



# Final Report

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## Executive Summary

In March 2007, a group of community activists, many living with HIV and hepatitis C virus (HCV), gathered with researchers, doctors, regulators, and representatives from Abbott, Roche, Schering, and Tibotec, in Sitges, Spain, at a meeting held by the European AIDS Treatment Group (EATG) and the Grupo de Trabajo sobre Tratamientos del VIH (gTt).

The meeting was held to address a critical issue: the clinical development of novel HCV therapies for HIV/HCV coinfecting people, who have urgent need for new treatments.

Hepatitis C is highly prevalent, progresses more rapidly, and causes significant morbidity and mortality among HIV-positive people. In Western Europe, an estimated 500,000 people are HIV-positive; 30% are coinfecting with hepatitis C. In the United States, more than a million people are living with HIV, and 25-30% (250,000 to 300,000) also have hepatitis C.

HCV-associated end-stage liver disease is a now a leading cause of death among HIV-positive people in Europe and the United States. HIV accelerates hepatitis C progression; coinfecting people may develop serious liver damage within a decade. The risk for cirrhosis is twice as great, and the risk for liver failure is six times greater for coinfecting people vs. those with HCV mono-infection. Although some centers in Europe and the United States are performing liver transplants in HIV-positive candidates, medical management of transplant recipients is complex, and access to transplantation remains limited.

HCV is treatable, regardless of HIV status, but there are serious limitations to the current standard of care. Coinfecting people are less likely to respond to treatment, and more likely to experience severe, potentially treatment-limiting side effects than their HCV mono-infected counterparts.

Several promising HCV therapies are currently in the pipeline; some have already entered phase III. HIV/HCV coinfecting people are excluded from participation in these studies. Companies often cite safety issues – such as uncharacterized pharmacokinetic profiles, and potential drug-drug interactions – as the rationale for excluding HIV-positive people. HCV treatment trials in coinfecting people are launched only after agents have been approved for HCV mono-infection.

Currently, there is no regulatory requirement or recommendation for studying novel HCV therapies in HIV-positive people prior to their approval for treatment of HCV mono-infection, but guidelines may be coming soon.

Since the Sitges Meeting, the European Agency for the Evaluation of Medicinal Products (EMA) has begun work on draft guidelines on HCV drug development. In the United States, a dialogue between industry, regulators, clinicians, researchers and community members began in October 2006, when the Food and Drug Administration (FDA) Antiviral Advisory Committee met to address development of products for the treatment of hepatitis C infection. The agency has not yet released their recommendations.

The Sitges meeting was a unique opportunity for stakeholders to discuss how coinfecting people will gain access to experimental HCV therapies through well-designed clinical trials.

The *Sitges Statement* was created at the end of the meeting, when all participants were asked to state their primary concerns about HCV drug development, trial designs, and access for coinfecting people. A draft was circulated to all participants for comments; these were incorporated and then a final document, as follows, was approved by the signatories. Signatories and their affiliations are listed at the end of the *Statement*.

The meeting was co-planned by Joan Tallada, Coordinator of Grupo de Trabajo sobre Tratamientos del VIH (GTT) and Tracy Swan, Coinfection Project Director at Treatment Action Group (TAG). We thank the staff of both GTT and the EATG, the speakers and the participants for their great contribution to the success of this meeting.

## SITGES STATEMENT

*Community activists, doctors, researchers, company representatives and members of regulatory agencies, concerned about the life expectancy and the quality of life of people living with HIV and HCV, hereby declare that:*

Collaboration between the community, regulatory agencies and industry is a crucial part of the HCV drug development process. The community is an important stakeholder, and must be given the opportunity to provide input into HCV drug development. We want to participate in:

### The development of regulatory guidance for HCV drug development

- We believe that regulators with experience in HIV drug development and treatment need to be involved in the development of regulatory guidance for new HCV drugs.

### The development of industry-sponsored clinical trials

- We ask to meet regularly with sponsors of novel HCV therapies, and to participate in designing clinical trials, and oversight of these trials via Data Monitoring and Safety Boards (DSMBs) of these trials.

### The development of research networks

- We support building additional research networks, public-private partnerships, investigator-initiated studies and registries of data from multi-center collaborations to bring HCV therapies forward quickly and explore new therapeutic paradigms before and after their approval.
- We encourage creating networks of investigators with expertise in treating HCV coinfection to study novel HCV therapies in coinfecting people.

We believe that the health care needs of different populations and the patient perspective must be considered part of the HCV drug development process. Studies should include people with the most urgent need for new HCV therapies.

Trials of novel HCV therapies in HIV/HCV coinfecting people should begin before approval is granted for their use in HCV mono-infection, once results from Phase 2B studies are known, and there are indications from earlier toxicology, pharmacokinetic and drug-drug interaction studies that the specific agent, or agents, under investigation will not have the potential for significant drug-drug interactions, or other toxicities relevant to HIV.

It is clear that combination therapy will be necessary to avoid HCV drug resistance. We need to consider the most expeditious methods for co-developing drugs; this may depend on the outcome of early monotherapy studies of each agent. Since safety is paramount, we believe that *in vitro* and *in vivo* drug interaction studies must be conducted early, to facilitate pre-approval multi-agent trials and studies in persons likely to be using other medication, such as coinfecting persons, and transplant recipients.

We support trials that look at methods to delay, or reverse fibrosis progression as well as trials to eradicate HCV. It is important that trials in different populations consider different outcomes for different patient populations (SVR vs. histological improvement or averting/delaying transplantation). We also support investigation into alternative and complementary therapies for HCV.

We ask that all possibilities are explored for conducting pre-approval studies of HCV therapies in the highest -prevalence population, people who use drugs. We encourage studies in people using methadone, buprenorphine, naltrexone and heroin substitution prior to approval.

In addition, we ask that sponsors design studies that:

- Enroll sufficient numbers of women to yield information on potential gender-specific side effects of new HCV treatments,
- Include TDM in studies of persons with advanced liver disease
- Accelerate pediatric research

When possible, trials should include:

- Characterization of resistance
- Non-invasive assessments of liver damage, to see if they can be validated as an alternative to biopsy
- Assay standardization

Research to optimize the current standard of care must continue. Studies on management of side effects and models of care, especially those that will continue to explore the use of multidisciplinary care, are a priority. Interferon will still be part of HCV treatment for the next few years, but it may be possible to find a less toxic alternative to ribavirin.

We have seen high rates of liver-related mortality in the last few years. Since it will take time for new drugs to become available, we must raise awareness of the need for donor organs, promote policies to increase organ donation, and remove obstacles to transplantation for HIV-positive and coinfecting people. Organ transplantation, and access to the highest-quality care and treatment, must be provided to HIV-positive and coinfecting people throughout Europe.

Massimo	Puoti	Università di Brescia, Italy
Raymond	Schinazi	Emory University, USA
Bruce	Polsky	St. Luke's-Roosevelt Hospital Center, USA
Tracy	Swan	TAG, USA
Wim	Vandevelde	BoD EATG, Portugal
Carmen	Tarrades	Int. Com. of Women LWHIA HIV/AIDS, UK
Miguel	De Melo	TRT-5, France
Jose Maria	Miro Meda	Hospital Clínic Universitari, Spain
Diego	García Morcillo	FEAT, Spain
Joan	Tallada	gTt / EATG, Spain
David	Ananiashvili	Georgian Plus Group, EATG, Geórgia
Stephan	Dressler	EATG / ECAB, Germany
Svilen	Konov	HIV i-Base, UK.
Luis	Mendao	GAT/EATG, Portugal
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Olle	Karlström	EMEA, Sweeden
Fernando	De Andrés	AEMPS/EMEA, Spain
Laura	Knipmeyer	Schering-Plough, USA
Clifford	Brass	Schering-Plough, USA
Frank	Duff	Roche, USA



Hotel Mediterráneo, Sitges, Barcelona, Spain

Program and Summary of Key Points  
(complete presentations are available on line at [www.eatg.org](http://www.eatg.org))

Wednesday, March 7<sup>th</sup>, 2007

Arrival

15:00 - Accreditation

16:00 - Community Pre-meeting

Training session: "The basics of drug development - the case for HCV"

*Overview of drug development*

*Svilen Konov (London, UK) and Tracy Swan (NYC. USA)*

KEY POINTS:

During the pre-meeting, Konov and Swan provided an overview of what happens in Phase I, Phase II, Phase III and post-marketing studies, and discussed the importance of well-designed studies, and the consequences of poorly-designed studies, using prior and ongoing HCV treatment trials as examples.

Thursday, March 8<sup>th</sup>, 2007.

09:00 - Opening remarks : Program: Overview

*Tracy Swan & Joan Tallada, Project Co-Leaders.*

**This meeting marks the beginning of a discussion between drug companies, regulatory agencies, doctors and community members about new HCV drugs, and how they will ultimately be studied, and used in co-infected people.**

09:15 - Epidemiology and Natural history of HIV/HCV co-infection

*Miguel de Melo, TRT-5, Paris, France.*

KEY POINTS:

- Globally, 130 to 180 million people have been infected with hepatitis C, and 3 to 4 million people become infected with HCV each year;
- 4-5 million people are HIV/HCV coinfecting;
- Over decades, chronic HCV infection leads to cirrhosis, liver cancer and liver failure in 20-30% of cases;
- HIV accelerates HCV progression, and a greater proportion of coinfecting people will develop serious liver damage;
- HCV treatment has significant limitations, particularly for coinfecting people, in whom it is less effective, and more difficult to tolerate;
- In the HAART era, HCV-associated end-stage liver disease (ESLD) has become a leading cause of death among HIV-positive people in Western Europe and the United States;

10:00 - Natural history of Liver Disease in HCV-HIV co-infected patients: end-stage and post-transplantation

*José M. Miró, Hospital Clínic-IDIBAPS, Univ. of Barcelona. Barcelona, Spain.*

#### KEY POINTS:

- Liver transplantation is no longer contraindicated for HIV-positive patients;
- HIV shortens survival of HCV/HBV coinfecting transplant candidates (vs. those with HBV and HCV alone);
- In Spain, 88 HIV-positive people have had liver transplants [at the time of the presentation];
- Serious interactions between immunosuppressive drugs and antiretroviral agents complicate care after transplantation, but HIV can be managed successfully;
- After liver transplantation, three-year survival rates are similar, regardless of HIV status;
- HCV is almost universally recurrent after liver transplantation;
- In HIV-positive transplant recipients, mortality is mainly due to recurring HCV infection-not HIV-related;
- Recurrent HCV is more aggressive and more difficult to treat among HIV-positive transplant recipients, vs. those with HCV alone;
- More effective and less toxic HCV treatments are needed, especially for coinfecting transplant candidates and recipients.

