading, and in some cases, preventable cause of death in HIV positive patients, so it is important to screen this population. Over the last decade, the treatment with pegilated Interferon (PEG-IFN) plus ribavirin (RBV) has represented the standard of care in the treatment of HCV mono and coinfected patients who are at the greatest risk for liver disease, however, the effectiveness of HCV therapy have low rates of Sustained Virological Response (SVR), especially in those coinfected with HCV genotype 1. Although the success of hepatitis C therapy has improved during the last years using weight-based RBV dosing and avoiding the concomitant use of some antiretroviral agents, overall a relatively small proportion of coinfected patients have been treated so far[41]. More recently, advances in pharmacogenetics have provided further opportunity for improving therapeutic management, as result of testing for interleukin 28B (IL28B). Indeed, only the arrival of direct acting antivirals (DAA) against HCV will dramatically shift the whole scenario, raising expectations of cure for most coinfected patients[42]. In 2009, some Authors identified polymorphisms at chromosome 19 near the interferon lambda (IL28B) gene, as strong predictors of treatment-induced clearance of HCV infection[43-45]. This observation was soon confirmed by others[46-48] testing HIV-infected pa-

tients. Although several polymorphisms around the IL28B gene have been associated with Sustained Virological Response (SVR) to PEG-IFN plus RBV, the strongest link stands for rs12979860[49]. Individuals carrying one or two copies of the T allele had a higher probability of failure compared to subjects carrying the CC genotype. The effect of IL28B variants on treatment response is mainly observed in individuals infected with HCV genotypes 1 or 4, while individuals infected with HCV genotypes 2 or 3 achieve high SVR rates, regardless of IL28B variants. The effect of IL28B variants on the likelihood of SVR in patients receiving the new DAAs against HCV is less strong than in those treated with PEG-IFN plus RBV alone, since drugs with more robust antiviral potency make host factors less relevant. IL28B variants predict SVR in HCV genotype 1 IFN-naïve subjects that started boceprevir[50] or telaprevir[51,52] based therapies, but not in IFNα-experienced patients[53]. Although IL28B variants are one of the strongest predictors of response to PEG-IFN+RBV in chronic hepatitis C, they are not able to foresee SVR in all treated patients. At this time, the new Protease Inhibitors, boceprevir and telaprevir, are not yet approved for the treatment of HIV/HCV coinfected patients. However, preliminary data have been presented at scientific conferences from phase 2a studies of telaprevir and boceprevir in combination with PEG-IFN + RBV compared to PEG-IFN + RBV + placebo in HIV/HCV coinfected subjects. In study 110, telaprevir was given along with PEG-IFN + RBV to IFNα-naive patients infected with HCV genotype 1[54]. A total of 44 patients had reached week 24 of therapy. The study population was mainly represented by Caucasian male, although 27% were African Americans. Overall 68% were infected by HCV subtype 1a; 3.3% had cirrhosis; and 85% had > 800,000 HCV-RNA IU/ml. The mean CD4 in this population was above 550 cells/mm^3. There were no drops in the percentage of these cells during therapy nor HIV-RNA rebounds in patients on antiretroviral therapy. Figure 1 records the virological response at weeks 4, 12 and 24 of therapy on triple therapy with telaprevir compared to controls. One patient had to discontinue telaprevir due to jaundice. The trial testing boceprevir in HIV/HCV-coinfected patients, recently presented at the last EASL (European Association for the Study of the liver) conference, had included 98 patients that had reached week 48[55]. The study population was mainly represented by whites (81%), HCV subtype 1a (66%), and high viremia (> 800,000 IU/ml in 88%). Only 6% had cirrhosis. The mean CD4 count was above 600 cells/mm^3, as all patients were on antiretroviral therapy (84% on HIV protease inhibitors). Overall, 14% of patients had to discontinue boceprevir due to serious adverse events, mainly anemia. All

