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 coinfection 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 telaprevir, 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, Telaprevir, HAART.
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.

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. 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. 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.

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.

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.

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. 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.

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 investigated the influence of coinfection on HIV disease progression in 267 HIV/HCV coinfected patients and 556 HIV monoinfected subjects. Coinfected patients had no 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 0.19 to 2.53], 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 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 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 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.
study 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. 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.

**Does HCV 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 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.

Liver-biopsy studies 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 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 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 co-infection 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. HIV/HCV-coinfected patients with any detectable HCV 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 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. In addition, HCV is not only hepatotropic, but can replicate in PBMCs (peripheral blood mononuclear cells) and in native human macrophages in vitro. 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. 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.

**Antiretroviral Drugs and Liver Fibrosis in Coinfected Patients**

Despite the protective effect of HIV therapy on immune system and liver function, in coinfected patients, HAART-related hepatotoxicity may occur and its frequency depends on type of drugs and regimens. 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 suggested a protective effect of protease inhibitors on fibrosis progression, while others 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. 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 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.

**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. 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. 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. This observation was soon confirmed by others 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 rs1297986049. 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 or telaprevir based therapies, but not in IFNα-experienced patients. 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. 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/mm³. 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. 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/mm³, 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).](image-url)
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 through this pathway. Boceprevir is principally metabolized by the enzyme aldoketo-reductase with a minor contribution from CYP3A4 (Cytochrome P-450 3A4); however, it inhibits CYP3A446. 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 death57,58.

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-related59-65. 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 hepatotoxicity 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 co-infection63-66. 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 treatment67,68, therefore, in patients with CD4 counts > 500 cells/mm3, some clinicians prefer to delay HAART until completion of HCV treatment.

Indeed, clearance of HCV has been associated with a regression of liver fibrosis69,70 and with a reduced risk of antiretroviral-related hepatotoxicity68. 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.

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Co-medication</th>
<th>Boceprevir</th>
<th>Co-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>≈</td>
<td>↑30%</td>
<td>↑8%</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓26% (tid)</td>
<td>↓7% (tid)</td>
<td>↓19%</td>
<td>↑20%</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>↓20%</td>
<td>↑17%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>↓35%</td>
<td>↓40%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>↓32%</td>
<td>↓47%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>↓54%</td>
<td>↑6%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ritonavir (low dose)</td>
<td>↓24%</td>
<td>–</td>
<td>↓19%</td>
<td>–</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>≈</td>
<td>≈</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>R-methadone</td>
<td>≈</td>
<td>↓29%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Midazolam</td>
<td>≈</td>
<td>9-fold</td>
<td>–</td>
<td>↑5-fold</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>≈</td>
<td>≈</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Contraceptives (estrogen/progestogen)</td>
<td>≈</td>
<td>↓28%/↓11%</td>
<td>–</td>
<td>↓24%/↑99%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–</td>
<td>↑8-fold</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>↑62%</td>
<td>↑46%</td>
<td>↑2.3-fold</td>
<td>–</td>
</tr>
</tbody>
</table>
reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) have been independently associated with HAART hepatotoxicity\textsuperscript{60,63-67}.

Hepatotoxicity events are more often idiosyncratic and unpredictable, have a low incidence and drug induced liver injury can be classified as allergic and non allergic\textsuperscript{71,72}.

Nunez et al\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 \( \leq 350 \) 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\textsuperscript{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\textsuperscript{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)\textsuperscript{60,68,79,82,83}.

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\textsuperscript{60,74,78}.

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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 (\( \geq 3 \) 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\textsuperscript{88,79}. 

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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.

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