## 11:15 – Overview of drug development: regulatory agencies

FDA HCV trial design meeting: a report  
*Tracy Swan, Treatment Action Group, NYC, USA.*

### KEY POINTS:

- Many novel HCV therapies are in development,
- Currently, there are no guidelines or recommendations from regulators on how to best study them;
- The FDA Antiviral Drug Advisory Committee met October of 2006, to discuss development of products to treat HCV;
- Topics included clinical trial design and key populations to study;
- FDA asked the committee if they wanted ongoing or completed pilot studies in certain populations, in addition to data from registration trials, at the time of approval;
- In regard to studies in HIV-positive patients, the Committee recommended that: “...prior to initial approval, efforts should be made to initiate early-phase studies; major drug interactions and pharmacokinetics...” ...At least early efficacy trials – pilot trials – are probably indicated to give some sense that patients can be treated both safely and with some degree of efficacy.”

EMEA perspective  
*Olle Karlstrom, Stockholm, Sweden.*

### KEY POINTS:

- At present, there are no specific guidelines for the development of anti-HCV agents;
- Currently, there is no regulatory advice on inclusion of HIV/HCV coinfecting people in trials of experimental HCV drugs;
- We can learn from HIV drug development, especially in regard to the need for combination therapy to avoid resistance;
- Experimental HCV drugs can be studied safely in coinfecting people, provided that activity against HIV is assessed, and proper drug-drug interaction studies are performed early in development;
- Conducting large trials of novel HCV drugs in coinfecting patients is challenging; prevalence and eligibility criteria must be considered;

- It is clear that regulatory guidelines for HCV drug development are needed; these should include guidance on populations to be studied, (including HIV-positive patients), as well as types of studies to be performed.

Spanish Agency of Drug and Health Products  
*Fernando de Andrés, Madrid, Spain.*

#### KEY POINTS:

- In the European Union (EU), access to registered medications is not always uniform, since member states decide on inclusion and pricing;
- Registration and reimbursement issues are complex;
- Approval may be conditional;
- Additional access may be possible via participation in clinical trials, and compassionate or off-label use;
- There are incentives for companies to continue developing products for public health needs.

12:30 – General discussion

#### **13:00 – Lunch**

15:00 – HCV: The Path of Least Resistance in Drug Development

*Raymond Schinazi, Emory University / Veteran Affairs Department, Atlanta, Georgia, USA*

Summary of Key Points:

#### KEY POINTS:

- Drug development is a complex, time-and-labour intensive endeavour; only 1 of 10,000 compounds makes it to market;
- HIV drug development has been fruitful; there are now 22 drugs available, which is a remarkable achievement;
- The development of a replicon system in 1999 was a major advance in HCV drug development, because researchers can use it to discover and develop anti-HCV compounds;
- Although there has been some progress in treating HCV – from interferon monotherapy to PEG-IFN and RBV – we need more tolerable and effective treatments;
- HCV drug development is challenging: there are issues with resistance, toxicity and sustained virological response;
- Investigators have identified targets for HCV-specific antiviral agents, and many are in development;

- We can anticipate significant progress over the next decade, when we may be able to construct interferon-free or ribavirin-free regimens with combinations of oral drugs.

**16:00 - Coffee Break**

16:30 -Early access to HCV drugs: interactions, safety, efficacy  
*Bruce Polsky, St. Luke's Hospital, NYC, USA.*

**KEY POINTS:**

- New drugs need to be studied in people who are coinfectd with HCV and HIV;
- There are multiple targets for HCV drugs, including preventing infection and preventing viral replication;
- Many different compounds are in pre-clinical and clinical development;
- Resistance testing will be required;
- Adherence will become crucial; novel therapies may require adherence rates of >95%.

17:30 - Roundtable  
*Dr. Schinazi and Dr. Polsky take questions*

**18:30 - Finish**

**Friday, March 9<sup>th</sup>, 2007.**

09:00 – Limitations of current HCV Treatment in Coinfected Population: overviews from the experience.

*Bruce Polsky, St. Luke's Hospital, New York, New York, USA*

KEY POINTS:

- HCV coinfection is a serious and prevalent co-morbidity among HIV-positive patients;
- HCV is difficult to treat in HIV-positive patients, due to drug-drug interactions, side effects and toxicities of PEG-IFN and ribavirin;
- There are significant barriers to HCV care and treatment for coinfecting people;
- Multidisciplinary care, which includes mental health and addiction treatment, is often necessary to successfully treat HCV;
- Treatment strategies for coinfecting patients, such as which virus to treat first, are addressed in treatment guidelines;
- There is no definitive treatment strategy for non-responders.

*Massimo Puoti, Università degli Studi di Brescia, Italy.*

Key Points

- There are significant limitations to the current standard of care for HCV, especially for HIV-positive patients
- Coinfecting patients are often ineligible for HCV treatment, in clinical trials and clinical practice;
- Medical contraindications and patient refusal are common;
- Doctors also set eligibility limits for HCV treatment;
- Data from clinical trials of HCV treatment is difficult to interpret, because of different formulations, regimens and patient populations;
- Doctors need experience in side effects management to help keep trial participants and patients on HCV treatment;
- The current standard of care is suboptimal for patients with genotype 1 and/or a high baseline HCV RNA;
- We need more effective, less toxic treatments.

*Carmen Tarrades, UK-CAB, UK.*

KEY POINTS:

- Deciding whether or not to treat HCV is a complex and personal decision
- Medical, psychosocial, and financial considerations are important factors;
- An individual treatment decision may balance what is known about treatment response, prognosis and side effects versus the unknowns involved with future treatment options
- Information from well-designed trials in all populations, is needed to inform treatment decisions
- Gender-specific questions need to be addressed
- Support is crucial
- HCV treatment decisions are best made with as much information as possible.

*Diego García-Morcillo, FEAT, Spain.*

KEY POINTS:

- HCV treatment decisions are difficult for many reasons:
  - Information about HCV treatment and clinical trials is often given in medical language, which most people do not understand;
  - Doctor's prejudice against current and former IDUs;
  - Inaccurate, second-or third-hand information about treatment;
  - Lack of access to proper counselling; and,
  - Fear, from both the doctor and the patient;
- Making an HCV treatment decision, and undergoing HCV treatment are easier when people feel empowered, have housing, and social, emotional and financial support, and a good relationship with their doctor;
- Can you wait for new treatments, and are you aware of your options for access to new therapies, such as expanded access programs and clinical trials?
- Treating hepatitis C is a personal decision, is it the right time in your life?

- Weighing pros and cons, and your present emotional situation will make it easier to stick to a decision;
- Whatever your decision may be, remember, it is yours;
- There are no universal recipes for successful HCV treatment;
- Adequate support, help and love will make everything easier;
- But more effective, less toxic drugs will make HCV treatment easier and more successful!
- We need more clinical trials, to validate non-invasive testing for staging liver damage, to identify new strategies, such as simplification of HIV treatment during HCV therapy, and to improve management of side effects.

#### **10:45 - Coffee break**

11:00 - Who and when should be treated with new HCV drugs - Stakeholders' perspective

- *Representatives from drug companies:*

*Dr. Barry Bernstein (Abbott), Drs. Clifford Brass and Laura Knipmeyer (Schering-Plough), Dr. Frank Duff (Roche), and Dr. Eric Pelkmans (Tibotec)*

- *Drs. Schinazi, Polsky, and Puoti.*

- *Regulatory agency representatives: Olle Karlström (EMA) and Fernando De Andrés (AEMPS).*

- *Activists.*

#### **13:00 - Lunch**

15:00 - Towards a research agenda

*Tracy Swan & Joan Tallada, Project Co-leaders.*

16:30 - Closing remarks

#### **17:00 - Finish**

## **Presentation Full Reports**

### **Epidemiology and natural history of HIV/HCV co-infection**

**Miguel de Melo, TRT-5, Paris, France.**

The liver is a vital organ, responsible for:

- filtering chemicals (including drugs) and waste from the blood;
- storing vitamins, minerals, and iron;
- converting nutrients from food into energy;
- helping to balance levels of sugar and hormones;
- producing cholesterol;
- making bile and other enzymes necessary for digestion; and,
- creating the hormone that helps to produce platelets (to stop bleeding).

#### **What is hepatitis?**

Hepatitis simply means “inflamed liver”. Liver inflammation can be caused by many things, such as viruses, parasites, bacteria, chemicals, auto-immunity, drugs or alcohol.

There are five known types of viral hepatitis: A, B, C, D and E, each named alphabetically, in the order of their discovery. Hepatitis B and C can become chronic.

#### **What is hepatitis C?**

Hepatitis C is a bloodborne virus that enters the bloodstream and infects liver cells. There is no vaccine to prevent HCV infection, but some people will spontaneously clear their HCV infection (without treatment), usually during the acute phase (within a few weeks to six months of becoming infected). Spontaneous viral clearance is more likely to occur among HIV-negative people, women, people who have symptoms during acute HCV (such as fever, appetite loss, fatigue and jaundice), and younger people.

