

May 9 - 10
2008
Sitges, Spain

Clinical Trial Design:
Experimental HCV Drugs for
HIV/HCV Coinfected People
2nd International Workshop



Meeting Report

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Joan Tallada



Hotel Mediterráneo, Sitges, Barcelona, Spain.

Program

Thursday, May 8th

Arrival

Friday, May 9th

10:00 to 10:30 - Opening remarks, introductions, and program presentation

Tracy Swan & Joan Tallada, Project Co-Leaders

10:30 to 11:00 - One year later: overview from the Sitges I meeting

Joan Tallada, EATG, Barcelona, Spain.

11:00 to 12:00 - The immune system in relation to HIV and HCV co-infection

Richard Jeffreys, Treatment Action Group, NYC, USA.

(At the end, this presentation was given first because the speaker had to unexpectedly leave the meeting earlier)

12:00 to 12:30 - Coffee break

12:30 to 13:30 - Towards a cure of HIV, BV and HCV?

Raymond Schinazi, Emory University and Veteran Affairs Dept., Atlanta, USA.

13:30 to 15:00 Lunch. Hotel Mediterráneo

15:00 to 16:00 - Update on new HCV drugs from EASL 2008

Tracy Swan, Treatment Action Group, NYC, USA.

16:00 to 17:00 - PK interactions with novel HCV drugs.

Saye Khoo, University of Liverpool, UK.

17:00 to 17:15 - Closing remarks.

17:15 - Afternoon coffee

Saturday, May 10th

10 to 10:45 – Access of co-infected people to new HC drugs: the community perspective.
Diego García, Spanish CAB FEAT, Murcia, Spain.

10:45 to 11:30 - Designing trials for drugs users: best practices for recruitment and retention.
Diana Sylvestre, UCSF, San Francisco, USA.

11:30 to 12:00 - Coffee Break

12:00 to 12:45 – EMEA Guidelines on HCV drug development
Joan Tallada, EATG

12:45 to 13:30 - Issues in Clinical Trial Design
Tracy Swan, TAG

13:30 to 15:00 – Lunch. Hotel Mediterráneo

15:00 to 16:00- Panel discussion with drug company representatives
Facilitation: Joan Tallada

16:00 to 17:00– Towards a consensus in clinical trial design.
All participants
Facilitation: Tracy Swan and Joan Tallada.

17:00 to 17:15 – Closing remarks
Tracy Swan & Joan Tallada

17:15 – Afternoon coffee

Opening remarks, introductions, and program presentation

Tracy Swan & Joan Tallada, Project Co-Leaders

This meeting is a smaller meeting than last year, where we opened the debate about how the novel Hep C drugs could be accessed and tested in co-infected people with HIV/HCV. This second meeting is much more focus on clinical trial design; we asked and selected people to be part of the discussion including community people, company representatives, researches and regulatory agencies.

One year later: overview from the Sitges I meeting

Joan Tallada, EATG, Barcelona, Spain.

Last meeting was held to address a critical issue: the clinical development of novel HCV therapies for HCV/HIV co-infected people who have urgent need for new HCV treatments. Hepatitis C is highly prevalent, progresses more rapidly, and causes significant morbidity and mortality among HIV-positive people.

HCV-associated end-stage liver disease is now a leading cause of death among HIV-positive people in Europe and the United States. HIV accelerates hepatitis C progression; co-infected 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 co-infected people versus those with HCV mono-infection. Although some centres 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. Co-infected 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. But HIV/HCV co-infected people are excluded from participation in these studies because 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 co-infected people are launched only after agents have been approved for HCV mono-infection.

The Sitges I meeting was a unique opportunity for stakeholders to discuss how co-infected 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 co-infected people. 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, declared 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. The community want to participate in:

- The development of regulatory guidance for HCV drug development. Casual or not, after the first Sitges meeting the EMEA decided to start the process to issue guidelines on recommendations for HCV drugs clinical development.

- The development of industry-sponsored clinical trials: Community 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. Nowadays the community has been much more successful dealing with some companies than others about it in this regard.

- The development of research networks.

- The community 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 co-infected people should begin before approval is granted for their use in HCV mono-infection.**

- We need to consider the most expeditious methods for co-developing drugs; this may depend on the outcome of early mono-therapy 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 co-infected persons, and transplant recipients.

- **The community 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 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:

- **enrol 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 co-infected people**. Organ transplantation, and access to the highest-quality care and treatment, must be provided to HIV-positive and co-infected people throughout Europe.

The Sitges Statement was distributed through EATG internal list, and was translated in Spanish, Italian, French and Portuguese, and probably in Russian. It was also circulated through different network. The Spanish version was circulated through the Spanish network of HIV physician. We also have printed copied sponsored by Roche. It was also posted in Treatment Action Group website and in their newsletter, and it was presented in different meetings.

The immune system in relation to HIV and HCV co-infection

Richard Jeffreys, Treatment Action Group, NYC, USA.

Immune control happens in hepatitis C, clearance relatively frequent (~20-40%). In HIV, sustained control of viral replication and long term non progression is less common (~1-5%). HIV infection reduces rate of HCV clearance.

Immune system plays a key role, so distinguishing what goes right (clearance) versus what goes wrong (persistence) may allow rational design of immune-based therapies to improve HCV treatment response.

The antiviral immune response

On first exposure to a virus, incoming particles are taken up by the sentries of the immune system, dendritic cells (DC). DCs can recognize pathogen-associated molecular patterns (PAMPs) shared by many different types of pathogens. DCs become activated (switched on) which causes them to migrate from the site of exposure to lymph nodes.

DCs break the pathogen down into protein fragments (called epitopes) which are then displayed on the outer surface by specialized molecules. Class II HLA (also known as MHC) molecules present epitopes to CD4 T cells and Class I HLA molecules present epitopes to CD8 T cells. In both cases recognition occurs via a docking bay structure on the outside of the cell, the T cell receptor (TCR).

T cells travel through lymph nodes on string-like pathways made of fibroblastic reticular cells (FRC) -these pathways form a complex traffic system with crossroads, junctions and dead ends. DCs hang out at crossroads like salesmen trying to interest T cells in the epitopes they have on offer.

A passing T cell that recognizes an epitope will engage in a prolonged embrace with the DC and eventually become activated. Activated T cells divide more than 15 times, generating a swarm of T cells specific for the same pathogen epitope. Dividing T cells switch on genes for making important signaling and antiviral proteins (chemokines and cytokines). Inflammatory cytokines and rapid T cell expansion contribute to the symptoms that can occur during acute infection (fever, malaise, swollen lymph nodes).

T cell subsets

Different T cell subsets engage in different tasks, typically defined by production of particular cytokines:

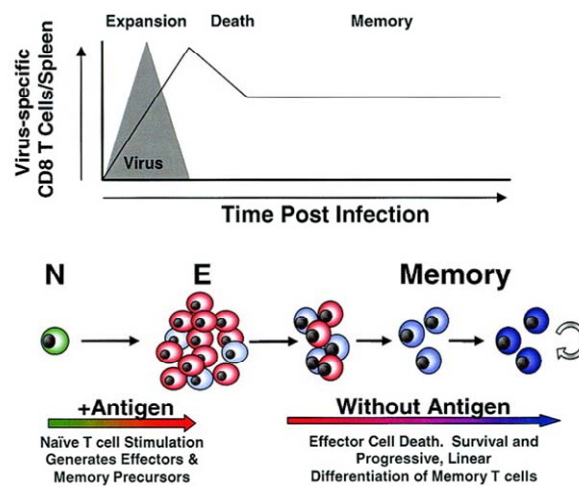
CD4 T cells

- Type 1 (Th1): help CD8 T cells kill infected cells
- Type 2 (Th2): support production of antibodies by B cells
- Regulatory (Treg): release immune-suppressive cytokines to dampen the immune response

- Th17: Recently discovered subset involved in responses to extracellular bacteria and autoimmunity

In many infections (e.g. influenza, measles, CMV, Epstein-Barr virus, herpes zoster) the virus is - in the vast majority of cases - cleared or brought under control by the immune response in a matter of weeks. The majority of the newly-produced pathogen-specific "effector" T cells are no longer needed and die in a process called activation-induced cell death (AICD).

Importantly, a subset of pathogen-specific T cell and B cells survive and these are described as "memory" cells. The quantity, specificity (parts of the pathogen that are targeted) and functionality (including proportions of different subsets) of pathogen-specific memory cells can be important determinants of whether immune control occurs.



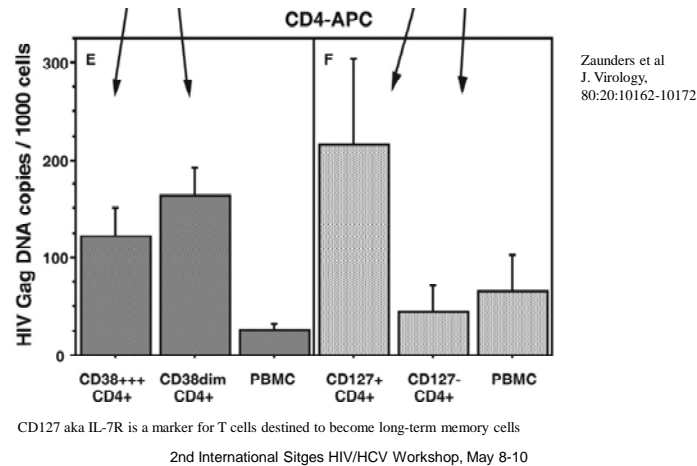
Wherry & Ahmed, J. Virology, 78;11:5535-5545

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Acute HIV infection

HIV-specific immune responses become detectable in 2-3 weeks. Symptoms of acute HIV infection associated with more rapid disease progression. Decline in viral load occurs in parallel with emergence of HIV-specific memory CD8 T cell response but is rarely fully controlled. Evidence of HIV-specific memory T cell dysfunction emerges early (HIV infection of developing CD4 responses may be the culprit). Neutralizing antibodies are not generated for several months and are rarely able to neutralize contemporaneous virus.