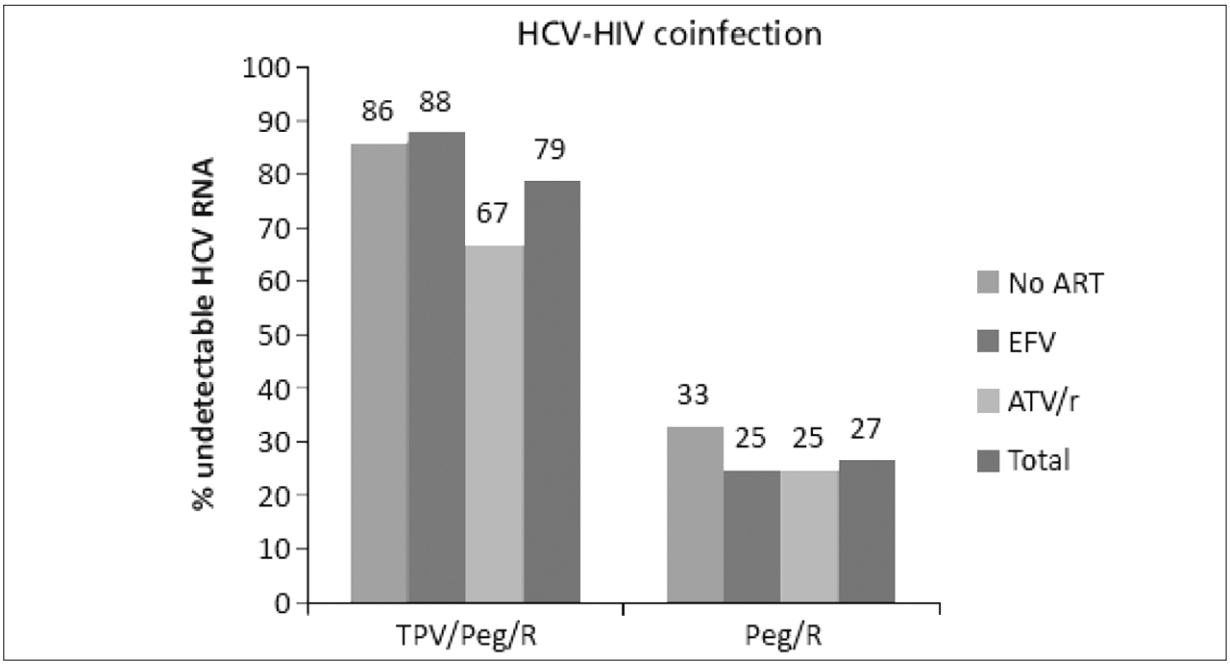

Figure 1. Percentage of co-infected subjects with undetectable HCV-RNA treated with triple therapy of telaprevir plus PEG-IFN+RBV compared with subjects treated only with PEG-IFN (Pegylated-Interferon) + RBV (Ribavirin).

patients on boceprevir had a lead-in phase of 4 weeks with PEG-IFN + RBV alone. While triple regimens may provide an enhanced antiviral efficacy in the HIV/HCV-coinfected population, several caveats merit a special consideration. Table I records the main challenges that may arise when using DAA in coinfected patients. Drug interactions between DAA and antiretroviral agents, selection of HCV drug resistance, poor drug adherence and high cost are amongst the most important caveats. Moreover, both telaprevir and boceprevir interact with CYP3A4 as inhibitors and substrates, raising potential interactions with drugs that are metabolized trough this pathway. Boceprevir is principally metabolized by the enzyme aldoketoreductase with a minor contribution from CYP3A4 (Cytochrome P-450 3A4); however, it inhibits CYP3A4[56]. Similarly, telaprevir is an inhibitor and substrate of CYP3A4. These effects on CYP3A4 suggest that drugs that are metabolized by this enzyme may have increased concentrations, and drugs that induce this enzyme may lower telaprevir concentrations. Table I summarizes the most relevant drug interactions for boceprevir and telaprevir in HIV/HCV-coinfected patients. Any change in drug exposure above 30% must be considered as clinically relevant, meaning that overexposure may enhance toxicities whereas underexposure may result in poor drug activity.