Hepatitis C becomes chronic in 55-85% of cases. Chronically infected people do not always develop serious liver damage. Overall, 20-30% of all people with chronic HCV will develop cirrhosis, usually decades after they were infected. People with cirrhosis are at risk for liver cancer and liver failure (when a transplant becomes necessary).

#### **HIV and hepatitis C**

Hepatitis C is more likely to become chronic, and progresses more rapidly in HIV-positive people. The risk for cirrhosis is doubled, and the risk for liver failure is six times greater for coinfecting people vs. those with HCV mono-infection. In Europe and the United States, end-stage liver disease from HCV coinfection is a leading cause of death among HIV-positive people.

HCV can be treated, regardless of a person’s HIV status, but HCV treatment is less effective for coinfecting people vs. those with HCV alone (see Table 1, Sustained Virological Response Rates from HCV Treatment Trials by Genotype and HIV Status).

Side effects of HCV treatment are debilitating for coinfecting people, as reflected in high drop out rates from clinical trials (up to 39%).

**Table 1. Sustained Virological Response Rates from HCV Treatment Trials, by Genotype and HIV Status (PEG-IFN plus ribavirin)**

	SVR, Overall	SVR, Genotype 1	SVR, Genotype 2 and 3
<b>HIV/HCV coinfecting</b>	27% -- 44%	14% -- 38%	53% -- 73%
<b>HCV monoinfected</b>	56% -- 61%	42% -- 44%	70% -- 82%

**Sources:**

Carrat F ,Bani-Sadr F ,Pol S, et al; ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004 Dec 15;292(23):2839-48.

Chung RT, Andersen J, Volberding P, et al. AIDS Clinical Trials Group A5071 Study Team. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfecting persons. N Engl J Med. 2004 Jul 29;351(5):451-9.

Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.

Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS. 2004 Sep ;18(13):F27- 36.

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001 Sep 22;358(9286):958-65.

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. APRICOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004 Jul 29;351(5):438-50.

HAART may delay HCV progression by maintaining immune health, but hepatitis C coinfection can complicate HIV treatment. Coinfecting people are at greater risk for antiretroviral-associated hepatotoxicity, and more likely to discontinue one or all of their HIV drugs for toxicity than people with HIV alone. Some drugs are less liver-friendly, than others, so antiretroviral agents for coinfecting people should be selected carefully, and liver enzyme levels should be monitored regularly. Choosing an HIV treatment regimen is particularly important for people who will also be on HCV treatment, to avoid potentially life-threatening drug interactions.

**HCV monoinfection**

*Globally:*

Approximately 180 million people have been infected with HCV

In Western Europe, approximately nine million have been infected with HCV

**HIV/HCV Coinfection**

*Globally:*

4 to 5 million persons are HIV/HCV coinfecting

- In Western Europe, approximately 30% of all HIV-positive people are coinfecting with HCV (150,000)

- In the United States 25-30% of all HIV-positive people are coinfecting with HCV (250,000-300,000)

**Table 2. Prevalence of HCV Coinfection in the EuroSIDA Cohort, by Region**

EuroSIDA Cohort	4,957	<b>Overall: 34%</b> ● Eastern Europe: 47.7% (412/864) ● Southern Europe: 44.9% (623/1,387) ● Northern Europe: 24.5% (346/1,410) ● Central Europe: 22.9% (280/1,221) ● IDU: 78%
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**Sources:**

Rockstroh J, Mocroft A, Soriano V, et al. (abstract 64) Influence of hepatitis C coinfection on HIV disease progression within the EuroSIDA Cohort. 9<sup>th</sup> European AIDS Conference (EACS), Warsaw, Poland. 2003.

Rockstroh JK, Mocroft A, Soriano V, et al; EuroSIDA Study Group. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis. 2005 Sep 15;192(6):992-1002.

**Factors associated with fibrosis progression**

HIV coinfection accelerates hepatitis C progression, as does:

- Older age at infection (>40 years of age), and/or longer duration of infection;
- Hepatitis B coinfection;
- Alcohol consumption of ≥50 grams/day for men, and possibly ≥30 grams/day for women;
- Hepatic steatosis (fat deposits in the liver), related to obesity, diabetes, and HCV genotype 3 ;
- Being male.

**KEY POINTS:**

- HCV complicates HIV treatment by increasing the risk for antiretroviral-associated liver toxicity;
- Coinfected people are more likely to discontinue antiretroviral treatment than people with HIV alone
- HIV coinfection doubles the risk of cirrhosis, and the risk for liver failure is six times greater among coinfecting people with cirrhosis;
- Coinfected people with <200 CD4 cells/mm<sup>3</sup> are most likely to progress to severe liver disease;
- Coinfected people have higher HCV RNA levels than HCV monoinfected people, resulting in poorer treatment outcomes.

**Why is HCV treatment is less effective for coinfecting people?**

- Use of low-dose ribavirin (RBV); due to concerns about anaemia, an 800 mg/day dose was given in coinfection treatment trials, and

clinical practice (weight-based RBV dosing is associated with better treatment outcomes);

- HIV-related immunodeficiency;
- More advanced fibrosis, due to later diagnosis and accelerated fibrosis progression;
- Higher rate of insulin resistance and liver steatosis;
- High baseline HCV viral load;
- Lower adherence rates, and higher discontinuation rates due to side effects;
- Possible reduction of RBV efficacy, due to uncharacterized interactions with antiretroviral agents;
- Lower initial HCV-RNA clearance during HCV treatment;
- Higher relapse rates after completion of treatment.

## Natural history of Liver Disease in HCV-HIV co-infected patients: end-stage and post-transplantation

Dr. Josep Maria Miró  
Hospital Clínic, Barcelona, Spain

Before the HAART era, HIV-positive patients died from complications of AIDS before they developed any liver disease. HAART has improved the prognosis, and we can treat coinfecting people for hepatitis C, but results have not been very good. HCV treatment works for only a third of coinfecting patients. We need new drugs to prevent coinfecting people from developing cirrhosis, and to avert liver transplantation.

In Spain, 55% of HIV patients are co-infected (about 77,000 people). An estimated 10% (7,700) have cirrhosis and 17% of them are potential transplant candidates.

HIV shortens survival after the first hepatic decompensation. The median survival of HIV-infected patients with a model for end-stage liver disease (MELD) score of above 20 is less than six months; this needs to be considered when allocating organs.

In Spain, transplant specialists have reached consensus: HIV is not a contraindication for any type of solid organ transplant (SOT). In addition to hepatic and immunological criteria (CD4 cell count of >100), HIV-positive candidates must be able to construct an effective HAART regimen after transplantation.

So far, 88 HIV-positive people have undergone orthotopic liver transplantation (OLT). Their three-year survival rate is 66%, which is very similar to mono-infected transplant recipients. Their HIV parameters (CD4 cell count and viral load) have remained stable, but 40% had to change their HIV regimen due to drug toxicity or interactions between antiretroviral agents (especially HIV protease inhibitors) and immunosuppressants. Members of the care team must communicate often to avoid these interactions, which may cause sudden organ rejection or death.

HCV almost always recurs after transplantation. Severe, recurrent HCV – which is difficult to treat – is the major cause of death among HIV-positive transplant recipients. Studies evaluating safety and efficacy of HCV treatment in coinfecting transplant recipients report an SVR rate of around 20%, which is lower than transplant recipients with HCV monoinfection.

### KEY POINTS:

- HIV significantly shortens survival of transplant candidates coinfecting with HBV and/or HCV;
- HIV is associated with a significant increase in mortality during the wait for transplantation;
- Three-year survival rates after liver transplantation do not differ significantly by HIV status;

- Recurring HCV infection is the major cause of death among coinfecting transplant recipients;
- The rates of SVR in HCV/HIV coinfecting patients treated with pegylated interferon (PEG-INF) plus RBV in Spain after OLT were high (>50%) for genotypes 2/4 and low (<20%) for genotypes 1/4;
- HCV/HIV co-infected transplant recipients who achieve SVR have a better long-term prognosis;
- New strategies and new drugs are necessary to improve the outcome of HCV recurrence in OLT in coinfecting patients

**Areas and Goals for Future Research:**

- Create an International/European registry of SOT in HIV-infected patients;
- Learn about long-term survival (5-10 years);
- Improve the management of pharmacokinetic (PK) and pharmacodynamic (PD) interactions between immunosuppressive, antiretroviral and anti-HCV drugs;
- Reduce the rates of acute rejection;
- Improve management and treatment of recurrent HCV in transplant recipients.

## **Overview of drug development: regulatory agencies**

*Tracy Swan, TAG, AIDS Treatment Activists Coalition (ATAC)*

What is the best way for regulatory agencies to coordinate their work?

*Barry Bernstein, Abbott Pharmaceuticals*

We need collaboration between companies, also with regulatory agencies.

*Joan Tallada, GTt, EATG*

In HIV, we have always heard that regulatory agencies slow down the development process. But I think that we have to find a balance, and know when we have to go slowly – some of the information is crucial.

*Clifford Brass, Schering-Plough*

I think that clear guidelines can be useful to plan the trials, but actually they could slow down the process. For example, FDA will slow down the things because, even if we have a potent treatment for 12 weeks, FDA will demand to administrate it in 48 weeks.

*Tracy Swan*

Slowing down the process will not benefit anyone. Maybe we need to front-load drug development by investing more in clinical development vs. post-marketing studies. It's a question of when the money is spent rather than doing things less quickly or efficiently.

## **The FDA perspective**

*Tracy Swan. TAG, New York City, USA*

## **HCV Treatment: What's happening?**

The hepatitis C pipeline is full; agents that specifically target HCV are in clinical trials.

## **Regulatory Issues**

The FDA held a meeting of its Antiviral Drug Advisory Committee in October of 2006, to discuss HCV drug development, such as designs for clinical trials, key populations to be studied, and other issues related to the development of products to treat hepatitis C.