HIV preferentially infects developing memory CD4 T cells



HCV-specific immune responses are delayed approximately 1 month. Symptoms, including jaundice, are associated with higher rate of HCV clearance. Prospective analysis of CD4 and CD8 T cells in the early phase of HCV infection showed recovery of CD8 T-cell effector function and a 5 log decrease in HCV viral load at the time at which HCV-specific CD4 T-cell responses become detectable (Thimme 2001). A more recent study of 67 people with acute HCV showed that if 5 or more HCV peptide pools (~15% of the HCV genome) are targeted by CD4 T cells, chance of recovery is >7x higher (Smyk-Pearson 2008).

Example of a study: 55 HIV+ individuals with acute HCV infection were enrolled in a study in London, outcomes compared to small cohort of 8 HIV-negative individuals (Danta et al JID 197 2008, June 1). 52 (95%) developed persistent infection (compared to 62.5% of HIV-negative individuals). 3 who cleared had higher CD4s (847 vs. 549 cells) and all were jaundiced. HCV-specific T cell responses were rare and targeted fewer epitopes compared to HIV-negative participants. No evidence of HCV mutating to avoid immune response (immune escape).

On the other hand, an epidemiological study reported that the risk of a recurrent HCV was significantly lower for IVDUs who had successfully cleared a previous HCV infection than those with no evidence of previous infection.

During follow-up the apparent immune protection was lost by IVDUs who had recovered from HCV infection but subsequently became HIV-infected, suggesting a role for CD4 T cells in protective HCV-specific immunity (Mehta, 2002). Two reports (human & chimp) of HCV viral load recurrence after 4 months undetectable, in both cases preceded by loss of HCV-specific CD4 T cell response (Gerlach 1999, Nascimbeni 2003).

The immunological consequences of chronic HIV & HCV infection

Immune responses become progressively more diverse: as the viruses replicate, mutant forms arise and these induce new immune responses (from the naïve T cell and B cell

pools); and effective immune responses pressure the virus to mutate in ways that prevent recognition, somewhat similar to the way HIV mutations can impair drug effectiveness.

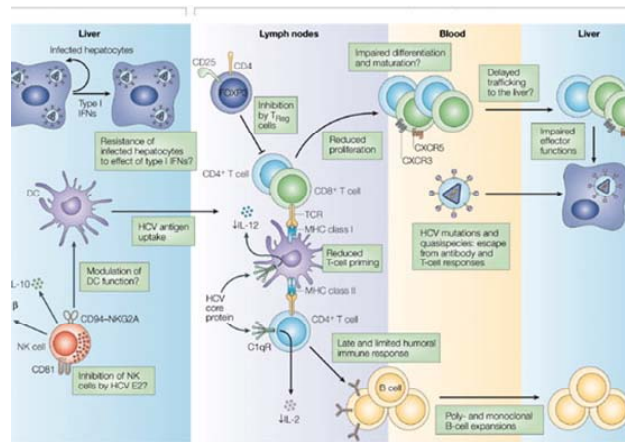
Virus-specific T cells become exhausted, because they lose the capacity to proliferate (copy themselves). There is also a sequential loss of cytokine production capacity: IL-2>TNF-alpha>interferon gamma.

In the case of HIV infection, there is persistent immune activation which slowly depletes CD4 T cells and levels of immune activation typically are higher in HCV co-infected people. In HCV, chronic activation & inflammation in the liver leading to immune-mediated liver damage (immunopathology) and disease.

Implications for Future Studies & Immune-Based Therapies

- Reasons for cases of loss of CD4 T cell responses and the requirements for sustaining responses need study
- Data suggests both HIV & HCV can impair dendritic cell function, problems with T cell responses could relate to the way the responses are switched on, DC-based immunotherapy has been proposed (Fan 2007)
- Limited studies of CD4 T cell differentiation, maturation and function during the natural course of HCV infection (emerging data suggests “polyfunctional” responses may be important in immune protection, not yet assessed in HCV)
- Importance of CD4 T cell interactions with CD8 T cells and B cells vs. direct antiviral CD4 T cell effects not known
- Role of Tregs unclear – bad or good?
- Need to map the HCV epitopes targeted by T cells of diverse populations (Los Alamos HCV Immunology Database recently defunded!)
- Improved strategies for inducing new, better HCV-specific immune responses needed
- Need to evaluate whether it is possible to improve function of existing responses (e.g. Gates Grand Challenge grant to Chris Miller/Rafi Ahmed to evaluate PD-1 blockade in HCV-infected chimps)
- Is there a role for immune activation-reducing strategies?
- What study designs for IBTs?

Dizzying array of factors proposed to contribute to HCV persistence



Rehermann & Nascimbeni, *Nature Reviews Immunology* 5:215-229, 2005

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Q&A

Q: What are the immune mechanisms induced by interferon that make therapy successful?

A: IFN-alpha it does help support CD4 responses that help infected cells to kill themselves. One potential mechanism, still controversial, is that the CD4 response is supported by IFN-alpha. Other people argue that it may be attributed to the direct antiviral effect of IFN-alpha.

Q: In co-infected people, when tacking SoC (IFN plus RBV) we see dramatic loss of white blood cells, including CD4 T cell. If SoC is going to be the background of new therapies, what are we going to do to deal with that loss of CD4?

A: This is a very good question, and I don't have an answer to it. I guess that at some point getting rid of IFN would be fantastic, but we are not scientifically there yet.

Q: Based on your presentation, given the interference between HCV and HIV, HIV should be treated first and put under controlled. But according to current guidelines, we only need to have a good amount of CD4 to treat HCV: do we need a different strategy?

A: Theoretically, based on the data we have, it is true that it would be better to control HIV first, and then address HCV.

Q: My impression is that we always we need an immune-based therapy (IFN, improved IFN, other types) to support antivirals: am I right?

A: It would depend on how potent new antivirals would be.

Towards a cure of HIV, BV and HCV?

Raymond Schinazi, Emory University & Veteran Affairs Dept., Atlanta, USA.

Note: This speaker did not authorize the reproduction of his slides: furthermore, some fragments of his talk have been omitted as they were about confidential, unpublished data.

This is going to be a very ambitious talk that requires a deep faith: we have seen vaccine failures in AIDS; in Hepatitis C we have no vaccine; and in Hepatitis B the vaccine is not available in most parts of the world.

I have been involved in drug discovery for the last 30 years. I was involved in the discovery of 3TC, that actually works for hep B and HIV, and then I studied hep C in the 90's.

In HIV we have made great advances. We have 25 drugs, clearly not all of them are used equally, but still it is a quite impressive achievement. We have very good drugs, although not everyone has access to them. Once we'll have a cure, however, everyone will be lining up for it, and even drug companies will make money out of it. Remember that 60 million are predicted to be infected in 2015.

In hep B we had nothing 20 years ago, and now we 5 drugs.

For hep C, we only have unfortunately two drugs. There are 200 millions infected in the world. Only in the US we have 800,000 patients with cirrhosis, with a similar trend in Europe. All we have learned studying in hep C will be useful for other flaviviruses: West Nile virus, dengue, and others.

HIV, HBV and HCV have in common several aspects: routes of transmission are shared, all these viruses are very dynamic, treatment is complicated and prolonged, and co-infection treatment is even more complicated.

Lesson number 1 here is that dead viruses do not harm: they don't mutate, don't transmit, aren't associated with disease progression, and are good! In that sense, you have to make sure what the status of the virus is when using a treatment, and reassuring what you are measuring is key.

We have done a great drug advance in HIV: reduced deaths, and at least in many Western countries maternal transmission is history. Standard of care may change from triple therapy to simplified regimen.

Viral loads are different for HIV, HBV and HCV, and current therapy standard is different. In HIV we are going to simplification, probably nucleoside-free combinations, although this may require more company collaboration. There is also more attention needed for Africa and developing countries.

In HCV, on the contrary, we will have multidrug combination for many years, based on my personal opinion.

Only half of HIV-infected individuals are currently on antiretroviral therapy in the US, partly because some are undiagnosed. But the situation is worst for hep B: only 21% of those chronically infected are diagnosed, and of those, only 17% are on oral antiviral treatment. For hep C the situation isn't better, as only 71,000 are on treatment out of 3,200,000: this tells you how bad the available drugs are. Patients are smart: they don't want this, and this is one of the reasons why we desperately need new drugs. More people will take drugs if they are better: earlier treatment with improved efficacy, safety

We do know that HCV related-illness is increasing: we are in a crisis, some people don't feel that way, but this is how I feel. A large number of people are going to die and only some will have access to transplant.

In summary, for HIV we have had great progress, from a high number of pills to much less, even just one, no food restrictions, etc., and now is much easier. More combined pills will come in the future.

One big problem with HIV is persistence: you use the drug, but if you stop, viral load goes up. We need something that controls viremia without daily treatment. Ongoing replication explains blips also, although we don't fully understand this.

Therefore, HIV eradication is still not feasible. What are the causes? Anatomical and cellular reservoirs are part of the explanation: CNS, lymphoid organs, gut, semen. Ongoing low level of viral replication can replenish reservoirs.

I think that is important to have drugs that can breach each compartment. I think systematic assessment of drug penetration into the various compartments is worth. We have very limited information, and more research needed. We have the tools and I believe it is possible.

Nevertheless, the compounds we have for HIV are very good, extremely potent, and we will see even more potent drugs. We can target practically any function of the HIV vital cycle.

Hepatitis B: is a different virus, although it has some similarities with HIV, like the polymerase region. The major difference is however that HIV integrates in the cell genome to modify it, while hep B virus (which is a very small virus) does not; it uses a quite stable particle called cccDNA, once introduced in the cell, to reproduce itself. Reducing the presence of Hep B virus inside the cell is then key to cure hep B.

There is one drug called Clevudine, only approved in Korea, not in the US or Europe, that helps to prevent the emergence of cccDNA. Clevudine gives you 6log drop in woodchucks. Viral load goes down and it stays there after interrupting treatment, different to any other available.

The story is different with hep C, because it can be cured! Some make Hep C disappear naturally (less in co-infected) and drugs also may do it.