Antiretroviral Therapy in HIV/HCV Coinfection

Introduction of highly active antiretroviral therapy (HAART) has made HIV infection a chronic illness. Significant reductions in the number of AIDS-related deaths have been accompanied by an increase in liver-related morbidity and mortality due to HBV or HCV co-infection; liver disease, in fact, is the second non-AIDS-related cause of death[57,58].

The benefit of HAART may be limited by the development of different side effects and liver toxicity plays an important role on patients' quality of life. In the last years the incidence and risk factors of liver toxicity due to HAART have been reported in different studies and chronic viral hepatitis increase the risk of severe hepatotoxicity HAART-related[59-63]. It's not easy to establish a causal relationship between a single drug and a liver event in patients receiving multiple medication with an underlying chronic viral hepatitis infection. In addition, to compare the results of one study to another is often impossible for different reasons as the definition of toxicity grading system, the different severity of the liver disease, the short time of the studies and the definition of hepatoxicity is usually based on transaminase values.

However there is an estimated 2.7-fold to 5-fold increased risk of severe alanine aminotransferase (ALT) elevation on HAART with HCV coinfection[63-66]. Up to 10% of all co-infected patients receiving HAART experienced hepatotoxicity of grade 3 or above, and almost one-quarter of these patients discontinued treatment[67,68], therefore, in patients with CD4 counts > 500 cells/mm^3, some clinicians prefer to delay HAART until completion of HCV treatment.

Indeed, clearance of HCV has been associated with a regression of liver fibrosis[69,70] and with a reduced risk of antiretroviral-related hepatotoxicity[68].

All antiretroviral classes, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside

Table I. Pharmacokinetic interactions between marketed first-generation HCV protease inhibitors and common HIV medications.

	Telaprevir	Co-medication	Boceprevir	Co-medication
Tenofovir	≈	↑30%	↑8%	↑8%
Efavirenz	↓26% (tid)	↓7% (tid)	↓19%	↑20%
Atazanavir/r	↓20%	↑17%	–	–
Darunavir/r	↓35%	↓40%	–	–
Fosamprenavir/r	↓32%	↓47%	–	–
Lopinavir/r	↓54%	↑6%	–	–
Ritonavir (low dose)	↓24%	–	↓19%	–
Raltegravir	≈	≈	≈	≈
R-methadone	≈	↓29%	–	–
Midazolam	–	9-fold	–	↑5-fold
Escitalopram	≈	↓35%	–	–
Esomeprazole	≈	–	–	–
Contraceptives (estrogen/progestogen)	≈	↓28%/↓11%	–	↓24%/↑99%
Atorvastatin	–	↑8-fold	–	–
Ketoconazole	↑62%	↑46%	↑2.3-fold	–

reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) have been independently associated with HAART hepatotoxicity[60,63-67].

Hepatotoxicity events are more often idiosyncratic and unpredicted, have a low incidence and drug induced liver injury can be classified as allergic and non allergic[71,72].

Nunez et al[63] summarizes the mechanisms of HAART-related liver toxicity in five categories: hypersensitivity reactions, direct mitochondrial inhibition, modification in lipid and glucide metabolism, direct cell stress, and immune reconstitution. Some of these mechanisms are specific for a single class of drugs, for example mitochondrial toxicity is correlated only to NRTI[73]), in particularly didanosine (ddI) and stavudine (d4T) that must be avoid in hepatopatic patients in advance stages, while hypersensitivity reactions with liver involvement are due to NNRTIs but are possible also for specific drugs in other classes[63,74,75].

Moreover, metabolic abnormalities and insulin resistance, directly involved in liver steatosis and faster liver fibrosis progression, can be caused by several drugs, especially boosted PI[76-78]. It's generally known that PIs are metabolized by the cytochrome P450 enzyme system and that, a deficiency in drug metabolism, may induce liver enzyme elevation (LEE) through a cumulative dose in patients with chronic liver disease.