## **Populations**

- HIV and HBV coinfecting people
- People w/ advanced liver damage
- Transplant candidates & recipients
- Pediatric
- TX naïve
- Relapsers & non-responders
- African Americans

## **Trial Design Issues**

- Endpoints
- Study designs/ multi agent trials
- Use of controls
- Duration of follow up

Three issues (multi-agent trials and inclusion of HIV-positive people, and individuals with decompensated cirrhosis) are particularly relevant to the HIV community. People with decompensated cirrhosis have the most urgent need for access to novel HCV therapies, yet they are the highest-risk population in terms of safety. Allowing people with such advanced liver disease to gain access to potentially lifesaving therapies in the context of a clinical trial is crucial.

Since many coinfecting people are likely to be on antiretroviral therapy, it is important that drug-drug interaction studies be conducted early in the development process so that pilot safety and efficacy studies can be conducted in HIV-positive people prior to approval.

It is apparent that multi-agent therapy will be necessary, to avoid the development of resistance to HCV protease and polymerase inhibitors. Conducting multi-agent trials may involve different sponsors, so cooperation is of utmost importance for designing registration trials that may identify HCV treatment strategies.

### **FDA Perspective on Inclusion**

FDA: "...To write a label we need to have a representative population. So, it is important that a good sampling of the patients who will receive the drug be part of registration trials".

**A Key Question:** Can FDA *require* data from pilot studies --not just large registration trials-- **before** granting approval?

Dr. Birnkrant (Director of FDA's Division of Antiviral Products) to the Committee:

"...At the time of marketing application, *in addition to the Phase III studies*, please tell us whether you would like to see these patients completing a pilot study, or would you like to have the studies just ongoing at the time of approval".

### **The Committee's Perspective on 3 Key Issues**

#### *a.- People with decompensated cirrhosis*

Safety studies, drug interaction & metabolism studies should be underway in people with decompensated cirrhosis at the time of approval

#### *b.- Co-infected people*

Prior to initial approval, efforts should be made to initiate early-phase studies; major drug interactions and pharmacokinetics...

...**At least** early efficacy trials--pilot trials--are probably indicated to give some sense that patients can be treated both safely and with some degree of efficacy."

#### *c.- Multi-agent trials*

"...Encourage use of 2 or more investigational agents, probably following Phase IIB level studies, safety needs to be established & we need early drug interaction studies..."

**NOTE: The following section has not been completely edited or approved by the speaker – who did not respond to messages on clarification questions by the editor [in bold].**

## EMEA perspective

*Olle Karlström  
Stockholm, Sweden*

Although there are guidelines for the development of medical products for HIV, Hepatitis B, and treatment of sepsis, at present, there are no specific guidelines for the development of HCV agents. Until recently, there were too few HCV therapies to warrant guidelines, but this is changing.

So far, there has not been any regulatory advice on inclusion of HIV/HCV coinfecting people. We can draw from guidelines that include HIV-positive people. For example, guidelines for HBV agents regard HIV-positive people as a target population, and there are considerations for study designs in coinfecting people. In fact, regulatory advice is recommended for studies in HIV/HBV coinfecting patients.

It is important to consider disease prevalence, and eligibility **[editor's note: can you explain the influence of eligibility?]** on drug development. In Western Europe, nine million have hepatitis C, and 250,000 are HIV/HCV coinfecting. This difference will influence drug developers.

It can be very hard to do large trials with coinfecting patients because some HIV centres have few coinfecting patients. Patient selection affects the outcome of studies; either by poorer outcomes with sicker patients, or if the exclusion criteria are too rigid, the results won't reflect how drugs work in real life..

## Lessons learned so far

Conducting studies is complex. For example, drug-drug interaction can't **[editor's note: is it okay to add "always" to this sentence?]** be seen in plasma, so interactions must be studied on intracellular levels to be properly measured. We learned this from a 1996 study that did not find an interaction between didanosine (ddI) and ribavirin, but **[editor's note: okay to add: "reports of life-threatening, and fatal interactions between these two drugs and"?)** results from a 2005 study indicated that there is an interaction and toxicity.

Entecavir is another lesson learned. Until recently, this agent was considered a perfect drug for HBV/HIV patients because had no HIV activity *in vivo*. Thus, HIV/HBV coinfecting patients who needed HBV treatment --but not HIV treatment-- could safely treat their HBV without acquiring resistance to therapies that are active against both viruses. However, FDA announced that the risk of developing HIV resistance cannot be excluded, since apparently entecavir does have HIV activity *in vivo*.

These examples show that we must do adequate interaction studies, and studies in HIV-coinfecting people must be conducted properly, not simply by doing a few

laboratory strengths [**editor's note: this word seems to have gotten mixed up; was it supposed to be "strains"?**].

## Resistance

Knowledge of HIV drug resistance should be used to inform development of HCV/HBV agents, since it is relevant, but this is not happening right now. In the HBV field, we are aware that resistance develops.

As with HIV, combination therapy should be used, and agents should be tested together, early in their development. There are many new agents in development for HCV. The first are protease inhibitors (VX-950 and SCH503034) and nucleoside analogues (R1626, HCV-796), the same classes of drugs that have been used to treat HIV for many years).

New HCV drugs can be tested safely in HIV-positive people, provided that properly conducted, extensive interaction studies are performed early in development, and there is a comprehensive assessment of activity against HIV.

## Conclusion

It's evident that there is a need for EMEA guidelines for HCV agents; within the EMEA this will be shortly discussed soon. The guidelines should be specific about subpopulations, including people who are HIV coinfecting, and should be specific in regard to interaction studies and activity testing on other viruses.

**NOTE: The following section has not been completely edited or approved by the speaker - who did not respond to messages on clarification questions by the editor [in bold].**

## Spanish Agency on Drugs - AEMPS perspective

*Fernando de Andrés – Trelles  
Spanish Agency of Drug and Health Products  
Madrid, Spain*

Some regulators think that regulation is everything and certainly, it's not everything.

Medicines are evaluated for registration, and to see how well they work in clinical practice. Access to registered medicines is not necessarily uniform throughout the European Union (EU), because the EMEA shall not affect the powers of Member States' authorities in setting *prices* for medicinal products, or for their *inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions...* (regulation (EC) No 726/2004 of 31 March 2004).

Valid, objective data are needed to assess quality, safety, and efficacy, and to establish normal conditions of use in which the risk/benefit ratio is favorable. This information is reflected in the *Summary of Product Characteristics*, the *Patient Leaflet* and in packaging.

Health benefit of medicines can be different, or may be perceived differently; for example:

- Vaccination to prevent mortal disease, vs.
- Morphine for severe pain, vs.
- Hormone pills for contraception, vs.
- Viagra for impotence, vs.
- Anesthetics to facilitate surgery, vs.
- Using radiology to increase diagnostic accuracy.

Registration and/or reimbursement issues may be complicated, because situations differ:

- Medicines potentially fulfilling a previously unmet medical need vs. 'me too drugs'
- Real needs vs. those perceived as invented needs (e.g. 'disease mongering', 'lifestyle drugs')
- Statistically significant vs. clinically relevant
  - Efficacy vs. effectiveness
  - Effect vs. outcome
  - Placebo vs. active comparator

Obviously, some cases may justify more uncertainty when a drug is initially approved; in these cases, initial approval could be 'conditional'. We have to consider certainty vs. speed, in assessment and availability. There are ways to accelerate availability, via "non-standard" marketing authorization (Conditional Marketing Authorization and Exceptional Circumstances). **[Editor's note: could you define these terms for the audience?]**

In addition, people may gain access to medicines before specific marketing via participation in clinical trials, through compassionate use, or by "off-label" use.

### **Compassionate Use and Off label use**

In the EU, the first guideline for harmonizing compassionate use of products likely to be accessed via the centralized system [via the EMA] is in the last stages of approval EMA/504533/2006/Draft. It excludes off-label use.

- In Spain, compassionate use will also probably be differentiated from "off label" use:
  - "Off label" use will likely be simplified and require less prospective administrative control by the AEMPS;
  - The AEMPS is developing compassionate use protocols for groups of patients; and
  - Is working to maximize the amount of useful information obtained (e.g. on safety).

What can be done **[editor's note: by regulators? ]** if companies do not find it profitable to develop drugs for public health needs?

*Several possibilities:*

- Ensure that products become profitable by:
  - Orphan drug status. In place in the EU for 7 years; competitors are artificially excluded by granting an exclusive, ten-year indication to the first successful applicant.
  - The new regulation on drugs for pediatric populations (as of 26 January 2007).

**[Editor's note: can you explain -briefly--the regulation on drugs for pediatric populations?]**

A further approach is for **public institutions to take the initiative to develop drugs themselves**. This is, for the moment, mostly a theoretical possibility in the EU, but promising signals start to appear, e.g.

- The recent regulation for pediatric medicines specifically mentions the **UE "Framework Programmes"** as source of funding for pediatric investigation plans.
- Some Member States are starting health-oriented medicines research programs funded by resources from pharmaceutical companies; the first call for projects in Spain (*BOE n° 28 1 de febrero de 2007*) has just been completed.

### **HCV: The path of least resistance in drug development**

*Dr. Raymond Schinazi*

*Emory University / Veteran Affairs Department, Atlanta ,Georgia, USA*

We still have a lot of work to do on HIV, especially as it relates to latency, vaccine development and a cure. Globally, there are 14,000 new cases each day, and, in the US, 45,000 new cases each year.

Globally, more than 200 million people have been infected with hepatitis C, and 3-4 million new infections occur each year. In the US, 1.4-3% of the population is infected with HCV.

Regarding viral hepatitis co-infection, up to one third of HIV patients globally are co-infected with HBV or HCV. That's a huge problem.