Primary target for new hep C antivirals: polymerase and the serine protease. As far as I know (but this may change in the future) polymerase inhibitors are difficult to develop resistance in humans, but protease are easy. In the future we will also see antifusion and anti-fibrogenesis drugs

Today we are still trying to improve interferon, basically, but there are many companies working in hep C antivirals.

As an example PSI-6130 (R7128¹) has very good response, up to 5 log reduction. Some people do not respond, probably because they are interferon resistance. There are other drugs, also very exciting, like TMC435450: only 5 days of treatment, then you stop, and get 4log drop in viral load, only with 200mg once a day.

One important thing is not to replace RBV for a new drug, this is a mistake we learnt from HIV, but add on new drugs to the existing SoC. Toxicity and drug interaction will be major issues, specially for co-infected people.

Protease resistance, we said, is easy. The bad codon is 156, in the alanine, that drives rapid resistance and clinical failure. Also the rest can confer cross- resistance.

Q&A

Q: Should be always consider that new drugs should be added to SoC in clinical trials? It will be not very efficacious and quite expensive as we sum up new drugs. Are we doing Phase II studies wrongly?

A: I am not a clinician. The problem we have to deal with is toxicity; otherwise we would have many other options, like giving the drugs earlier and for shorter periods of time. But still, in some cases, like in Roche's, they have the opportunity to mix up two different drugs they are working with (other companies cannot because commercial issues) and are not antagonistic. There is also a regulatory issue because the FDA may ask you "which drug exactly are you testing?"

¹ Dr Schinazi has disclosed personal financial interest in Pharmasset, the company developing R7128 together with Roche.

Update on new HCV drugs from EASL 2008

Tracy Swan, Treatment Action Group, NYC, USA.

Every time I got to a meeting where new HCV drug development is discussed, and clinical trial results are presented, I always look for these elements:

Who is in this trial? How fast viral load has declined? How far viral load has been reduced? What is the dosing? What about toxicities? How many people abandoned? And what are company's plans for the future?

If one or two elements of this list are missing, I start to question about the trial. Please, refer to TAG's report on HCV drug development for further details and analysis of clinical trials.

There is a lot of stuff going on, but we do not know exactly what. I decided to concentrate on protease and polymerase inhibitors, plus the controversial nitazoxanide.

We are still stuck with SOC as the backbone. No one is sure how ribavirin works, but it is a very important component of HCV treatment, even with new HCV-specific anti-virals on board. Development of several candidates halted, due to concerns about toxicity, efficacy, & financial issues (NM283, HCV-796 ACH-806, AVI-4065, Actilon, VGX 410, MAXY-alpha, XTL 2125 and XTL 6865), but many more are in preclinical development

I have first to explain some concepts I am going to use:

- **RVR: rapid virological response** means undetectable HCV RNA at week 4
- **EVR: early virological response** means \geq a 2-log drop in HCV RNA, or undetectable HCV RNA @ W12
- **pEVR: partial early virological response** means \geq a 2-log drop in HCV RNA at week 12
- **cEVR: complete early virological response** means HCV RNA undetectable at week 12
- **SVR-12:** is often used to report data; according to retrospective data analysis, relapse is most likely within 12 weeks after completing HCV treatment

RVR is less likely in people with HCV-1, and less likely with HCV RNA below 400,000-600,000 IU/mL. Only 24% of people with HCV-1 will have RVR, but ~89% of people with HCV-1 & RVR will have SVR. All these data come from trials in mono-infected people.

RVR predicts SVR for co-infected people: RVR is less likely in genotype 1 when HCV RNA >500,000 IU/mL, but 100% of people with RVR had SVR (HCV 1/ LVL) and 50% with RVR had SVR (HCV 1/ HVL). In HCV genotype 1, 82% with RVR had SVR.

Co-infected people with LVL, genotype 3 and RVR may only need 6 months of HCV treatment with adequate dose of RBV, but still under discussion.

Study Populations

Usually the term treatment failures is used up against treatment naives, but I prefer the term treatment-experienced, because there is more than one type of experience: what was the original treatment regimen, duration, dose, how were side effects managed?

TX Experience & Outcome: some concepts:

Null responder: Little or no decrease in HCV RNA at week 12

Non-Responder: <2 log drop in HCV RNA at week 12 (Re-treatment with the current SoC is ineffective)

Partial Responder: EVR, but detectable HCV RNA at week 24

Viral Breakthrough EVR, subsequent emergence of detectable HCV RNA during TX (Re-treatment more likely to succeed)

Relapse HCV RNA undetectable at EOT (end of treatment); re-emerges within 6 months of treatment completion (Re-treatment with current SoC most likely to succeed)

Additional factors to understand the treatment results are the condition of the liver, the race, the age, geography, and adherence to treatment during initial therapy.

Oral antivirals in development belong to different classes or types: protease inhibitors, polymerase inhibitors, NS5a inhibitor, cyclophilin B inhibitor and alpha glucosidase inhibitor. Other agents under study are nitazoxanide and taribivirin. There is also research on novel interferon formulations (injection), immunomodulators (infusion) and anti-fibrotics (oral).

HCV Protease Inhibitors

In HCV PI resistance develops quickly, as it has been said. Activity may be genotypic-specific active against HCV-1. For instance, Tibotec is studying telaprevir in HCV-2 and HCV-3. And anemia may be class-wide side effect

We have so far:

- **790052:** Phase 1 (BMS)
- **Boceprevir:** Phase 2 (Schering)
- **ITMN 191:** Phase 1 (Roche, Intermune)
- **Telaprevir:** Phase 2/3 (Tibotec/Vertex)
- **TMC435350:** Phase 2A (Tibotec/Medavir)

BMS 790052

SAD (single ascending dose) trial in people with HCV is open and MAD (multiple ascending dosing) trial is opening in May 2008 – we need to wait to check the results.

Boceprevir

The lessons learnt from studying boceprevir in treatment experienced people (SVR 2% to 14%) is that we must use RBV and PEG-IFN, people must be responsive to IFN, the dose should be 800 mg tid, and early response (undetectable HCV RNA by week 8) is crucial.

Boceprevir interim data:

- Study HCV SPRINT-1: Phase II (treatment naïve, HCV genotype 1) ~26% discontinued
- 4 week PEG/RBV lead-in, followed by 24 weeks triple therapy: **SVR-12 was 57%** (n=103)
- 28 week triple therapy (no lead-in): **SVR-12 was 55%** (n=107)
- 26-28% discontinued treatment (in 28 week arms) versus 14% of the control arm
- 11-15% in boceprevir arms discontinued due to AEs (versus 8% of the control arm)
- AEs associated with boceprevir: anemia & dysgeusia (distortion or decrease of the sense of taste)

ITMN-191

There is a Phase 1b study in treatment naïve and treatment-experienced people with HCV-1: 3 log drop with 200 mg every 12 hours and 200 mg q 8 hours. AEs are mild, no discontinuations reported. They are looking to create a once-daily formulation, and moving into a 14-day triple combination study in Europe in mid-2008

PF-868554

It is in Phase 1 in treatment-experienced people (that means in this case non-response, or partial response to previous HCV treatment) with HCV-1, to be opened in 4/2008.

Telaprevir

There is much more data on this drug.

PROVE-1 is a US study with HCV-1 in treatment naïve, of those ~24% had bridging fibrosis. It is a 4-arm study, with 12-48 weeks of treatment. They had to have RVR and EVR for 12 or 24 week study arms.

Results of PROVE-1:

- 12 weeks triple therapy: **SVR: 35%** (6/17) RR: 33% (3/9)
- 12 weeks triple therapy plus 12 weeks SOC: **SVR 62%** (48/79) RR 2% (1/41)
- 12 weeks triple therapy plus 36 weeks SOC: **SVR 67%** (53/79) RR 6% (3/51)
- SOC 48 weeks: **SVR 41%** (31/75) RR 23% (8/35)
RR stands for Relative Risk

Rash and anemia are telaprevir-related AEs. The cause of rash is undetermined, but it can be serious, although it resolves after stopping telaprevir. In this study, 18% discontinued from telaprevir arms vs. 4% in SOC arm.

PROVE-2 is an European study targeting HCV-1 in treatment-naïve, of those 6-14% had bridging fibrosis. It is a 4 arm study with a duration of 12-48 weeks. Attention: one arm was ribavirin-free!

Results of PROVE-2:

- 12 weeks telaprevir plus PEG: **SVR 36%** (28/70), RR 48% (22/46)
- 12 weeks triple therapy: **SVR 62%** (51/82), RR 29% (18/63)
- 12 weeks triple therapy plus 12 weeks SOC: **SVR 68%** (55/81), RR 14% (8/56)
- SOC 48 weeks: **SVR-12 48%** (39/82), RR 20% (9/45)

RR: *relative risk*

In PROVE-2 discontinuation rate was 10% in SOC and 12-week telaprevir + PEG arms, and 12-16% in telaprevir + SOC arms (12 and 24 weeks). Again, rash was a problem, and again it resolved when treatment was stopped.

Telaprevir in TX-experienced are being tested in the PROVE-3, and data are expected in November 2008. Vertex also studied relapsers and people who did not respond by week 12 from control arms. They were treated with 12 weeks of triple therapy, followed by 12 weeks of SOC. HCV RNA had to be undetectable at week 4 and week 12

Week 12 Results (HCV RNA <25):

- N=24; people with <1 log drop at week 4: 8/9
- N=20; people with <1 log drop at week 12: 3/3
- N=19; people w/≥2 log drop at week 12, then became detectable: 1/1
- N=1; person who became detectable on PEG/RBV (breakthrough): 1/1
- N=5: people who relapsed: 2/2

TMC-435350

It has been studied in people with HCV-1. It is once-daily dosing, with mild (grade 1) AEs (headache, fatigue). It has good anti-viral activity (maximum median decrease of 3.9 log at day 6). Currently it is in a 4-week trial with SOC.

Nucleoside/Nucleotide HCV Polymerase Inhibitors

The class of Nucleoside/Nucleotide is active against all HCV genotypes, with a high genetic barrier. We have: R1626 Phase 2 (Roche) and R7128 Phase 2 (Pharmasset/Roche).

