TREATMENT OF CHRONIC C HEPATITIS IN HIV INFECTED PATIENTS

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INTRODUCTION

Both hepatitis C virus (HCV) and HIV infections are global public health problems. More than 42 million people are estimated to be living with HIV worldwide, while HCV infection is found in 2-3% of the world population (about 175 million).1 Overall nearly 10 million people are co infected with both HIV and HCV.2 (Fig. 1)

Transmission of either HCV or HIV is frequent throughout parenteral exposure to blood and blood products, with HCV being 10 times more infectious than HIV.

The distribution of HCV genotypes in the HIV population reflects the main route of HCV transmission. Genotype 1b accounts for more than two thirds of post-transfusion HCV infections. Genotype 1a and 3a are much more frequent among IV drug users. HIV accelerates HCV liver disease, especially when HIV-associated immunodeficiency progresses.3-4

Hepatitis C virus (HCV) is found in 30% of HIV-positive people. HCV-related liver disease is a leading cause of morbidity and death among HIV-infected people, where classical opportunistic complications of severe immunodeficiency have declined dramatically as a result of the use of potent antiretroviral therapy (HAART = highly active antiretroviral therapy). There is probably a greater risk for accelerated liver disease

Figure 1. Global distribution of hepatitis C virus and HIV infections.
in subjects with HIV/HCV coinfection. HIV/HCV coinfection can result in a higher incidence of HIV drug-related liver toxicity and the mechanisms for this are not precisely understood. Interactions between drugs used to treat HCV and HIV can cause toxicity in unpredictable ways.

MECHANISMS OF ACTION OF RIBAVIRIN AND INTERFERON

Dosing of Ribavirin differs by HCV genotype. Ribavirin treatment duration also depends on genotype: 24 weeks for genotypes 2 and 3 and 48 weeks for genotypes 1 and 4. A viral load that is undetectable six months after stopping therapy is considered a sustained viral response (SVR). For genotype 1, SVR is attained by approximately 47% of those with a high viral load (more than 800,000 IU/ml) and by 65% of those with a lower viral load. For genotypes 2 and 3, the proportion of patients attaining SVR is similar regardless of viral load, approximately 84%.

The mechanism of action for Interferon alfa is complex as it exerts its effect at multiple sites. It augments cellular immunity by:
- Increasing Th 1 immunity;
- Up-regulation of human leukocyte antigen (HLA) class I (A, B, C) and II (DR, DP, DQ);
- Enhancing innate immunity (NK).

TH 1 promotes cytotoxic T-lymphocyte activity against viruses. Interferon-alfa has also anti-proliferative effects.

Ribavirin is a synthetic guanosine analogue, which inhibits IMPDH (inosine-5’-monophosphate dehydrogenase), nucleic acid (RNA and DNA) synthesis, and has activity against some RNA and DNA viruses. It has a weak or inhibitory effect on HCV replication and the way it works in a synergistic manner with interferon-alfa may be an immunomodulatory effect.

There are 21 HCV-specific cytotoxic T lymphocytes (CTL) and nine HCV targets. It seems essential for HCV clearance that liver CTLs simultaneously target multiple HCV proteins, with many CTLs targeting even single peptide epitopes. When there are attacks at many sites, each site needs many different T cells, due to plasticity and the existence of many mutations.

In natural immunity, CD4 T cells determine the strength and type of immune response by secreting cytokines and the TH 1 cytokines stimulate CTLs. In therapeutic immunity, the augmentation of the TH1 response may be an important component of induced HCV clearance.

INTERACTIONS BETWEEN ANTIRETROVIRAL DRUGS AND HCV MEDICATION

Liver complications that may occur with use of nucleosides and nucleotides include the effect of treatment of hepatitis with Lamivudine (3TC) and Tenofovir (TDF) and steatosis and increased liver enzymes with Zidovudine (ZDV). Elevated liver enzymes are not uncommon with the non-nucleoside reverse transcriptase inhibitors (NNRTI). For the protein inhibitors (PI), increase in alanine aminotransferase (ALT) has been documented with Indinavir (IDV), Nelfinavir (NFV), Ritonavir (RTV) and Saquinavir (SQV). An increase in unconjugated bilirubin has also been noted with IDV. Hyperbilirubinemia has been seen with IDV as well as case reports of portal vein thrombosis. Hepatitis has been seen with RTV, IDV, NFV and SQV.