As others speakers have discussed, we need to learn from previous experience with HIV and HBV drug development and treatment. We have learned that we need combination therapy for HIV, and also for HBV. Now, certain persons believe that monotherapy will be enough to treat HCV, but that is a big mistake. The data are beginning to appear to suggest that combination antiviral chemotherapy will become the norm.

### **The progress in HIV**

A lot of work has been done on HIV drug development, and we've not finished. We have 22 drugs available to treat HIV; some patients can take multiple compounds in only one pill. This is important progress, especially when you consider that HIV was discovered only 25 years ago! In addition, we are now able to reduce HIV RNA to undetectable levels (< 50 copies per mL), even in patients who have developed resistance to some drugs. There are more compounds in development in 2007, and there will be more choices as time goes on. It's a very good picture, but we're not there for HCV.

It takes a lot of time to develop these drugs. At the start, there are as many as 10,000 compounds in development, but only one may make it to market. Drug development is very hard work, but as we go forward, we learn, all of the time. We learn how to resolve issues, such as toxicity and drug delivery. How we do this? Our approach to drug discovery of antiviral agents starts with access to large chemical library, and a pool of medicinal chemists, expert advisors, and through corporate memory and experience. Then, we need a robust and validated screening technology.

Drug discovery includes toxicology, pharmacology, biochemistry and experimental virology. The next step is to reach a strong, defensible intellectual property position and then, to share reagents among scientists, especially drugs for comparative purposes and viruses that have interesting mutations. In all this process, speed, economy and efficiency are essential.

### **HCV/HIV co-infection**

We've done great work with HIV, but now there are other opportunistic infections that we have to address, such as HCV. In the USA, around 30% of HIV patients are co-infected by HCV and in Spain, around 50% of HIV patients are also co-infected. We are not doing a good job treating HCV and morbidity and death can occur from these co-infections.

We need to consider the increasing mortality from end-stage liver disease (ESLD) in the HAART era, in almost every country where there is access to antiretroviral therapy. In this period, 50% of the patients who have died from ESLD had undetectable HIV RNA. So, it is very clear that there is an increase in liver-related mortality in patients who are doing very well with their HIV treatment.

### **HCV treatment: Where are we today, where are we going?**

**1990-1997:** Interferon monotherapy. We had no choice.

**1997-now:** We have pegylated interferon + ribavirin; sustained virological response rates range from 30-60%. Peg-interferons also have a longer life in plasma and don't need to be given daily.

**2008-2010:** 20 drugs are in process to be approved. I still believe we will be using IFN, possibly with 1 or 2 oral drugs.

**2010 and beyond:** All oral drugs, maybe within one single pill, as we have with HIV, and a very high sustained virological response (SVR).

### **Challenges for antiviral therapy: innovation drivers**

1. Potent simplified therapy is required.
2. There is a high viral burden, so we have to hit hard.
3. We have big genetic diversity in HCV, and a lot of genotypes, there is a high replication capacity and, resistance development is common especially for non-nucleoside drugs.

4. Toxicity is a key issue, which may start to develop 12 weeks or more after initiation of treatment.
5. And finally, host immunologic control becomes important once viral load and compartments where the virus hides are controlled.

### **Anti-HCV Pipeline: Molecules that can Cure Disease**

PEG-interferon and ribavirin, the current standard of care for the treatment for hepatitis C, is a good option. Sustained virological response rates can be as high as 80% in people who have HCV genotype 2 or 3. Unfortunately, this combination is poorly tolerated and has to be given systemically by injection.

In 1999, there was a major advance in HCV drug development. A European group published data on a replicon system that produces a lot of non-infectious HCV RNA, like a xerox machine. This system made it possible to measure HCV RNA inside cells. When you add an inhibitor, it can almost completely reduce the production of HCV RNA. This has been a revolution, and now a lot of people are working to discover and develop new HCV drugs. Many companies are involved in the development of new HCV compounds (Abbott, Roche, Schering-Plough, Merck, Idenix, Pharmasset, Boehringer Ingelheim, Gilead Sciences, etc). There are robust ways to determine synergy between compounds in this cell culture system.

Regarding targets for HCV antiviral agents, investigators have identified the enzymes involved in the HCV replication process. The most important targets are three enzymes: the HCV protease, the RNA-dependent RNA polymerase and helicase. The polymerase is particularly interesting since there are several targets within this enzyme.

The field of HCV drug development changed a couple of years ago, when a French scientist presented data from a pharmaceutical company called Boehringer Ingelheim on an HCV protease inhibitor. The HCV RNA dropped by more than 3 log after 2 days of treatment. This compound works very well against HCV, but unfortunately, if you stop the treatment, the virus load comes up again very quickly. This drug, called BILN 2061, established proof of concept although development was halted due to cardiotoxicity.

There are more drugs in development, some very promising. A good example is the study of the polymerase inhibitor MK0608 done in two chimpanzees. When they were given the drug, their HCV viral load dropped by more than 6 logs (i.e., by more than 99.9999%), which is very impressive for this class of compound known as a nucleoside analog. This study demonstrated that is possible to have drugs that can give us more than 2 or 3 log decreases in HCV RNA. Some nucleoside analogs can give you more than one log drop, and in general, it is more difficult to develop resistance to nucleoside analogs than to the protease inhibitors.

Telaprevir (VX-950) is a potent HCV protease inhibitor being developed by Vertex in collaboration with Johnson&Johnson. When it is used with PEG-interferon, there is a very significant reduction in HCV RNA, but resistance can appear, and there are some toxicities too, especially after prolonged treatment. There is a lot of excitement about this drug, but it is still not clear if a sustained virological response is possible in more

than 60% of the patients taking this drug in combination with PEG-interferon and ribavirin.

The field of HCV drug development is becoming complex, because of drug resistance. So, we need a lot of work, in cell cultures as well as in humans, isolating this virus, selecting for using the replicon system, characterizing the mutations and subsequently confirming the full resistance profile. By using combinations judiciously, we can reduce the toxicity and reduce viral resistance. Drug-drug interactions especially when the new anti-HCV drug is added to the standard of care could result in adverse effects. For example, the use of adenosine analogs could be compromised when used with ribavirin, since ribavirin is known to use adenosine kinase for activation to ribavirin-5'-monophosphate. Thus, the two analogs compete for the same enzyme; that could be detrimental.

In 2007, add-on therapy to the current standard of care will be the way to go forward. Valuable lessons were garnered from the failures of numerous anti-HCV agents. The task at hand is quite complex, but there is hope that a cure is possible, since there is no latency for HCV. It is clear that the development of new agents will require clinical proof that they will be safe, and produce sustained virological responses in controlled clinical trials, leading eventually to high curative rates.

#### *Joan Tallada*

There are a lot of people who cannot wait, and some people who cannot tolerate IFN. So, will new drug regimens without interferon be possible?

#### *Polsky*

Studying two new experimental drugs in combination presents many complications. But I think certainly we will find clinical investigators and patients who will be willing.

**NOTE: The following presentation has been updated to reflect results of more recent research. Since the meeting in Sitges, it has become clear that new anti-HCV therapies will need to be studied in combination with pegylated interferon and ribavirin for the next several years. Hopefully, the first generation of new HCV drugs, when used with pegylated interferon and ribavirin, will shorten duration of treatment, and improve response rates by at least 10%.**

#### **Early access to HCV drugs: Interactions, Safety, and Efficacy**

*Bruce Polsky, St. Luke's Hospital, NYC, USA*

#### KEY POINTS:

- New drugs need to be studied in people who are coinfecting with HCV and HIV;
- There are multiple targets for HCV drugs, including preventing infection and preventing viral replication;
- Many different compounds are in pre-clinical and clinical development;

- Resistance testing will be required;
- Adherence will become crucial; novel therapies may require adherence rates of >95%.
- Early access to HCV drugs: interactions, safety, efficacy

I need to start with this statement: new drugs need to be studied in people who are coinfecting with HCV and HIV.

### Treatment of HCV in the Setting of HIV

- Goals of therapy
  - Eradicate HCV RNA;
  - Improve liver histology;
  - Decrease rate of disease progression;
  - Reduce risk of hepatotoxicity associated with HAART, because the liver needs to be functioning well to effectively treat the HIV.
- Optimal therapy for HCV
  - Pegylated interferon and ribavirin

### HCV Treatment: Evolution of Therapy for HCV Mono-infection

Treatment outcomes have improved over time as we have moved from standard interferon alone to PEG IFN in combination with RBV. Now, the rate of sustained virological response (SVR) is 60% in mono-infected patients, but we really need to do better.

The situation with coinfecting people is worse; overall SVR rates in clinical trials in coinfecting patients range from 27% to 44%. The results are worse for coinfecting patients with genotype 1. The urgency for new therapies in coinfecting patients is justified, given these results.

There are 3 steps of interaction between the hepatitis C virus and the cell, where drug developers can target specific areas. One is initial infection of the cell with entry and uncoating of the virus. Inhibiting entry --and the entire replication process-- can be targeted. Replication inhibitors are where the main action is; most of the drugs we have in clinical trials are replication inhibitors. The third major area is assembly and budding. There are similarities with HIV, so we have already learned about these steps.