R1626

It is in Phase 2A, in people with genotype 1, treatment-naïve, no cirrhosis (less than 50% F2). The design is 4 week lead-in, followed by SOC for 48 weeks: 1500 mg bid + PEG vs. 3000 mg bid + PEG vs. 1500 mg bid + PEG/RBV vs. SOC.

The known results of R1626 show 84% RVR in triple therapy arm (1500 mg/ bid), with no evidence of resistance with triple therapy. There is however a significant problem, which is neutropenia. In Phase 2A, they are looking at 24 weeks of triple therapy, followed by 24 weeks of SOC full or half dose of PEG-IFN, plus RBV 500, 1000 or 1500 mg of R1626.

R7128

Preliminary results with 14-day MAD trial in treatment-experienced showed no evidence of resistance with a mean 2.7 log decrease in viral load. There is an ongoing trial with HCV-1 in treatment naïve with no cirrhosis, of those 80-90% had high viral load.

The study design is 4 weeks triple therapy with 500 mg bid vs. 1500 mg bid, vs. placebo (efficacy), followed by 4 weeks of SOC (safety), roll-over into SOC for the duration of the trial.

85% had RVR with 1500 mg bid (vs. 10% for placebo, 30% for 500 mg bid). AE's were serious neutropenia (15% G3 and 5% G4) and also anemia (15% G3 and 15% G4). They are now adding 2 cohorts: 1000 mg bid and 1500 mg bid in G2/3 treatment-experienced. They have also planned Phase 2B which will be up to 12 weeks of triple combination with 1000 and 1500 mg.

Non-nucleosides HCV Polymerase Inhibitors

They are genotype-specific and resistance-prone.

GS 9190 by Gilead has been studied in treatment naïve people with HCV-1. It is twice-daily dosing. Changes in HCV RNA ranged from 1.4 log (40 mg) to 1.7 log (120 mg) after 8 days.

The Upstart Trial: Nitazoxanide

FDA approved Nitazoxanide in 2002 for treating intestinal parasites. It has activity against HBV and HCV, which was discovered during cryptosporidium treatment of HIV/HBV and HIV/HCV co-infected people. Prior Phase 2 study supported further investigation as part of HCV therapy

It was studied with PEG-IFN, with or without RBV, in treatment naïve and treatment - experienced people with HCV-4, for 48-week duration of treatment in all study arms. Everyone got 12 weeks of NTZ as a lead-in (except for the control arm).

3-11% of treatment naïve study volunteers had serious liver damage. No treatment-experienced volunteers had serious liver damage. All participants were fairly young (29 to 52), and almost all were white.

Results:

- SVR triple therapy: TX naïve 79% and TX experienced 25%.
- SVR, no RBV: TX naïve 61% and TX experienced 8%.
- SVR, control arm: TX naïve 50% and TX experienced N/A (NTZ 500 mg bid).

There was one death (car accident; PEG-NTZ arm), one SAE (fever, hospitalization in the control arm), and 8 people discontinued treatment due to AEs (5 in control arm; 3 in PEG/NTZ arm). There will be studies in people with HCV-1 who are treatment naïve and treatment experienced (any type of interferon and PEG-IFN plus RBV).

Q&A

Q: The different stage of disease it is a little bit of a problem. My experience is that people are using Fibroscan for which you have the same cutoff, but interpretation may vary from

one center to the other. I was wondering how do you classify people for these trials? Even some doctor trust this system and other do not.

A: These studies used liver biopsies done to people in different times. But we have the same problem as different doctors will tell you different things about the same biopsy. I love that Fibroscan is not invasive as biopsies are, but a biopsy will tell you things that Fibroscan will not. Another confusing thing is that there are different scales to interpret biopsies, and you have to pay attention to which scale is using each study. It would be great to have a high liable non-invasive test, but we don't.

PK interactions with novel HCV drugs.

Saye Khoo, University of Liverpool, UK.

Note: Some of the presented data were confidential and therefore have been omitted in this report.

Quote from Sitges Statement 2007: “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”

I have taken this very important statement from last year to emphasize the word safety, which is key in interaction studies. I'm going to mention a little bit about drug interactions trial design: what you should be thinking about when you see drug interaction trial data? And then safety, that is to do with safe prescribing or quality prescribing. Drug interaction studies by themselves have no use whatever, but clinicians have to use them: the information is used to improve the quality of care, so it's a quality issue.

In the development of a drug from discovery to licensing there is a whole process of assessing drug metabolism and PK from preclinical in test tube and in animals, right through to man in Phase III.

This process is at best incomplete, and it is very incomplete in some cases. If you look to the preclinical process there is a limited transporter assessment, the P- protein is sometimes the only transport that they look at, but we know now from the HIV PI's that there is a lot of interesting other transporters that are very important. And then when you move into the clinical section there is an incomplete coverage of the drug and population variability is not fully characterised.

If you are lucky and get a license and then you make well you might discover uncommon toxicity issues. Very likely in the HIV world you will discover unsuspected interruptions, you are likely or possibly likely to discover that your drug behave differently in different ethnicity, by bodyweight or gender, or children doesn't respond with the drug in a way that you expected to, and there is also other things.

Here is an interesting paper that I found:

ORIGINAL REPORT

Postmarketing changes in
new molecular entities

James Cross MS^{*1}, Howard
Charles Grudzinskas PhD

¹Division of Metabolic and Endocrine
²Center for Drug Development

SUMMARY

Purpose Risks and benefits of
indicated populations. Such post-
review, and postmarketing surveil-
and investigated trends over time
have yielded fewer postmarketing
Methods We compiled a list of
Freedom of Information Act requir-
original labeled dosages and indica-
covariate-adjusted risks for dosa-
Results Of 499 NMEs, 354 (71%)
A total of 58 (79%) were safety
ranged from 27.3% for neuropt
approval fell from 6.5 years (1.5
3.15 times more likely to change

Conclusions Dosages of one in five NMEs changed, four in five changes were safety reductions. Increasing frequency of changes, independent of therapeutic group, may reflect intensified postmarketing surveillance and underscores the need to improve pre-marketing optimization of dosage and indicated population. Copyright © 2002 John Wiley & Sons, Ltd.

Dose change:

- ZDV, d4T, ddI, SQV

Unsuspected interactions:

- TDF + ddI
- ATVr + PPIs
- SQVr + PPIs
- SQVr + Rif
- TPVr + enfuvirtide
- LPVr + rosuvastatin
- RBV + ddI / ABC

Population variability:

- EFV & ethnicity
- gender effects

Dose incorrect:

- very young children
- pregnancy

FDA-approved

armD², Julie Nelson MBA²,

Research, FDA, Rockville, MD, USA

els to optimize dosage regimens for
-marketing development, regulatory
ved new molecular entities (NMEs),
nproved drug development methods

December 1999 using FDA's website,
(Manufacturers of America) database. Ori-
stician's Desk Reference[®]. Time and
ere estimated by survival analysis.
lations occurred in 73 NMEs (21%).
s with changes by therapeutic group
. Median time to change following
r premise, 1995–1999 NMEs were
k analysis).

Increasing frequency of changes, independent of therapeutic group, may reflect intensified postmarketing surveillance and underscores the need to improve pre-marketing optimization of dosage and indicated population. Copyright © 2002 John Wiley & Sons, Ltd.

Taking into account all the FDA approved new molecular entities in 20 years, this group looked at changes in the original licence dose and found that nearly one in five drug have had a licence changes. That's a lot! In other words the preclinical work is not a complete one. And examples in HIV are common. Dose changes have been instituted for ZDV, d4T, ddI, SQV, we now that, also we have unsuspected interactions. We found a huge population ethnicity effects with EFV and then there are issues where the original dose was simply wrong.

We have got five classes of drug currently (PIs, NRTIs, NNRTIs, entry inhibitor and integrase inhibitor) and hopefully soon maturation inhibitor, and at least these groups of drugs work intracellular, so that gives you another dimension of interaction, other than plasma. So you need to look inside cells, which implies that a whole magnitude of technical difficulty are to be counted.

So let me take you through to the life of tablets, and forgive me if I'm making things really blinding obvious. You swallow and hopefully it's getting dissolve. Before it's getting dissolve, the way the tablet dissolves and how it behaves in the pressure of the gastric acid is quite important. Certainly there are drugs susceptible to gastric acid; for example there are some drugs that actually require acid in order to dissolve and to be absorbed. And also there are food effects -food can make the drugs levels state the same, go up, or go down.

The drug has to make the way across the gut wall to get to the liver, using some transports, and the liver cells metabolized it and need to pump it out. But this is half of the story, because your drug has to work inside the cell.

Let's go to the HIV/HCV co-infected person. Let me illustrate what I think are gaps in my knowledge. We don't know much and I couldn't find much key interactions data against

with methadone, buprenorphine, naltrexone, and heroin substitution of course, but this data will emerge. There are little data on HIV drugs and even less in intracellular interactions between nucleoside(tide) analogues. We need to investigate the 'usual suspects' that you see in any SPC. But there are other things that you clinicians have to think about and this was identify in your document last year, the Sitges Statement, very hard to do ethical studies of ecstasy and amphetamine. Also we have to take into account people who get liver transplant and take immunosuppressants, antifungal and transplant drugs.

Here you have a website of drug interaction where you can find much information about it:

The screenshot shows the homepage of the HIV-Drug Interactions website. At the top, it says 'welcome to the www.hiv-druginteractions.org website' and is associated with 'THE UNIVERSITY of LIVERPOOL' and 'THOMSON eMED-MEDIA'. A navigation bar includes links for 'Interaction Charts', 'News', 'LHPG Resources', 'Pharmacology Resources', 'Links', 'Meetings', 'TDM', 'Feedback', and 'Home'. The main content area is titled 'HIV CHARTS 2 GO' and features a section for 'LATEST NEWS' with sub-sections for 'Hot Topics', 'Recent Publications', and 'Drug Interactions'. There is also an 'EMAIL UPDATES' section with a link to register for updates. To the right, there is a 'DRUG INTERACTION CHARTS' section with a table of drug interactions. The footer includes logos for 'THE UNIVERSITY of LIVERPOOL', 'gsk', 'ABBOTT LABORATORIES', 'Roche', 'Other Sponsors', 'Disclaimer', and 'Glossary'.