An increased hematological toxicity is seen due to interactions between Interferon/Ribavirin and antiretroviral therapy. Erythropoietin helps patients with anemia maintain the ribavirin dose, with better quality of life and better safety. For patients with neutropenia, it is unknown at what level to introduce granulocyte-colony stimulating factor (GCSF).

Patients on nucleoside reverse transcriptase inhibitors (NRTI) and Ribavirin have an increased risk of mitochondrial toxicities (MT), pancreatitis or lactate above 7.4 mmol. Patients with HIV/HCV co-infection should avoid Didanosine (ddI), since Ribavirin can enhance the intracellular concentrations of phosphorilated Didanosine (ddI) metabolites and result in a higher risk of toxicity. Several cases of pancreatitis and/or lactic acidosis have been reported when Ribavirin is given together with ddI. Most recently, cases of hepatic decompensation have been reported in subjects receiving Ribavirin with ddI.

For the next five years, interferon-based therapy is expected to remain the mainstay of HCV treatment. Lower doses of Interferon/Ribavirin might be achieved with newer combinations, which may benefit HIV co-infected patients by increasing effectiveness.

HEPATOTOXICITY AND HAART

The liver is the conduit for biotransformation of almost all drugs. The phase 1 oxidative reactions of CYP450 have the potential to create harmful metabolites, while the phase 2 conjugation reactions may protect the liver from active metabolites. Deficiencies in glutathione conjugations can
contribute to drug-induced liver disease. This may be predictable or unpredictable. These reactions are dose-dependent and host-independent, occur with high incidence and have early onset. Unpredictable drug reactions are host-dependent, have a low incidence and are not dose-related. The majority of drug reactions in HIV patients are unpredictable: here the drug metabolite affects immunologic response as well as exerting direct toxicity.

Host-mediated hypersensitivity reaction is one type of unpredictable side effect. Symptoms include fever and rash; eosinophilia is also possible. There are two hypotheses pertaining to mechanisms of hypersensitivity reactions. The Hapten hypothesis asserts that reactive metabolites covalently bind to a macro-molecule. This is perceived as a neoantigen, which stimulates both arms of the immune system, leading to hepatic sensitization. The “danger hypothesis” adds to the understanding: it asserts that the right environment is necessary for the reaction. The immune response to the perceived neoantigen only occurs if the “danger signal” is seen.

Host-mediated “idiosyncratic” metabolism accounts for the vast majority of reactions. These host differences in drug metabolism may lead to an excess of reactive drug metabolites or perhaps deficiencies of certain enzymes that are necessary to break down the drug.

Nucleoside reverse transcriptase inhibitors (NRTI) have been associated with mitochondrial function (MT). Impaired mitochondrial function can lead to a decrease in free fatty acid oxidation. Free fatty acids accumulate and are metabolized to triglycerides, leading to hepatic steatosis. There are two patterns of steatosis:

- Macro-vesicular steatosis: hepatocytes contain a single large vacuole of fat, which fills up the cell, pushing the nucleus to the periphery;
- Micro-vesicular steatosis, where hepatocytes are filled with numerous small lipid vesicles which leave the nucleus in the center of the cell.

Short and long-term success of HAART in HIV/HCV – co-infected patients is limited by an increased risk of hepatotoxicity. Multiple studies have demonstrated that underlying hepatitis C is an independent predictor of liver enzyme elevations after initiating HAART.