**Table: Novel HCV Drugs in Clinical Trials**

	Type/class of agent	Name of agent	Sponsor	Stage of Development
<b>Step One: Preventing cell infection</b>	Monoclonal antibody	HCV-AB68	XTL bio	Phase I
	Monoclonal	bavituximab	Peregrine	Phase I

	antibody		Pharmaceuticals	(also being studied in HIV/HCV coinfecting people)
	Monoclonal antibody	infliximab	Centocor Pharmaceuticals.	Phase III
	Immune globulin	Civacir	Nabi Biopharmaceuticals	Phase II
<b>Step Two: Preventing Viral Replication</b>	Antiviral	Taribavirin	Valeant Pharmaceuticals	Phase II
	Cyclophilin inhibitor	DEBIO-025	Debiopharm	Phase II (completed a Phase I study in HIV /HCV coinfecting people)
	alpha-glucosidase I inhibitor	Celgosivir	Migenix	Phase II
	IRES inhibitor	Mifepristone; VGX-410	Viral Genomix	Phase II
	NS5A/IRES inhibitor	NS5A-831	Arrow Therapeutics	Phase I/II
	Polymerase inhibitor	GSK625433	Glaxo Smith Kline	Phase I
	Polymerase Inhibitor	R1626	Roche	Phase II
	Polymerase Inhibitor	R7128	Roche/Pharmasset	Phase I
	Polymerase Inhibitor	PF-00868554	Pfizer	Phase I
	Protease inhibitor	VX-950; Telaprevir	Vertex	Phase II
	Protease inhibitor	SCH 503034; Boceprevir	Schering-Plough	Phase II
	Protease inhibitor	TMC435350	Medivir/Tibotec	Phase I
	Protease inhibitor	ITMN-191	Roche/Intermune	Phase I
	Protease inhibitor	MK7009	Merck	Phase I

Immunomodulators and several different formulations of interferon have entered clinical trials. Albuferon, a long-acting interferon, is being studied in HIV/HCV coinfecting people (Phase I), as well as in people with HCV alone (Phase III).

#### Issues with Novel HCV Therapies

- Development of combination therapies

- Different classes of agents, different targets; these drugs will need to be studied in combination
- HCV resistance testing is definitely required, since resistance to new HCV drugs has already been identified
  - Clinical role
- Adherence
  - 80-80-80 (taking 80% of the full dose of pegylated interferon and 80% of the ribavirin dose, 80% of the time) will not be sufficient
  - >95% is probably necessary, since resistance to experimental HCV drugs appears to develop quickly

## **Roundtable**

Dr. Schinazi and Dr. Polsky take questions

### ***Maxime Journiac***

We have heard about IFN resistance. How does this occur?

### ***Raymond Schinazi***

As far as we know, it's not possible to develop viral resistance to IFN. It could be "clinical resistance", not virological drug resistance. That's the good thing about IFN: you cannot develop resistance to IFN because IFN acts on the cell, not the virus, to prevent infection. It prepares the cell for a potential infection. No one clearly understands how "clinical resistance" to interferon occurs, although many hypothesis and unconfirmed reports suggest that it could be a function of the virus.

### ***Joan Tallada***

I recently read a report about mutations in the HCV protease, in people who had used HIV protease inhibitors, but no hepatitis C protease inhibitors. The author's assumption was that HIV protease inhibitors can cause mutations in the HCV protease. Thus, coinfecting people who had used, or were using an HIV protease inhibitor would need HCV resistance testing before starting a hepatitis C protease inhibitor.

### ***Raymond Schinazi***

HCV and HIV are two different protease enzymes. Although they look functionally quite similar (one is a serine and the other is an aspartyl protease), they are very different. I'm not aware of any cross-resistance between HIV and HCV protease inhibitors. I am also not aware of any HCV protease inhibitor that inhibits HIV and vice versa.

### ***Bruce Polsky***

If it is true, this would have major implications.

### ***Diego García***

From the HIV experience, we have learned that boosting other protease inhibitors with ritonavir makes drugs more effective, and they only need to be taken once or twice a day. Could we explore boosting HCV protease inhibitors, to improve adherence and efficacy, and study a ritonavir-boosted HCV protease inhibitor in coinfecting people?

### ***Raymond Schinazi***

Last year Abbott presented at the EASL conference data in animals, demonstrating potential boosting principles of HCV drugs. I guess they will be the first to try in humans. Ritonavir is available commercially so if Vertex wants to use it, they certainly could. Boosting is something that has to be studied pharmacologically, and for safety. Sometimes boosting is not a good idea, because you cause more toxicity due to increased plasma levels and increased half-life of the drug in the plasma. That's an important point to keep in mind. Clearly proof of principle studies need to be conducted, but in my opinion, the best protease inhibitors will be the ones that are self-boosting (meaning we will not need to add drugs like ritonavir to boost plasma levels).

***Bruce Polsky***

It is so complicated. We will do interaction studies with HIV and HCV protease inhibitors, and actually analyse the effects. All of this has to be worked out before we move forward with any kind of dual protease inhibitor therapy.

***Olle Karlström***

Resistance is an issue, so companies have realized that they have to work together. It makes economic and scientific sense. Working together benefits the companies and the patients.

***Begoña Bautista***

We're talking about the non-responders, but there is another group, the people who discontinued HCV treatment because they could not tolerate it. They cannot go back on INF and RBV, so what is their alternative?

***Bruce Polsky***

This is a large population of patients. The treatment we have today is hard, and challenging for coinfecting people. From my point of view, we will be able to prove we can treat patients without IFN, but it will take time. I think interferon-free regimens will be the answer for that group of patients.

***Begoña Bautista***

The landscape described is triple therapy for HIV and triple therapy for HCV. Isn't this a very complicated landscape, including different interactions, tolerance and safety issues?

***Bruce Polsky***

Yes, it gets very complicated, and that's one of the challenges. It's not going to be easy to treat coinfection but we've to start somewhere.

***Raymond Schinazi***

I think the key is to treat HCV as quickly as possible. I don't think HCV treatment is going to be more than 6 months -since in general the immune system is intact. If one is coinfecting with HIV/HCV, this is much more complex because the immune system is not intact and one will need to get CD4 levels close to normal with HAART, before embarking on HCV therapy. However, the issue of drug-drug interactions are complex, especially for co-infected individuals (since one cannot yet take a drug holiday for HIV in order to treat HCV). Hence, it would seem logical to me to try to "cure" HCV first before embarking on HAART for HIV and to treat the HCV infection early, before the immune system is completely destroyed by HIV.

**Barry Bernstein (Abbott)**

There are significant concerns about doing clinical trials. Our perspective is largely of a regulatory nature. We don't know the implications of studying multiple investigational drugs together from the regulatory point of view. We have a FDA advisor, and we have some guidance. The consensus seems to be pathways forward for approval are conventional therapy, and that usually implies single drug. It would be great if we had additional guidelines from regulatory, as to what are the risks of combining these small molecules, and what the implications for development plans will be. I think we have to find the way to get combinations examined in a robust fashion, but still allow for them to be approved as individual agents to keep flexibility.

**Maxime Journiac**

We've been saying that the goal of HCV treatment is really viral eradication. Can you elaborate on the term eradication? How long should be one undetectable before stopping treatment? At what point does SVR occur? What happens in cases when the HCV reappears after six months, or years later?

**Bruce Polsky**

Eradication is not a dream in HCV. We're doing good work with genotype 2 and 3. Eradication is doable, but we have to do more. What we mean by eradication is getting the SVR. So, for genotype 2 and 3 that means 24 weeks of treatment (48 for genotype 1), followed by 24 weeks of observation and then monitoring the virus. It is very rare for HCV to come back after 24 weeks of being virus negative. Because that's very unusual, we declare someone cured who has undetectable HCV RNA 24 weeks after completing treatment.

**NOTE: The following section has been edited and approved by the speaker**

**Limitations of current HCV Treatment in Coinfected People: Overviews from Experience**

*Bruce Polsky, St. Luke's Hospital, New York City, USA.*

**KEY POINTS:**

- HCV coinfection is a serious and prevalent co-morbidity among HIV-positive patients;
- HCV is difficult to treat in HIV-positive patients, due to drug-drug interactions, side effects and toxicities of PEG-IFN and ribavirin;
- There are significant barriers to HCV care and treatment for coinfecting people;
- Multidisciplinary care, which includes mental health and addiction treatment, is often necessary to successfully treat HCV;
- Treatment strategies for coinfecting patients, such as which virus to treat first, are addressed in treatment guidelines;

- There is no definitive treatment strategy for non-responders

Commonalities: HIV – HBV – HCV

- Shared routes of transmission;
- All three are very dynamic viruses, with high rates of viral replication and turnover, and high probability of mutations;
- Treatment for each virus is complicated, and prolonged;
- Co-infection treatment is even more complicated;
- Dead viruses don't mutate;
- Dead viruses aren't associated with disease progression;
- Dead viruses are good.

Viral hepatitis is a significant co-morbidity for HIV-positive patients. In the HAART era, end-stage liver disease from HCV and/or HBV coinfection is a leading cause of death for HIV-positive people.

Management Difficulties in Co-Infected Patients

- HIV + HBV
  - Drugs overlap
  - Combination therapy recommended
    - Based on very little data, if any
  - Relatively easy to manage and treat on a comparative scale
- HIV + HCV
  - Drugs don't overlap
  - IFN + RBV very poorly tolerated
  - Very difficult --to manage and treat on a comparative scale
- HIV + HBV + HCV
  - Very rare

HIV/HCV Coinfection

- ~30% HIV-infected are coinfecting with HCV
- HIV accelerates HCV disease
- HCV infection influence on HIV:
  - ARV-associated hepatotoxicity;
  - Response to ARV therapy;
  - Natural history of HIV disease (although this is controversial; conflicting results have been reported and the evidence is not solid);
  - Extrahepatic manifestations.

Major Issues in HCV/HIV Co-Infected Patients

- Difficult --most newly- diagnosed patients are injection drug users, who have multiple diagnoses and traditionally poor access to care. They have problems tolerating HCV treatment and managing psychiatric side effects; some people struggle with a treatment that requires injection. There are problems that are inherent with addiction, and social milieu. Some of the women are single moms. We need to support patients and their families, and carefully monitor side effects.

- Difficult drugs;
- Difficult drug-drug interactions;
- Genotype and race;
- Biopsies;
- Sequencing strategies unknown;
- Management of non-responders.