Design of interactions studies

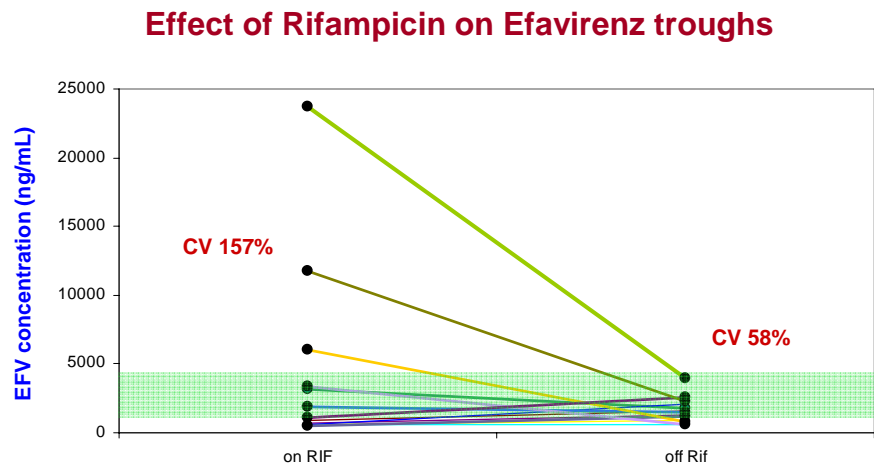
What would you look at? The first thing you look at is if you are using healthy volunteer or patient group. Studies in HIV have clearly shown that HIV positive patient have lower plasma exposure of drug than healthy volunteer. And that's true for ATV/r and TPV/r, and less clear for LPV/r, SQV/r, DRV/r and FPV/r. The question then is what effect does HIV and HCV infection have on HCV drug disposition?

Then you move to single dose or steady state? Single dose does not reflect the reality. If you got boosted tipranavir that is enzyme-inducer and ritonavir which is enzyme-inhibitor, if you get an interaction drug and you get a single dose, all you see is boosting effects, and a wrong result from your study. This is very important for how you interpret drug interaction study.

Other considerations are fed vs. fasted, inclusion of women, body weight, cocktail of probe drugs, and what is the important PK parameter? Although there is not harmony between EMEA and FDA guides. If you look at the FDA guide based on interaction study which was

published in 2006, the major outcomes that you see are C_{max} and clearance. But there is not necessarily the parameter for efficacy – although for HIV is clear, one of the major parameter for efficacy is the C_{min}. And also the other thing they don't bring out is variability. Drug interaction might raise your drug level or might low your drug level, or might just increase your variability.

There you can see the effect as example the effect of rifampicin on efavirenz troughs, which was a study that we made in South Africa:



START Study (Durban)
 n=19 HIV+TB starting EFV (600mg) shortly after commencing TB therapy
 EFV measured at M1, M2, M4, M6 and off Rifampicin
 >50% patients had EFV levels outside therapeutic range

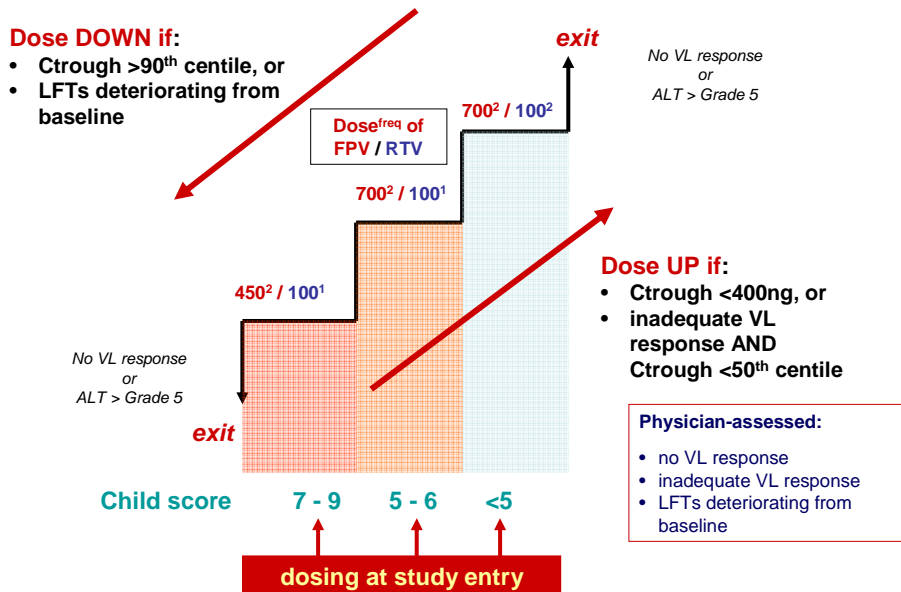
Friedland, Khoo, Jack et al. JAC 2006

We have safe prescribing in liver dysfunction, we most prescribe safely. And of course, you can have hepatitis C and minimum hepatic impairment, and you can have hepatitis C and major hepatic impairment. So hepatitis C patients are not the same. So you might have to alter dose or frequency dose and also see what biomarkers of liver dysfunction to use. But you might change your unbound fraction of drug because if your drug is heavily bound to plasma protein and your liver is the factory for this plasma protein and your liver is not producing them, you ought to check the free fraction of drug. So this things need to be studied.

What is the role for therapeutic drug monitoring?

Here you can see interesting example from a European study about how to give fosamprenavir safely in hepatitis B and hepatitis C co-infected patients. The preliminary data validated these three doses against people with Child score, so we've proposed a trial design where people with hepatitis B have been scored and growing in different dose. And then look how to treat the patients safely.

Example – fosamprenavir study



So we have to look also the population variability, as effect of gender, weight, ethnicity, children and pharmacogenetic influences. Here we have some results from different studies:

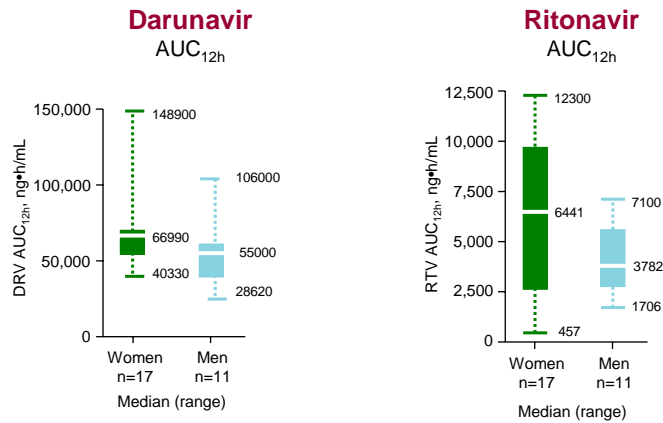
Gender	Women vs Men	ZDV -TP & 3TC-TP ↑ [1] NVP ↑ [2-4] EFV conflicting SQVr ↑ [5-7] DRVr ↑ [8]
Weight	Increasing weight	NVP conflicting EFV ↓ [9] SQVr ↓ [10]
Ethnicity	B African vs Caucasian	NVP ↑ [9,10] EFV ↑ [9,11-13] SQVr ↑ [14]
	Thai vs Caucasian	NVP ↑ [10] SQVr ↑ [14,15]

1 Anderson. AIDS 2003;17:2159
2 LaPorte. 4th IWCPHT 2003
3 Zhou AAC 1999;43:121
4 Regazzi AIDS 2003;17:2399
5 Fletcher JID 2004;189:1176
6 Ribera. AAC 2004;48:4256
7 Dickinson. 6th IWCPHT 2005
8 Sekar. 9th IWCPHT 2008

9 Stoehr. 9th IWCPHT 2008
10 Kappelhoff Antivir Ther 2005; 10:145
11 Csajka et al. CPT 2003; 73:20-30
12 Pfister et al. AAC 2003; 47:130-137.
13 Burger et al. BJCP 2006; 61:148-154.
14 Dickinson (in preparation)
15 Autar JAC 2005;56:908

But a really good study has shown a few weeks ago in New Orleans, with darunavir in the Grace Study, in which they looked to enrol a specifically different ethnicity group and women. The data showed that women had about 20% higher DRV exposure than men and that was independently on bodyweight. And in terms of ritonavir, because it was boosted DRV, the levels was 70% higher in women than men.

GRACE Study



- Median exposure to DRV (AUC_{12h}) was approximately 20% higher in women
- Median exposure to DRV (AUC_{12h}) was approximately 70% higher in women

Pharmacodynamic interactions: what is the effect of HIV on HCV response? And the big question of when to start. And also the effect of HCV therapy on HIV, what happens with CD4, particularly with interferon, and the viral load? And then the overlapping syndromes as deteriorating LFTs (flare, drug hepatotoxicity, IRIS), jaundice, NASH, lactic acidosis, glucose intolerance, lipoatrophy vs wasting...

Let me move to the last point that is the most important, which it is the quality of prescribing. Numerous examples exist of suboptimal prescribing in HIV therapy. There is lack of knowledge of drug interactions account for a large part of this poor quality of prescribing. In CROI last year there was a study that showed that 14% of patients in a large cohort had significant interactions and almost 30% of these increased the risk of failure treatment. So let me go back on this. I think what is needed to see equivalence for drugs interactions in the clinic next to the patients to prescribe safely, and a great tool for everyone is this website: www.hiv-druginteractions.org.

Let's finish. The urgent need to characterise HIV/HCV drug interactions and intracellular interactions cannot be ignored; PK-PD relationships need to be defined, the role of TDM should be explored, also industry - academia partnerships, identify factors that influence population PK variability and develop tools to support good quality prescribing in complex therapeutic scenarios.

Q&A

Q: TDM is so important and it is going to be increasingly important in the next years, for HIV medications, and for everybody who have to treat cholesterol, blood pressure,

diabetes, etc, and we don't know what happens with all these things. I have curiosity about how much does this test cost?