Drug-to-drug interactions can increase hepatotoxicity, as co-administration of d4T and ddI, or use of PI and other drugs metabolized by cytochrome P450; in these cases use of therapeutic drug monitoring (TDM) can be useful[79].

So important questions are when to start HAART and what antiretroviral drugs use especially if concurrent HIV and HCV treatment, with PIs active on HCV NS3/4A enzyme complex, is feasible.

The rate of liver disease progression is accelerated in HIV/HCV-coinfected patients, particularly in subjects with CD4 ≤ 350 cells/mm^3, HAART may slow the progression of liver fibrosis by preserving or restoring immune function and reducing HIV-related immune activation and inflammation[80,81]. Latest Antiretroviral American Guidelines (Department of Health and Human Service guidelines – DHHS) suggest that HAART should be initiated for most coinfected patients, regardless of CD4 count and also patients with cirrhosis can be treated because the benefits of HAART outweigh the concerns regarding hepatotoxicity[79].

HAART choice in co-infected patients is no different from non co-infected subjects. Particular considerations are required when both HIV and HCV treatments are indicated, the choice of drug regimen should be guided by the HCV treatment regimen with careful consideration of potential drug-drug interactions and overlapping toxicities (zidovudine and abacavir with ribavirine and Peg Interferon or interaction among new HCV PIs and HIV PIs)[59,68,79,82,83].

Although all antiretroviral drugs have some risk of hepatotoxicity, some are implicated more than others: nevirapine (NVP) is the NNRTI most associated with hepatotoxicity (4-18%), even if some reactions have been reported with etravirine (ETV), while efavirenz can cause hepatotoxicity (1-8%) less frequently than NVP or ETV[63,74,78].

LEE associated with PIs generally occurs weeks to months after drug initiation. PIs boosted with higher dose of RTV, as tipranavir, were strongly associated with hepatotoxicity, while those with low dose (atazanavir [ATV], darunavir [DRV], fosamprenavir [FPV] and lopinavir [LPV]) don't appear to increase the risk of hepatotoxicity[63,84-88].

ATV as other PIs is metabolized by the CYP3A isoenzyme. Ritonavir, used in booster dose, is a potent CYP3A inhibitor, which increases the plasma levels of PIs. In the Castle substudy there are no difference in 2-4 grade liver events between HIV mono-infected and HCV co-infected patients except for bilirubin value[86,87]. Other PIs, as LPV and darunavir, and integrase inhibitor as raltegravir reported no difference in liver safety compared with HIV mono-infected individuals[88,89].

Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system and it should be planned a TDM in order to perform a tailored HAART in patients with Child-Pugh class B and C disease[79].

Transaminase levels should be monitored at 1 month after initiation of HAART and then every 3 to 6 months. Mild to moderate elevations in ALT and/or AST are typical in individuals with chronic HCV infection and do not require interruption of HAART. Significant ALT and/or AST elevation (≥ 3 grade) should prompt careful evaluation for signs and symptoms of liver insufficiency and for other reasons of liver damage; short-term interruption of the HAART regimen or of the specific drug suspected to be responsible for the liver injury may be required[78,79].

Conclusions

Currently, an estimated 180 million humans are infected with HCV and 34 million individuals are living with HIV, worldwide. In Italy HCV infects 30% of HIV-positive patients (60,000 HIV/HCV co-infected individuals), and, although the intravenous drug use is now less important as a risk factor for HIV, the percentage of co-infected in the addict population reaches 70%. The issue of HIV/HCV co-infection is relevant as both viruses can cause chronic infections, a severe organ damage, a life-threatening conditions and they are likely to mutually influence the course of disease. Nevertheless, effective treatments are available for both. HAART had a positive effect on HIV-HCV co-infection, otherwise it does not appear to fully correct the adverse effect of HIV infection on HCV-related outcomes, so the timing of HIV and HCV therapies has to be individualized and tailored basing on personal patient history in order to construct HAART regimens with optimal liver safety profile. A new landscape is emerging for HCV care providers. The arrival of HCV directly acting antivirals will offer new opportunities for eradication of the virus, but also pose new challenges like drug interaction with HAART and overlapping toxicities.