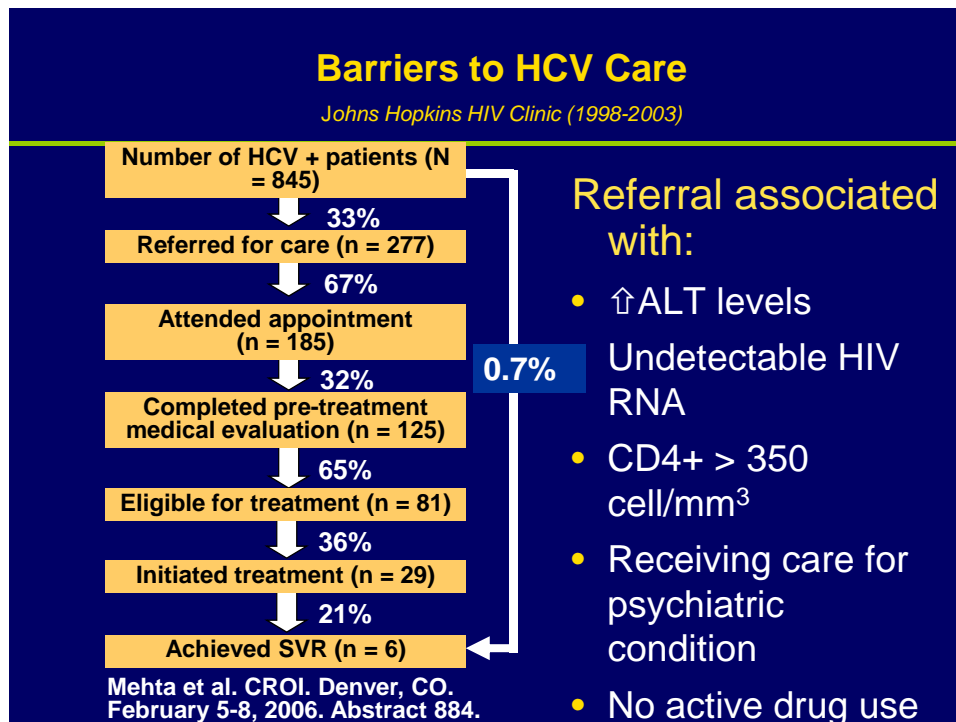
Interferon/Ribavirin is the cornerstone of HCV therapy in HIV-Infection

- Ribavirin
  - Interaction with zidovudine (AZT): due to a PK interaction, coadministration with AZT and some other NRTIs is not recommended;
  - Interaction with didanosine (ddI): cannot be used together, due to potentially life-threatening interaction; coadministration of ddI with HCV treatment can precipitate liver failure in people with cirrhosis;
  - Anemia: ribavirin causes anemia (via hemolysis), as does AZT (via bone marrow toxicity); coadministration increases the risk for anemia;
  - Added toxicity: use of stavudine (d4T) during HCV treatment may potentiate lipodystrophy during HCV TX;
  - Teratogenic;
- Interferon
  - Decrease in CD4 counts during treatment, but not CD4%;
  - Bone marrow toxicity;
  - Commonly associated with depression and other constitutional problems like nausea, fatigue, malaise, alopecia;
  - Injection;
  - Expensive.
- Side effects in virtually 100% of patients and they require attention, involving more visits to the health care team.

For these reasons, we have to replace interferon and ribavirin as soon as we can.

### **Barriers to care**

A study from Mehta and colleagues at the Johns Hopkins HIV Clinic reported on the low uptake, and efficacy of HCV treatment in their coinfecting patients. The results reflect all the barriers to care. The best is to get simple drugs, and take the treatment out of the hands of the system.



Source: Mehta SH, Lucas G, Torbenson M, et al. (Abstract 884) Barriers to referral for hepatitis C virus care among HIV/HCV co-infected patients in an urban HIV clinic. 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colorado.

### Management of HIV/HCV Infection

Guidelines for the management of HIV/HCV infection are available in the appendix at the end of this chapter.

We need to get multidisciplinary teams (HIV, HCV, mental health, addiction specialists, etc).

### HCV Treatment and Status of HIV Disease

For patients with advanced and uncontrolled HIV disease, we have little justification to treat HCV first. We really need to get the HIV under control before starting HCV treatment.

Patients with stable HIV disease, who do not require antiretroviral therapy (ART), are candidates for HCV treatment. But these patients are unusual. Most patients have stable HIV disease, and they are on ART. These patients are good candidates, particularly if they have CD4 cell counts of >200 cells/uL. We know they respond better to therapy. We try to get them on drugs other than AZT and ddl because of drug interactions with RBV, and increased toxicity.

### Predictors of HCV Response to PEG-IFN plus Ribavirin

- Virus: Genotype, HCV RNA (the lower, the better, in terms of response) and HIV status. Better control of HIV, a higher CD4 cell count... all of these factors predict a better response to PEG-IFN plus ribavirin.

- Host: Race (African-Americans do worse than Caucasian; probably related to unfavorable pharmacodynamics of IFN), age (younger is better), weight (lighter is better), genetics and immune status.

### Initiating HCV Treatment

Clinical evaluation of:

- HIV disease (treat HCV first? HIV first? Simultaneously?)
- Psychiatric status
- Substance use
- Alcohol use

Management of Non-responders

- No definitive strategy for management of non-responders
- There are data showing less inflammation even in non-responders
- Investigational strategies\*
  - Daily IFN-alpha
  - PEG-IFN induction
  - Low-dose PEG-IFN for years
  - Investigational agents
    - Drug-drug interactions critical! Interaction studies must be conducted before giving experimental HCV drugs to coinfecting people

### Discussion

#### *Olle Karlström*

We work in teams: doctors, nurse, counsellors, etc. A multidisciplinary approach makes it quite possible to treat HIV and HCV.

#### *Massimo Puoti:*

Many patients should wait for new HCV treatments. We had less experience treating patients, less knowledge on drug interactions and managing side effects in 2001-2002. Now we are more confident about using these drugs. A patient with mild HCV disease could wait, because in the future we will be more knowledgeable about treatment, drug interactions, and management of side effects, etc.

<p><b>NOTE: The following section has not been completely edited or approved by the speaker - who did not respond to messages on clarification questions by the editor [in bold].</b></p>
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### Limitations of current HCV Treatment in Coinfected People: Overview from Experience

*Massimo Puoti, MD*

Poor tolerability is the main limitation to HCV treatment. We know that almost all patients have side effects (fatigue, headache, myalgia, insomnia, nausea, etc). Almost half of the patients have psychiatric symptoms, 1 to 5 **[editor's note: is this figure accurate?]** have gastrointestinal symptoms. Often, these symptoms add to HIV-related symptoms that are less important in these combinations of drugs **[editor's note: can you explain this – is it side effects of ARVs, symptoms of HIV, or both?]**

The efficacy of HCV treatment has improved. In the first two pilot studies of IFN mono-therapy, the SVR rate was 5%. The best results have been obtained with PEG IFN + RBV. In these trials, the SVR ranges from 27% to 50%.

Dr. Puoti compared the results of 5 trials to highlight limitations of current HCV treatment in co-infected people.

The first important limitation is exclusion criteria. Many patients are not eligible for HCV treatment. In the majority of cases, patients are excluded because of medical contraindications, or because the patient refuses to participate in the study.

Doctors also limit access to HCV treatment. The major reasons to exclude patients, from the doctor's point of view, are:

- because the patient consumes alcohol;
- because the doctor thinks that the patient will not be adherent to clinic visits;
- because of a concomitant disease;
- or because of active substance abuse.

The second limitation is heterogeneity; randomized controlled trials and pilot studies differ highly by settings, study populations, and treatment regimen.

Premature withdrawal from clinical trials is another important limitation. In most studies, the patients withdraw during the first month of treatment. The doctor's expertise in side effects management is crucial for maintaining patients on treatment. The cumulative toxicities of HCV therapy in combination with ART are also a significant limitation.

Many coinfecting patients relapse after HCV treatment. The high relapse rate may be related to treatment duration and ribavirin dose.

We can assume that we can improve treatment results, but we have subgroups of patients with poor results:

- HCV genotypes 1 & 4, and high viral load ( $> 4 \times 10^5$  IU/mL)
- Patients with poor adherence.

Even in the best-case scenario, 64% of patients fail current HCV treatment. For these reasons, we need new drugs and new studies.

<b>NOTE: The following section has been reviewed, edited and approved by the speaker.</b>
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*Carmen Tarrades*

*UK-CAB, UK and ICW (International Community of Women Living with HIV/AIDS)*

**Who I am:**

- Carmen Tarrades
- 46yr old female
- Former IDU – now an occasionally recreational drug user who also smokes
- Coinfected with HIV and HCV
- Diagnosed with HIV in 1989
- Diagnosed with HCV in 2000 - by accident - after volunteering for a trial that looked at interferon as a possible treatment of HIV in patients who had no other treatment options
- Left the study 8 weeks into it, due to side effects
- CD4 count – 673
- Viral load – undetectable
- HCV genotype 1
- ALT – 51 (slightly raised)
- Fibroscan – showed a degree of damage (recommendation to repeat scan after a year).

I work full time, and I am dependent on my income to support myself and fulfil commitments

**The pros**

- Have a good CD4, undetectable... would HCV treatment be more successful if I did it now?
- Would a decrease in viral load be better than nothing at all?
- Would that decrease maintain me until something better comes along?

**The cons**

- Side effects of tx – at the moment...
- Lack of research, especially from a gender perspective (PK, interactions, hormones, age...)
- Lack of psychological and social support network
- QoL – is it worth it (at the moment) to put my life on hold for a year... considering the actual prognosis (at best 20-30%)

**The maybes**

- Would it be best to wait for a while until new products can be added to the standard-of-care?
- Should I try to wait for new compounds altogether?

**What to do ????**

It's a very personal decision that needs to be informed by all available --and future-- data, that includes all populations.