A: It depends on the lab, but I think is about 60 pounds for one drug. Although I think for the second drug is cheaper.

Q: Do you think that when designing the first clinical trial for testing hepatitis C drug in co-infected people TDM should be included as a regular basis?

A: I think is not practical. In the first clinical trial you need to define your PK-PD relation.

Q: Can you talk about the difficulties in estimating free fraction of drugs? I mean there is something in TDM that you really don't pick up and in other occasions could be quite significant.

A: It's difficult. And people have whole conferences and workshops about protein binding. Something that I never fully understood, I have to say.

Q: How do you determine what the threshold is in getting a particular drug to steady-state vs. the risk of resistance safe with hepatitis C protease inhibitor? Because it is a terrible idea that someone that is a volunteer in a study is going to be left with nothing but with drug resistance.

A: You're right. This is very difficult. You need to do both, you need to do the control study and you need to do the population variability study the later on.

Access of co-infected people to new HC drugs: the community perspective.

Diego García, Spanish CAB FEAT, Murcia, Spain.

Last year in the Sitges Statment we all agreed that trials of novel HCV therapies in HIV/HCV co-infected people should begin before approval is granted for their use in HCV mono-infection. We really need this point to become a reality for us. It's time to start work and hard work to say how we can solve the big problem.

Talking about access, who is going to have access to those clinical trials? Reading the draft from the EMEA about clinical trials on novel HCV drugs, they wrote that "it is anticipated that initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection, do not have advanced fibrosis and are not co-infected with HIV". That's a pretty disappointing start for a guideline taking into account what we are treating to move forward here.

We need to understand what does exactly the EMEA mean by initial clinical development?

Key issues:

- The community think that all parts should **agree** and **commit to develop** specific trials for co-infected people as **early** as possible.

- Co-infected people, with moderate-advanced fibrosis and treatment experienced are a large and a very representative population, even more large and representative that the EMEA focus on. Where are those?

Swan and Chung put a letter to the editor in *Hepatology* (April 2008). They wrote that "there are ethical, practical and scientific reasons for studying experimental therapies in representative populations: **regulators 'should' want a representative sample of patients who will be using a drug included in registration trials; patients and clinicians want a realistic idea of safety, efficacy and tolerability of a given treatment;** and sponsors benefit from pursuing a broad indication". We all gain; we really need to take these words very seriously because they are very wide, very clever and very well oriented.

- The community demand , **safe access** to experimental DAAs for Hep C for co-infected people which implies **early** drug to drug **interaction studies** between experimental Hep C drugs, anti-retroviral for HIV, transplant medications, substance abuse substitution therapies and commonly used drugs to palliate AEs of SOC

So, the community think that participant in those trials should have a stable viral load and an appropriate CD4 count. To have a stable viral load means most of us have to have an anti-retroviral regimen, they are going to be large of possible drug-drug interactions, etc. We think that novel and simplified regime of anti-retroviral should be explored to reduce possible interactions.

In these last few years we've come across with new families that use different targets of HIV replication that may not interfere so severely with novel hepatitis C drugs. So we could explore those possibilities, for example:

- CCR5 +/- or Fusion Inhibitor + Integrase Inhibitor +/- or Nuke if Hep C PI
- HIV PI mono-therapy if nukes for Hep C
- HIV PI + Integrase Inhibitor if nukes for Hep C
- HIV NNRTI + PI if nukes for Hep C
- HIV NNRTI + HIV nuke/s if Hep C PI

Also we think it is very important that a minimum number of CD4 should be taken into account and agreed between parts to assure there would be no health problems due to low numbers of CD4 cells. We need to establish like a minimum of CD4 cells people should have before enrolling in this kind of trials to assure that they are going not to be any health hazard for the person enrolling them.

People with advanced fibrosis or cirrhosis (Child Pough A-B) and/or with high ALT levels who are not contraindicated to use Peg interferon + Ribavirine, should be able to enter those trials. But we need to document the safety and the efficacy of new Hep C drugs in people whose liver condition may imply dose modifications to find the optimal dosing.

People on methadone, buprenorphine, naltrexone, heroine, alcohol and other substance substitution programs should be able to take part of those trials. We would like to point out that it would be very nice if we for once were able to explore the legal and ethical implications of designing interaction studies with non legal street abuse substances like cocaine, ecstasy and methamphetamine, because this is a reality.

The inclusion of active drug users should be considered individually and not considered exclusion as a general rule. There already are experiences of active drug users participating in trials and this can be done with appropriate support and close follow up.

People with minor psychiatric and/or psychological problems if stable and controlled should participate in clinical trials. Interferon seems to be the backbone of future therapies for Hep C, so we already know that interferon can lead to psychiatric and/or psychological events. In recent years we have gained knowledge of how to handle these events and most people have been able to deal with interferon therapy in a safer and more successful way. So **any trial of new Hep C drugs using interferon as a backbone therapy should include ongoing screening for depression and access to free mental health care.**

We need **a sufficient number of women** to do sex-specific analysis of toxicities, side effects, etc.

It is necessary to explore the possibility of access to stable transplant people or people with decompensated cirrhosis either on transplant list or not. We need to know the results from interaction studies with current drugs used in transplant people, how the new drugs work for them as for viral response and pharmacokinetics.

Apart from access is important to know the safety concern. **We need drug-drug interaction studies as early as possible and specify which ART shouldn't be used:**

- Due to increased risk of toxicities
- Due to possible cross resistance with ART families
- Due to possible loss of efficacy of HIV or Hep medication

And we have a lot of questions to be answered:

- Will it be safe to use PIs for HIV and PIs for Hep C at the same time?
- For the DAAs which are nucleosides what implication will have their phosphorylation and current HIV nukes phosphorylation?
- Which combinations of ART or new Hep C drugs would need dose adjustment?
- How could interaction the drugs used to palliate the AEs of interferon and ribavirine with the new drugs?
- How to prevent the development of resistance to new class drugs?
- What effects will have on new DAAs with immunosuppressors

Management of Adverse Events

- Close follow up and management of adverse events.
- Grant psychiatric or psychological care if needed during trial
- Grant adequate coverage by social services
- Provide free of charge all other medications needed to palliate adverse events.

We learnt from the HIV that:

- A clinical trial must provide, in a safe and ethical way for participants, answers to a wide range of questions and concerns:
- We need to make sure we don't put in risk future options for participants
- We need to make sure that a diversity of affected people could be able to participate
- People in difficult health situations should be able to benefit from new drugs as soon as possible

Discussion:

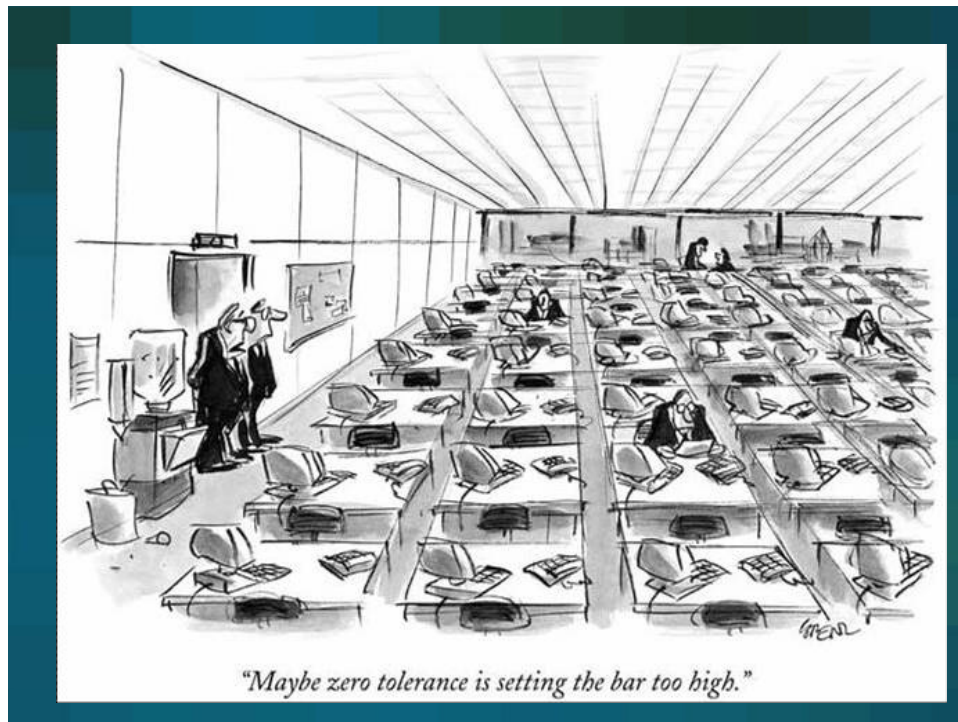
What often happens is that everybody says that all these points presented by Diego are important but none does it.

We cannot reduce risk to zero in any part of the development of a given drug on clinical trial. The same things about testing the drug even in the most clean population in risk for resistance and risk for interaction with approved drugs. That risk won't be zero. The point is that community representatives working on treatment issues and working with all these populations we are willing and available to engage and follow up conceptualizing designing and monitoring clinical trials with you, with companies. By involving community there are two benefits: we can jointly decide what level of risk is acceptable in each step; and we would have more power when discuss with regulators.

Designing trials for drug users: best practices for recruitment and retention.