Changes reported are for the areas under the plasma concentration time curves (AUCs) of telaprevir and boceprevir (blue columns) and agents commonly used in HIV therapy (tan columns) when both agents are co-administered. Data for other pharmacokinetic parameters (e.g., Cmax and Cmin) are also available.

Refer to **www.hep-druginteractions.org** for a full and updated list of established and other potentially significant drug interactions.

References

1) Puoti M, Manno D, Nasta P, Carosi G. The burden of HIV and hepatitis C virus coinfection. Curr Opin HIV AIDS 2007; 6: 460-465.
2) Lavanchy D. The global burden of hepatitis C. Liver Int 2009; 29(Suppl 1): 74-81.
3) WHO. AIDS epidemic update 2004. Available online: http://www.unaids.org/wad2010/report_pdf.html.
4) Wiessing L, Likatavicius G, Hedrich D, Guarita B, van de Laar MJ, Vicente J. Trends in HIV and hepatitis C virus infections among injecting drug users in Europe, 2005 to 2010. Euro Surveill 2011; 16: pii: 20031.
5) van de Laar TJ, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, van der Meer JT, de Vries HJ, Mulder JW, van Agtmael M, Jurriaans S, Wolthers KC, Coutinho RA. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007; 196: 230-238.
6) Fox J, Nastouli E, Thomson E, Muir D, McClure M, Weber J, Fidler S. Increasing incidence of acute hepatitis C in individuals diagnosed with primary HIV in the United Kingdom. AIDS 2008; 22: 666-668.
7) Gambotti L, Batisse D, Colin-de-Verdiere N, DelaroqueAstagneau E, Desenclos JC, Dominguez S, Dupont C, Duval X, Gervais A, Ghosn J, Larsen C, Pol S, Serpaggi J, Simon A, Valantin MA, Velter A; Acute hepatitis C collaborating group. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro Surveill 2005; 10: 115-117.
8) Fierer DS, Uriel AJ, Carriero DC, Klepper A, Dieterich DT, Mullen MP, Thung SN, Fiel MI, Branch AD. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. J Infect Dis 2008; 198: 683-686.
9) Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, Fisher M, Johnson AM, Dusheiko GM; HIV and Acute HCV (HAAC) group. Recent epidemic of acute hepatitis C virus in HIVpositive men who have sex with men linked to high-risk sexual behaviours. AIDS 2007; 21: 983-991.
10) Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al. AIDS 2007; 21: 2112-2113.
11) Rauch A, Rickenbach M, Weber R, Hirschel B, Tarr PE, Bucher HC, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. Clin Infect Dis 2005; 41: 395-402.
12) Serpaggi J, Chaix ML, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. AIDS 2006; 20: 233-240.
13) Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIVinfected men who have sex with men: an expanding epidemic. AIDS 2009; 23: F1-7.
14) van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology. 2009; 136: 1609-1617.
15) Istituto Superiore di Sanità. Tassi annuali/100.000 per tipo di epatite, età, sesso ed area geografica. SEIEVA 2010. Available on-line: http://www.iss.it/binary/seie/cont/Area_geografica_2010.pdf

16) Salmon-Ceron D, Rosenthal E, Lewden C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalité 2005 study. J Hepatol. 2009; 50: 736-745.

17) Benhamou Y, Bochet M, Di Martino V et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999; 30: 1054-1058.

18) Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. Hepatology 2009; 50: 1056-1063.

19) Martinez-Sierra C, Arizcorreta A, Diaz F, et al. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. Clin Infect Dis 2003; 36: 491-498.

20) Soto B, Sánchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997; 26: 1-5.

21) Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS 2008; 22: 1979-1991. Review

22) Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis 2005; 192: 992-1002.

23) Salmon-Ceron D, Lewden C, Morlat P, et al. Mortality 2000 study group. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 2005; 42: 799-805.

24) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Last access March 27, 2012.

25) Tedaldi EM, Baker RK, Moorman AC, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Clin Infect Dis 2003; 36: 363-367.