We need studies that ensure gender is factored into the equation.

We need support – clinically (adherence, toxicities, interactions...) as much as socially and emotionally, especially if we have dependants.

There are too many questions that require answers before informed decisions can be made!

**NOTE: The following section has been reviewed, edited and approved by the speaker.**

*Diego García Morcillo*  
*FEAT, Spain*

It's very difficult to make the right choice about hepatitis C treatment, especially when you don't have the right information. Most HCV treatment trials have been in mono-infected people; duration of treatment and response rates may not be the same for coinfecting people. Many people hear about HCV on the street. They get second-or third-hand information, inaccuracies and myths. Or, they are only getting information from their doctors in language that is usually too technical for ordinary people to understand. It is hard to make the right choice when there is fear from the doctor's side, and from the patient's side. Fear and misinformation can take control, and these make treatment decisions very hard.

Many doctors do not want to treat current and former injection drug users, so their prejudice creates additional barriers to treatment.

### **Who am I?**

- 42 year old gay man
- ex-IDU, on low-dose methadone maintenance treatment, occasionally use recreational drugs;
- have had episodes of minor depression in the past;
- I am an easy-going guy.

### **More things about me that make an HCV treatment choice difficult:**

- HCV+ for 20 years; HIV+ for 11 years;
- Progression of fibrosis from F0 to F4;
- HIV drug-related toxicities;
- Liver enzymes > x 3 the upper limit of normal;
- HCV genotype 1, high viral load (>8,500,000 copies);
- Good control of HIV infection;
- No other health concerns....

When considering HCV treatment, it definitely helps if you are in empowered situation. And for me, that means:

- Being retired;
- At a good socio-economic level
- Having support of family and friends

- Good adherence to treatment
- Having the skills to understand medical information, and access to updated information
- I am socially accepted

It does not help

- If you live in the streets;
- If you lack support;
- If medical help is not easy to reach;
- If people pre-judge you.

### **What should we do?**

- Bad prognosis for SVR with current treatments;
- Establish second-line goals; especially if you have genotype 1, a high viral load, and are HIV-positive:
  - sometimes clearing hepatitis C is not a realistic goal, whereas improving the condition of your liver may give you time to wait for new, more effective and less toxic treatments, make it easier to take ARVs, and will improve platelet production, your immune system and your overall health
- Fear does not help;
- There is not much data from clinical trials.

### **What can to help us to make the right choice?**

- Understanding of what HCV treatment means and implies for our lives (pros and cons)
- A good relationship with the doctor
- New, less invasive techniques need to be validated, so that people can get the information they need to make an HCV treatment decision without having to undergo a liver biopsy
- New strategies for HIV treatment to lower toxicities during HCV treatment
- Wider knowledge on management of side effects from HCV treatment
- Facts and data from clinical trials conducted in coinfecting people
- No decision-making based on assumptions/prejudices
- Support systems
- Personal situation, is it the right moment for you?
- Can you wait until better drugs are on the market, or to enrol in a clinical trial, or for an expanded access program – what are your treatment options?
- Have you been on treatment before?

### **Panel discussion**

#### *Olle Karlström*

I'm working with HIV/HCV coinfecting patients. In our unit, the HCV coinfection is treated in the HIV unit, that's helpful because we can quickly rearrange HIV treatment before starting HCV treatment if needed. We work in teams (doctors, nurse, counselors, etc.). A multidisciplinary approach makes it quite possible to treat HIV and HCV; it's very effective.

### *Joan Tallada*

If the standard of care has so many limitations, I don't see we can go further than where we are now with it. But furthermore, we don't know the side effects, complexities, and interactions, with new drugs, and there is still a lack of social support structures for coinfecting people.

### *Massimo Puoti*

The first point for successful treatment is organizing the structure. If you are treating both mono- and coinfecting people, you'll have a higher level of adherence. You need doctors who are dedicated to treating coinfection, and who manage the side effects, to attain good results. Being well-organized can optimize treatment for HCV and HIV, but HCV treatment outcomes will not be good in the majority of coinfecting patients.

The second point is that I think many patients should wait for treatment. We had less experience treating patients, less knowledge on drug interactions and managing side effects in 2001-2002. Now we are more confident about using these drugs. A patient with mild HCV disease could wait, because in the future we will be more knowledgeable about treatment, drug interactions, and management of side effects, etc.

### *Polsky*

Studying two new experimental drugs in combination presents many complications. But I think certainly we will find clinical investigators and patients who will be willing.

### *Puoti*

Before starting studies of new combinations, we need very good information about pharmacokinetics, because people will develop resistance to HCV anti-virals if they don't get the right amount of each drug. We need information about the potency and genetic barriers of these drugs, and – more importantly – information about the consequences involved in using these drugs. For example, if we use weak drugs, we can induce mutations in the virus, and then the virus will be resistant when better drugs from the same class become available. Trials have to be designed for people who cannot wait anymore for treatment. The problem is that drug companies do not consider these people as the best candidates for new drugs, because side effects are more frequent among sicker patients.

## **Who and when should be treated with new HCV drugs – Stakeholders' perspective**

We held an open discussion among all stakeholders at the meeting. Representatives from drug companies were invited to give their impressions on our discussions, and their perspective on how new HCV drugs will be used in clinical practice, particularly for co-infected people.

Drug development is tough; companies invest substantial time, money and effort to bring drugs to market, and companies have responsibilities in regard to patients who will use these drugs.

### **Barry Bernstein (Abbott)**

Abbott has been involved in polymerase development for several years. Recently we reached an agreement with another small biotechnology company to develop protease

inhibitors. We're currently involved in development of both programs. All compounds are in preclinical development. No compound will be ready for human trials before 2008. We still are a year away from clinical trials. We recognize the importance of having a broad-based population studied in Phase 2b, and that includes coinfecting patients.

**Frank Duff (Roche)**

The most important thing is to be here, to understand what the issues and the challenges are, to really get the personal stories. The group discussion is going to be very helpful as we build the programs.

We are looking at further optimizations of ribavirin dosing in genotype 1 patients and we are collaborating with the AIDS Clinical Trials Group (ACTG) to find low doses for non-responders.

The APRICOT study gave us some lessons about things that we have to be careful about. For example, there are a lot of small pilot studies moving forward, so we need to balance the need for small trials with the need for sufficient patient numbers, because there are some difficult safety matters we're not able to predict.

At this point, in Roche's portfolio, we have two polymerase inhibitors, one on Phase 2 development and another in Phase 1 moving quite well. There is also a protease inhibitor in the portfolio, also in Phase 1. And finally, we have a second generation of PEG-IFN in Phase 1.

There are good opportunities to consider combinations of drugs and we are absolutely looking for all possible opportunities to collaborate on early drug development with other companies that are developing drugs.

We will need to generate data through Phase IIb. There is a solid understanding of the dose in combination with traditional IFN-based therapy, and a reasonable safety database. We will probably arrange in 12 weeks before we can move more aggressively into combining compound with another one.

From my point of view, all options are open until there is some data that suggests a compound cannot be used in combination with another.

**Clifford Brass (Schering -Plough)**

I have an optimistic point of view. I think that the perspective we have of the disease has evolved, we've made great progress in the last 10-15 years.

Now, the major challenge is to totally eradicate the viral load and for that, I think that IFN will stay with us for some time. However, we are trying to find other options.

We have to analyse the different affected populations, but we will start first with the common population, to define the dose and then we will have a good base to go forward. We can't demand data from every population, but have a clear strategy.

**Panel discussion**

***Olle Karlström***

We need clear guidelines, especially for co-infected people, because they are the target population.

In another way, we have to invite the companies to a pragmatic discussion in order to address the issues about drugs interactions.

***Clifford Brass***

I think that clear guidelines can be useful to plan the trials, but actually they could slow down the process. For example, FDA will slow down the things because, even if we have a potent treatment for 12 weeks, FDA will demand to administrate it in 48 weeks.

***Clifford Brass***

There is no conflict for the companies to reach agreements to develop agents, because more easy would be the treatment, more drug users we will have.

***Barry Bernstein***

We need collaboration between companies but also with regulatory agencies in order to get successful.

***Joan Tallada***

In HIV, we always heard that regulatory agencies would slow down the development process. But I think that we have to find a balance and know when we have to go slowly because the information we need is crucial.

***Tracy Swan***

Slowing down the process will not benefit anyone. Maybe we need to front-load the process by investing more in clinical development vs. post-marketing studies. It's a question of when the money is spent rather than doing things less quickly or efficiently.

## **Appendix: HIV/HCV Coinfection Treatment Guidelines and Resources**

Spanish Guidelines for HCV treatment in Coinfected Patients. Grupo Español del SIDA (GESIDA).

[http://www.gesida.seimc.org/pcientifica/fuentes/DcyRc/DcyRc\\_Coinfeccion%20por%20las%20hepatitis.pdf](http://www.gesida.seimc.org/pcientifica/fuentes/DcyRc/DcyRc_Coinfeccion%20por%20las%20hepatitis.pdf)

Hepatitis C for people living with HIV: testing, coinfection, treatment and support. By HIV iBase and TAG.

UK version <http://www.i-base.info/guides/hepc/index.html>

US version <http://www.aidsinfonyc.org/tag/coinf/guidetohcv.pdf>

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<http://www.ashm.org.au/uploads/File/coinfection-mono.pdf> (Accessed 13th September 2007)

Nelson M, Matthews G, Brook MG, Main J; BHIVA Coinfection Guideline Committee; British HIV Association. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis C virus infection (2005). HIV Med. 2005 Jul;6 Suppl 2:96-106

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United States Department of Veterans Affairs. Management and Treatment of Hepatitis C Virus Infection in HIV-Infected Adults: Recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office.

Available on-line at: <http://www.hepatitis.va.gov/vahep?page=prtop06-gd-01> (accessed on 12 September 2007)