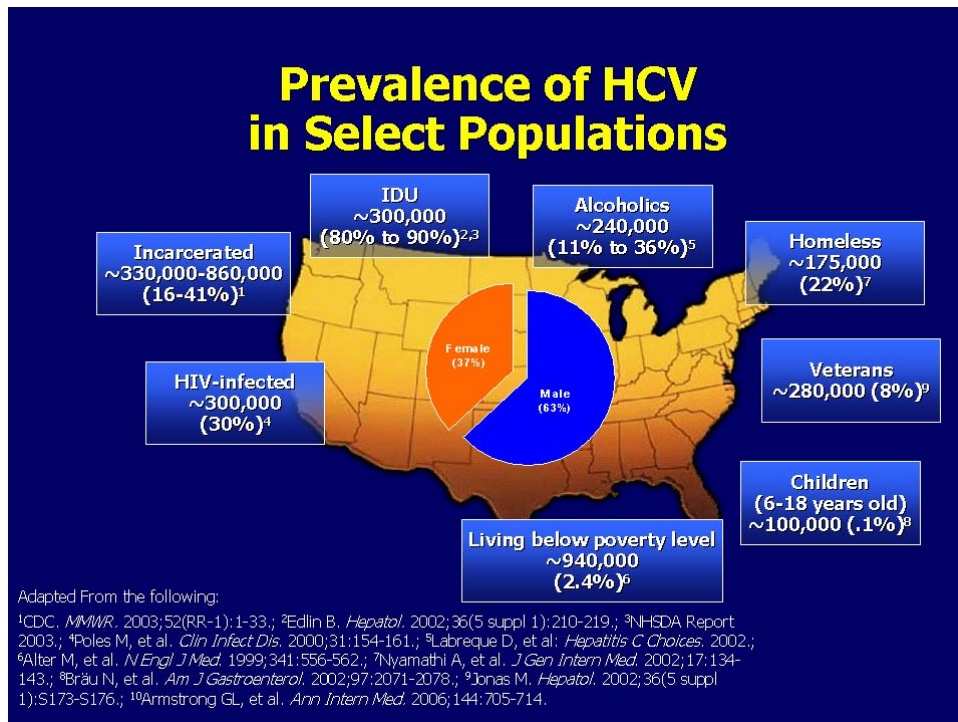
Diana Sylvestre, UCSF, San Francisco, USA.

I've changed the title that I was supposed to make two days ago and this is instead "Designing trials that include drug users: best practices for recruitment and retention". And you'll see I believe that we should be separating drug user away in the way that we do for a variety of reasons, but since we are separating drug users away this is kind of what we see, isn't it?:



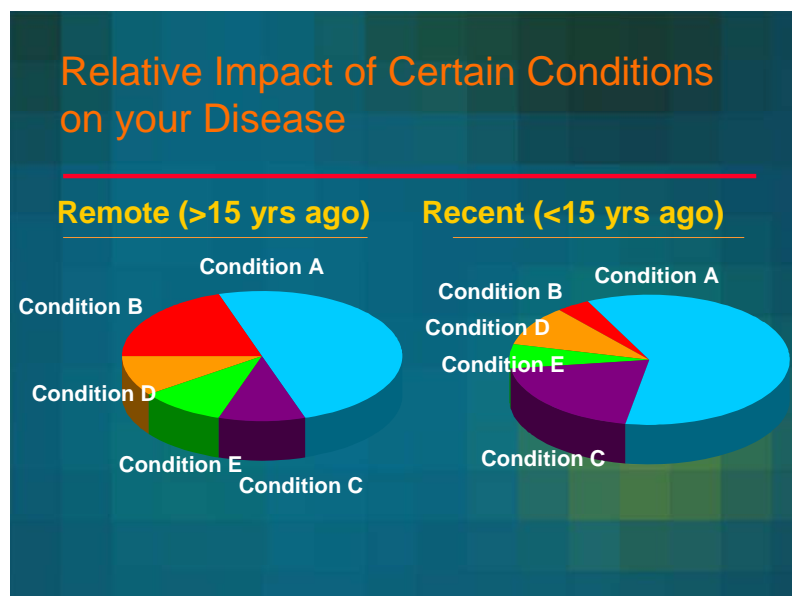
We are not really seeing the people that we think are seeing in these trials. I mean, where is the SVR with the use of peg-interferon and ribavirin, where is it? Where is it? 55%? What per cent of people who are real eligible are actually enrolled in those studies? More than 5%? We cannot overcome now this fewer rates of peg-interferon and ribavirin because we set the bar too high and we need to change that.

Look what hepatitis C in the USA looks like. And how many of these people are in clinical trials?

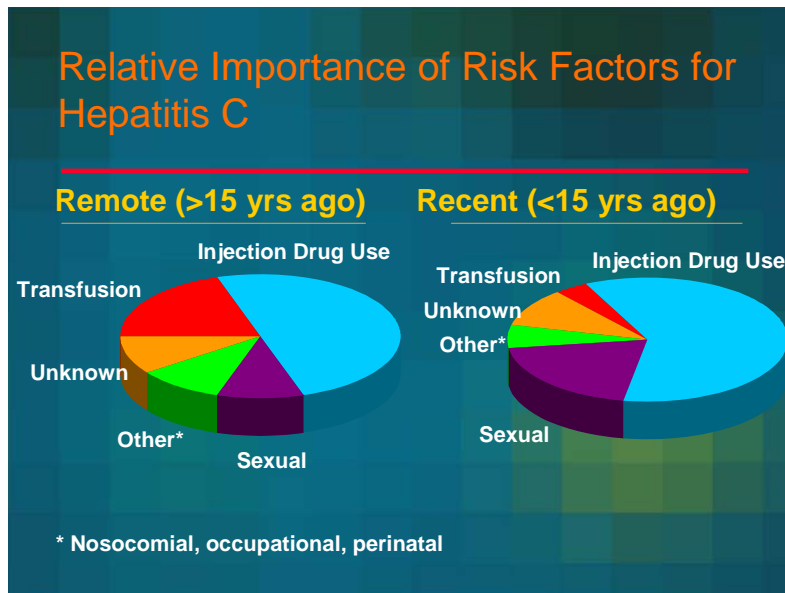


Incarcerated people, injection drug users, alcoholics, HIV infected, veterans: they are never on trials. So we don't know what this medication does, really.

If you are running a company and I ask you: "I'd like you to design a drug for this disease and this condition impact upon this disease". What will you focus on? What will you really specifically want to study in your clinical trial? This is how the disease acts in all the different conditions.



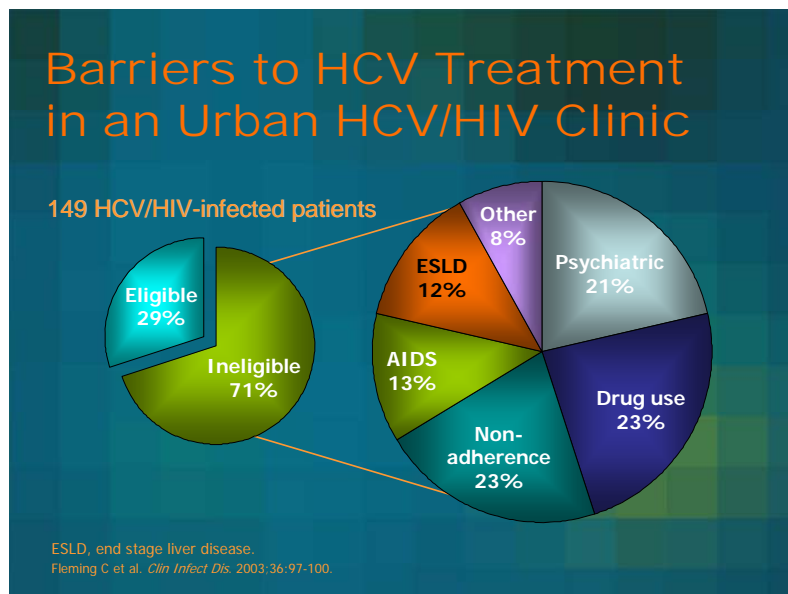
And which one will you choose? Will be A, right? You will certainly look at A because that is the biggest piece of the pie. This is hepatitis C:



Injection drug use is increasing the impact over the years and injecting drug user. We had 50% of seroprevalence 15 years ago and now we have 70%. And we are ignoring that.

And here is what we look like worldwide in terms of HIV patients co-infected with 30% in USA and 50% here (Spain). Co-infection is gigantic problem we talk over, over and over again and the prevalence of hepatitis C in HIV patients varies widely: in the USA is 85 to 90% in injecting drug users. If you have an HIV-patient that is drug user and the HCV test is negative, test again!, because I don't believe the test.

Look at the percentage of patients who are considered ineligible for care (71%).



And look at some of these reasons: psychiatric conditions (21%), drug use (23%), non-adherence (23%), AIDS (13%), ESLD (12%), other (8%). This is a reality, and this entirely unacceptable, and then we have more cases than we've been just talking about.

If we do this study sequentially rather than can concurrently, a general sketch would be: we're going to start Phase III study with the new PI this year, but it's going to take a few years to approve it in 2012, and then we can finally start Phase IV studies - we won't have the results until 2015. So we are looking at almost a decade away for getting the results of the impact of new drugs in the so-called especial populations.

There are so many benefits to do it early and timely. We can reduce morbidity and mortality, that's number one. And what a wonderful public health opportunity to get rid of this disease, particularly in drug users, because it reduces the spread and reduces new cases. So we should be focusing on drug users and not excluded them from the trial.

If we don't take part in that all together we can't eliminate hepatitis C from the planet. Because you can give me the perfect drug but if we don't go out with the real population who have hepatitis C we are not to make the impact we need to, and we should be able to cure the hepatitis C from the planet:

"All the News
That's Fit to Print"

The New York Times

Late Edition
Today: Hot, Really Hot. Global warming hot.
Flight 58, Lower 57. Tomorrow: 50% Chance
of sunspot, 60% Chance of food. Yesterday:
Tropical Storm Florence ravaged Brooklyn and
Manhattan. Weather Map on page D15.

VOL. CLIV NO 53,011
MONDAY, MAY 15, 2023
12 DOLLARS

HCV ELIMINATED FROM PLANET

Deadly bloodborne virus cured. Joins list of unthreatening diseases; polio, consumption, scurvy, cabin fever.

By Rómulo A. Tenés

Veteran, in his Dictionary Philosophique says:

"What? A rigorous test is requested to affirm that the surface of a sphere is equal to that of the quadruple of the surface of the circle round its central point." and yet does it not have to be rigorous, for example, in certifying the whole of Picasso's false work between 1891 and 1937 which was undoubtedly made by his father, José Ruiz Blasco? Or the centenary canvas, 1935 "Dama en Eden Concert" as is that one?"