26) d'Arminio Monforte A, Cozzi-Lepri A, Castagna A et al. Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis. Clin Infect Dis 2009; 49: 612-622.

27) Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Clin Infect Dis 2009; 49: 1605-1615.

28) Kovacs A, Karim R, Mack WJ, et al. Activation of CD8 T cells predicts progression of HIV infection in women coinfected with hepatitis C virus. J Infect Dis 2010; 201: 823-834.

29) Körner C, Krämer B, Schulte D et al. Effects of HCV co-infection on apoptosis of CD4+ T-cells in HIV-positive patients. Clin Sci (Lond). 2009; 116: 861-870.

30) Brau N, Salvatore M, Rios-Bedoya CF et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol 2006; 44: 47-55.

31) Verma S, Wang CH, Govindarajan S, Kanel G, Squires K, Bonacini M. Do type and duration of antiretroviral therapy attenuate liver fibrosis in HIV-hepatitis C virus-coinfected patients? Clin Infect Dis 2006; 42: 262-270.

32) Pascual-Pareja JF, Caminoa A, Larrauri C, et al. HAART is associated with lower hepatic necroinflammatory activity in HIV-hepatitis C virus-coinfected patients with CD4 cell count of more than 350 cells/microl at the time of liver biopsy. AIDS. 2009; 23: 971-975.

33) Natarajan V, Kottilil S, Hazen A, et al. HCV in peripheral blood mononuclear cells are predominantly carried on the surface of cells in HIV/HCV co-infected individuals. J Med Virol 2010; 82: 2032-2037.

34) Laskus T, Radkowski M, Jablonska J, et al. Human immunodeficiency virus facilitates infection/replication of hepatitis C virus in native human macrophages. Blood 2004; 103: 3854-3859.

35) Parodi C, Belmonte L, Baré P, de Bracco MM, Ruibal-Ares B. Impact of human immune deficiency virus infection on hepatitis C virus infection and replication. Curr HIV Res 2007; 5: 55-67.

36) Qu J, Zhang Q, Li Y, et al. The Tat protein of human immunodeficiency virus-1 enhances hepatitis C virus replication through interferon gamma-inducible protein-10. BMC Immunol 2012; 13: 15.

37) Pineda JA, Macías J. Progression of liver fibrosis in patients coinfected with hepatitis C virus and human immunodeficiency virus undergoing antiretroviral therapy. J Antimicrob Chemother 2005; 55: 417-419.

38) Benhamou Y, Di Martino V, Bochet M et al. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. Hepatology. 2001; 34: 283-287.

39) Martin-Carbonero L, Benhamou Y, Puoti M, Berenguer J, Mallolas J, Quereda C et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis 2004; 38: 128-133.

40) Branch AD, Van Natta ML, Vachon ML, Dieterich DT, Meinert CL, Jabs DA. Mortality in HCV-infected Patients with a Diagnosis of AIDS in the Era of Combination Anti-retroviral Therapy. Clin Infect Dis 2012 Apr 24

41) Soriano V, Puoti M, Sulkowski M et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. AIDS 2007; 21: 1073-1089.

42) Soriano V, Sherman K, Rockstroh J et al. Challenges and opportunities for hepatitis C drug development in HIV-HCV coinfected patients. AIDS 2011; 25: 2197-2208.

43) Ge D, Fellay J, Thompson A et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009; 461: 399-401.

44) Tanaka Y, Nishida N, Sugiyama M et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009; 41: 1105-1109.

45) Suppiah V, Moldovan M, Ahlenstiel G et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009; 41: 1100-1104.

46) Rallón N, Naggie S, Benito JM et al. Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. AIDS 2010; 24: F23-F29.

47) Rauch A, Kutalik Z, Descombes P et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 2010; 138: 1338-1345.

48) Pineda JA, Caruz A, Rivero A et al. Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfected with HIV and hepatitis C virus. Clin Infect Dis 2010; 51: 788-795.