**STAGING OF CHRONIC HEPATITIS C IN HIV/HCV CO-INFECTION**

The time interval between HCV acquisition and development of liver cirrhosis is significantly shortened in co-infected patients. On average and within 10-15 years of initial HVC infection, 15-25% of HCV/HIV co-infected patients develop liver cirrhosis.9 (Fig. 2)

![Figure 2. Liver fibrosis according to age in HCV/HIV coinfected patients.](image)

Recent evidence suggests that the immune restoration that follows the use of antiretroviral therapy might reverse the unfavorable course of hepatitis C in co-infected patients. The data available suggest that HAART has a favorable impact on the future course of hepatitis C in co-infected patients.10-12

**HIV CANDIDATES FOR HCV THERAPY**

All HIV-infected patients should be screened for HCV antibodies; in cases of negative HCV-antibodies, but positive HCV-RNA, the cause mainly is due to severe cellular immune suppression.13-15 All patients with repeatedly elevated aminotransferase levels should be tested for HCV load and HCV genotype. Since the response to HCV therapy is dependent on the CD4 count, this should be prescribed only when the CD4 count exceeds 350 cells/µL. In subjects with CD4 count between 200-350 cells/µL and already under long-term antiretroviral therapy, the decision to treat HCV might be considered taking into account the severity of liver disease, the extent of suppression of HIV replication, the HCV genotype and viral load.16,17

Therapy should be deferred in patients with less than 200 CD4 T-cells/µL, since the response rate is very low in these patients.18,19

Patients with liver decompensation (ascites, gastrointestinal bleeding, and hepatic encephalopathy) should not be treated, given the higher risks of serious side effects of Peginterferon/Ribavirin. However, patients with compensated cirrhosis (Child-Pugh class A) must be treated, since they will benefit the most from HCV clearance.

Following 2002 NIH Consensus Conference recommendations, patients with normal liver enzymes might benefit from HCV therapy, particularly those infected with genotypes 2 or 3. In drug naïve individuals
with HCV/HIV co-infection, HCV should be treated first, if the CD4 count is greater than 350 cell/µL.\textsuperscript{20,21}

**TREATMENT RESULTS IN HCV/HIV CO-INFECTED PATIENTS**

The combination of Peginterferon α2a and Ribavirin is effective and well tolerated in patients with HCV/HIV co-infection. A standard dose of Peginterferon α2a of 180 mcg/week plus Ribavirin 1000 mg/day produce higher virological response rates at the end of treatment than the combination of Peginterferon α2a plus Ribavirin 800 mg/day (43% vs. 29%).\textsuperscript{22,23} In patients infected with genotype 1, the overall end-of-treatment virological response rate was 33%; in those harboring HCV genotypes 2 or 3, the overall end-of-treatment virological response rate was 50%.\textsuperscript{24} (Fig. 3)

![Figure 3. HCV/HIV co-infection- virological response at week 24 and 48.](image)

The reasons why anti-HCV therapy provides a poorer response in HIV-infected patients are numerous:\textsuperscript{25,26}
- Use of lower-than-optimal doses of Ribavirin;
- Less activity of anti-HCV therapy in the setting of HIV-related immune dysfunction;
- More advanced liver fibrosis stage;
- Higher rate of steatosis (alcohol, nucleoside analogs);
- Unfavorable HCV virological features (high HCV-RNA titers);
- Lower initial HCV-RNA clearance;
- More frequent relapses after treatment discontinuation;
- Higher rate of treatment withdrawals due to side effects;
- Lower drug compliance.

**MONITORING THE THERAPY**

Kinetic studies suggest that HCV clearance after beginning therapy with Peginterferon plus Ribavirin may be delayed in the setting of HIV infection.\textsuperscript{27} (Fig. 4)

Patients with high HCV loads may show a good early virological response, but may not reach undetectable viral load at week 24, despite which they will clear HCV much later.\textsuperscript{28} (Fig. 4a) There is a second phase of clearance of HCV-RNA in patients on prolonged HCV therapy that accounts for the steadily destruction of infected hepatocytes. (Fig. 4b) A slower decay in HCV-RNA could explain why early discontinuation of therapy might result in higher relapse rate.\textsuperscript{29,30}

![Figure 4. Hepatitis C virus kinetics under interferon therapy and influence of HIV infection. a). early phase; b). second phase.](image)

**CONCLUSIONS**

The use of Peginterferon plus Ribavirin improves the rate of SVR in HIV infected patients with chronic hepatitis C and therefore should be considered the best treatment choice.\textsuperscript{31,32}

**REFERENCES**