49) Afdhal N, McHutchison J, Zeuzem S et al. Hepatitis C pharmacogenetics: state of the art in 2010. Hepatology 2011; 53: 336-345.

50) Poordad F, Bronowicki J-P, Gordon S et al. IL28B polymorphisms predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir combination therapy. J Hepatol 2011; 54(Suppl 1): 6.

51) Jacobson IM, Catlett I, Marcellin P et al. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial. J Hepatol 2011; 54(Suppl 1): 542-543.

52) Akuta N, Suzuki F, Hirakawa M et al. Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. Hepatology 2010; 52: 421-429.

53) Pol S, Aerssens J, Zeuzem S et al. Similar SVR rates in IL28B CC, CT or TT prior relapser partial- or null-responder patients treated with telaprevir/ peginterferon/ribavirin: retrospective analysis of the REALIZE study. J Hepatol 2011; 54(Suppl 1): 6-7.

54) Sherman K, Rockstroh J, Dieterich D et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV co-infected patients: a 24-week treatment interim analysis. 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). San Francisco, CA, November 4-8, 2011 [abstract LB-8]

55) Mallolas J, Pol S, Rivero A, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: end of treatment (week 48) interim results. J Hepatol 2012; 56(Suppl 2): S22. Abstract 50.

56) Ghosal A, Yuan Y, Tong W, et al. Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. Drug Metabolism Disposition 2011; 39: 510-521.

57) Pineda JA, Garcia-Garcia JA, Aguilar-Guisado M, Rios-Villegas MJ, Ruiz-Morales J, Rivero A, del Valle J, Luque R, Rodriguez-Bano J, Gonzalez-Serrano M, Camacho A,Macias J, Grilo I, Gomez-Mateos JM. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology 2007; 46: 622-630.

58) Weber R, Sabin CA, Friis-Moller N et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006; 166: 1632-1641.

59) Sulkowski MS, Mehta SH, Thomas DL, Chaisson RE and Moore RD. Hepatotoxicity associated with protease inhibitors based antiretroviral regiments with or without concurrent ritonavir. AIDS 2004; 18: 2277-2284.

60) den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, Pakker NG, Reiss P, Danner SA, Weverling GJ, Lange JM. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS 2000; 14: 2895-2902.

61) Sulkowski MS, Benhamou Y. Therapeutic issues in HIV/HCV-coinfected patients. J of viral Hepatitis 2007; 14: 371-386.

62) Nunez M. Clinical Syndromes and Consequences of Antiretroviral-Related Hepatotoxicity Hepatology 2010; 52: 1143-1154.

63) Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 27: 426-431.

64) Servoss JC, Kitch DW, Andersen JW, Reisler RB, Chung RT, Robbins GK. Predictors of antiretroviral-related hepatotoxicity in the Adults AIDS Clinical Trial Group (1989-1999). J Acquir Immune Defic Syndr 2006; 43: 320-323.

65) Wit FWNM, Weverling GJ, Weel J, Jurriaans S, Lange JMA. Incidence of and risk factors for severe hepatotoxicity assocated with antiretroviral combination therapy. J Infect Dis 2002; 186: 23-31.

66) Soriano V, Puoti M, Garcia-Gasco' P, Rockstroh JK, Benhamou Y, Barreiro P, et al. Antiretroviral drugs and liver injury AIDS 2008; 22: 1-13.

67) Labarga P, Soriano V, Vispo E, Pinilla J, Martín-Carbonero L, Castellares, C, Casado R, Maida I, García-Gascó P, Barreiro P. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis 2007; 196: 670-676.

68) Soriano V, Labarga P, Ruiz-Sancho A, Garcia-Samaniego J, Barreiro P. Regression of liver fibrosis in hepatitis C virus/HIV-co-infected patients alter treatment with pegylated interferon plus ribavirin. AIDS 2006; 20: 2225-2227.

69) Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, Castellares C, González-Lahoz J, Soriano V. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. Antivir Ther 2006; 11: 869-877.

70) Russmann S, Kullak-Ublick GA, Grattagliano I. Current concepts of mechanisms in drug-induced hepatotoxicity. Curr Med Chem 2009; 16: 3041-3053.

71) Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nature Rev 2005; 4: 489-499.

72) Montessori V, Harris M, Montaner J. Hepatotoxicity of nucleoside reverse transcriptase inhibitors Semin Liver Dis 2003; 23: 167-172.

73) Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002; 35: 182-189.

74) Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J Hepatol. 2006; 44(Suppl 1): S132-S139.

75) Noor MA. The role od protease inhibitors in the pathogenesis of HIV-associated insulin resistance: cellular mechanisms and clinical implications. Current HIV/AIDS Report 2007; 4: 126-134.

76) Blanco F, Barriero P, Ryan P, Vispo E, Martin-Carbonero L, Tuma P, Labarga P, Medrano J, Gonzalez-Lahoz J and Soriano V. Risk factors for advanced liver fibrosis in HIV-infected individuals: role of antiretroviral drugs and insulin resistance. J Viral Hepat 2011 Jan; 18: 11-16.

77) Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet 2011; 377: 1198-1209.

78) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/Adultand AdolescentGL.pdf Considerations for Antiretroviral Use in Patients with Coinfections J5-J6 march 2012.

79) Macias J, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus Hepatology 2009; 50: 1056-1063.

80) Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? BMC Res Notes. 2008; 1: 46.

81) de Kanter CB, Blonk M, Colbers A, Fillekes Q, Schouwenberg B, Burger D. The Influence of the HCV Protease Inhibitor Bocepravir on the Pharmocokinetics of the HIV Integrase Inhibitor Raltegravir. 19th Conference on Retroviruses and Opportunistic Infections (CROI); March 5-8, 2012; Seattle, WA.

82) Hulskotte E, Feng H-P, Xuan F, van Zutven M, O'-Mara E, Youngberg S, Wagner J, Butterton J. Pharmacokinetic interaction between the HCV protease inhibitor bocepravir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, lopinavir, and darunavir 19th Conference on Retroviruses and Opportunistic Infections (CROI); March 5-8, 2012; Seattle, WA.

83) Rivas P, Morello J, Garrido C, Rodríguez-Nóvoa S and Soriano V. Role of atazanavir in the treatment of HIV infection. Therap Clin Risk Manag 2009; 5: 99-116.

84) Merchante N, Lopez-Cortes LF, Delgado-Fernandez M, et al. Liver toxicity of antiretroviral combinations including fosamprenavir plus ritonavir 1400/100 mg once daily in HIV/hepatitis C virus-coinfected patients. AIDS Patient Care STDs 2011; 25: 395-402.

85) McDonald C, Uy J, Hu W, Wirtz V, Juethner S, Butcher D, McGrath D, Farajallah A and Moyle G. Clinical Significance of Hyperbilirubinemia Among HIV-1-Infected Patients Treated with Atazanavir/Ritonavir Through 96 Weeks in the CASTLE Study. AIDS Patient Care STDs 2012; 26: 259-264.

86) Molina JM, Andrade-Villaneuva J, Echevarria J, Chetchotisakd P, Corral J, David N, Moyle G, Mancini M, Percival L, Yang R, Wirtz V, Lataillade M, Absalon J, McGrath D, CASTLE Study Team, et al. Oncedaily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. J Acquir Immune Defic Syndr 2010; 53: 323-332.

87) Fourie J, Flamm J, Rodriguez-French A, Kilby D, Domingo P, Lazzarin A, Ballesteros J, Sosa N, Van De Casteele T, DeMasi R, Spinosa-Guzman S, Lavreys L. Effect of baseline characteristics on the efficacy and safety of once-daily darunavir/ritonavir in HIV-1infected, treatment-naïve ARTEMIS patients at week 96HIV. Clin Trials 2011; 12: 313-312.

88) Macias J, Neukam K, Portilla J, Iribarren J et al. Liver tolerance of raltegravir-containing antiretroviral therapy in HIV-infected patients with chronic hepatitis C. J Antimicrob Chemother 2011; 66: 1346-1350.