Well, dear investors in art, that is how it is. In valuing arbitrariness, contrary to the most elemental common sense, and to the exclusive benefit of unscrupulous art merchants, science is not used in certifying Picasso's work.

A grotesque example of this is Josep Pallas i Fabre, "biographer" whose only credit resides in isolating Picasso to his own benefit. A clumsy heaving aid to his end, he pretends to listen, expecting the paintings to speak. He is dead. Fine.

Cure Attributed to Stem Cell Research

But, capitalist Conception, Claudio, and Patricia Ruiz-Picasso defend the esoteric, clumsy, and grotesquely irrational system of certifying the work of their father, to their own benefit, and with catastrophic results: thousands of false works, and the subsequent loss of credit.

Would an investor not allow such an individual to enter his company entrusted with its management, or as an instructor for his clients?

Why then does he accept him in his investment in art? Why does he not demand medical, rigorous, scientific certificates?

"Dama en Eden Concert", timely remained silent in the face of the grotesque system of certifying its virginity.

JOSÉ RUIZ BLASCO, 1895. LIK ON CANVAS, ATTRIBUTED TO PICASSO. THE "P" OF JOSÉ, HAS BEEN LABELLED TO



Photo: GUSTAVO HAZELI, C.

"Dama en Eden Concert", oil on canvas, 80x59 cm. Picasso 1903. Signed in the top right-hand corner, with scientific certificates issued by Doctor Marianne Tauber from the Swiss Institute for Art Research, Prof. in Chemical Engineering, Francesc Siverna, from Leuvenne and Barcelona University; and by Historian and friend of Picasso, Pierre de Champfleury, Pierre Delsa says in his Dictionary that "We own Champfleury the best study on Picasso's pictorial sources, written about in his book, *Omnia et sola, Paris 1960*. Analyzed by X-Ray, appearing on the sub-layer, is the father of the artist reading." Picasso marked the frame with the numbers "1937" and "1937".

ness that Picasso had taken over by deceitful means all the works whose author was undoubtedly his father, José Ruiz Blasco in the period between 1892 and 1897. Specifically, the "P" of José Ruiz had been labelled to the "P" of Pablo, and was untruthfully and deceptively assumed by Pablo Ruiz Picasso; this is how much worse with the fraudulent Picasso donation in 1970 to Barcelona City Council: a donation which contained all the works of José Ruiz between 1892-1897.

What did Conception Ruiz Walter, Claudio, and Patricia Ruiz Blasco know?

This circumstance, would not worry us if it were not for the fact that the researcher was compelled to register the irregularities before the Central Course of Jurisdiction of Madrid on 10th June 2003 and 15th July 2004 and request by Law the separation of the work of both artists, father and son. This separation is compulsory by Law.

As a result, the successors of Picasso must lose all their rights regarding the works of their grandfather, José Ruiz Blasco.

The chief Curator of the Prado Museum of Madrid, Antonio Solano, concerning the present system for valuing Picasso affirms: "Authentications by the descendants of painters would not be accepted. Some are so discredited, it is embarrassing".

However, we see what has been done by Christian Zevada, 1932, Juan Richardson, Pierre Delsa, Marilyn McCully, Henry Gidde, Douglas Cooper, Pierson, Colleen Hurlin-Blay, William Rubin, Barula Popcar, María Teresa Ovejuna, Josep Pallas i Fabre and Norman Mailer, 1966, one of the latest writers

archy, which is verified in a Calligraphy Report dated 27th December 2002 by the expert calligrapher Ms. Rosa Torrens Boley and Ms. Silvia Tarrago Goarri, from Barcelona, Spain.

**Hepatologists Party
Like it's 1999.**

This report contains 250 pages and certifi-

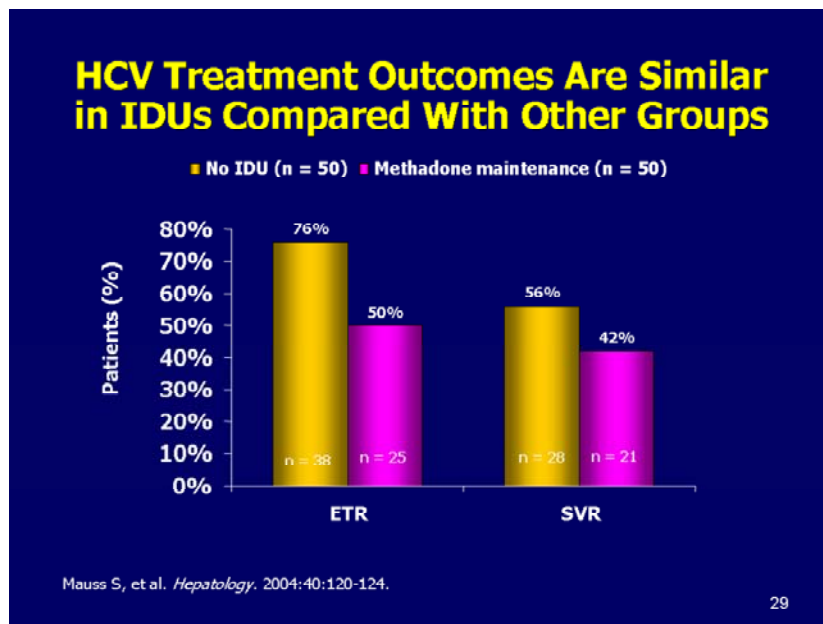
**Former President
Bush indicted for
War Crimes**



Rómulo-Antonio Tenés, Spain, art researcher and artist, is the author of the book *Fraud Picasso*. He talks to Court Goya's New Caprice Exhibition for proven fraud at the National Library of Spain, La Vanguerda, 11.8.81. He achieved the removal of a false painting, attributed to Dario de Rayoyas from the Prado Museum, news flash by REUTERS and EFE World Press Agency: 20.02.1988. He participated in the Homage to Picasso 1991 at Eliza Art Gallery along with Henry Moore, Chiloa, Taylor, Miro, Rafael Alberti, Casagor, Oliva, Saura, and other famous artists. In La Vanguardia, dated 8-10-1983, he published a study on Picasso's plagiarisms of the Horse in the Stadium, which was painted by Ricardo Martín, Nuevo Mundo, Madrid, 6-08-1914.

Why are addicted patients (and co-infected patients) excluded from Phase 3 HCV studies? The first reason is to reduce the efficacy. If I run a company and I want this drug running on the market, if the company includes in the Phase III studies patients who could reduce their outcome then they might not get on the market. Because there is good evidence from the immunologic perspective that HIV co-infection reduces your outcome, alcohol intake reduces your outcome also. So you are going to give results you don't like.

But in fact, there is no evidence that this is the case. Actually, I can show you some data that prove the contrary, like this one by Mauss et al.



Another reason we have traditionally excluded patients from this trial is safety issues, the potential for overdose. But you know that happens anyway. If you take care of addicted patients you don't have to put them on a hepatitis treatment to see them on overdose. Overdose may happen, and may not necessarily be due to the drug in trial.

There is also a lot of co-morbid psychiatric disease in drug users. And evidence suggest that some psychiatric patients can be very capable treated when they are in settings that take care of their needs. There is evidence that depressive patients can do quite fine.

We heard over and over again about the potential drug-drug interactions. But what bothers me is that we talk about hypertension, or diabetes, but not other drugs we need to look at. For instance, in a recent study methadone was excluded, but not other agents with a similar action, and this prejudicial. And then we have peg-interferon and heroin, cocaine, methamphetamine, etc., there is no evidence of any interaction there. But we exclude the people because there may be a "possible" interaction.

We have listened many times that drug users reduce adherence, but there is evidence suggesting that drug users adhere as poorly to medication regimens as non-drug users. It is more a perception than a reality.

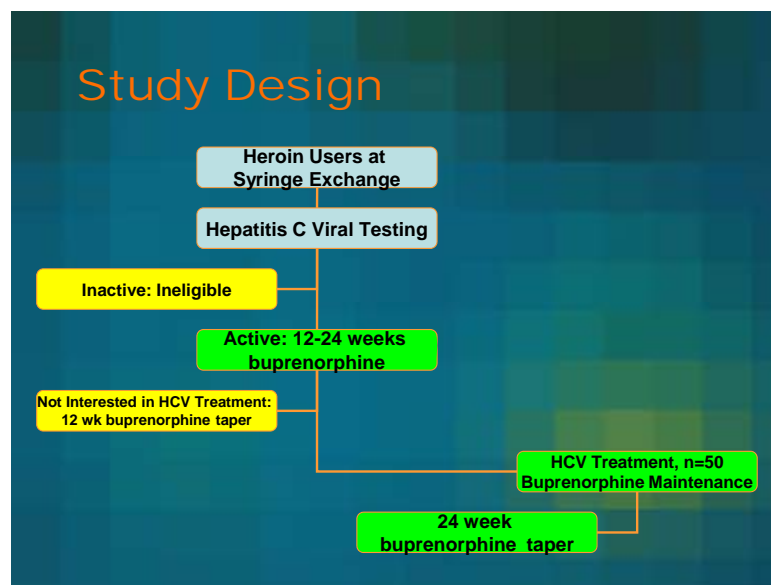
In summary the real reasons why drug users are excluded are 1) the perception that drug users can be more challenging (and certainly they can be, given the way we usually treat drug users), 2) the failure to understand that addiction is a medical illness, and 3) the investigators that are chosen to conduct Phase 3 studies lack relevant expertise.

Now I'm going to show the OASIS study that we, a non-profit clinical based clinic, organized to achieve solutions on substances abuse. We are located in Oakland, California. Our situation is that we have a high rate of poverty and drug users (heroin, crack cocaine, metamphertamine), very high seroprevalence of hepatitis C (it's about 95% of IDU's in my

clinic), there are low rates of health insurance (limited access to medical care and drug treatment), and we have syringe exchange, that is sometimes tolerated.

Our hypothesis of this particular study which is sponsored by the National Institute of Drug Abuse in our country was that active, street-recruited heroin users can be safely and successfully treated for hepatitis C after 12-24 weeks of buprenorphine stabilization.

The is the study design,



When we are on the street we do venopunction for viral testing because we have to find if they have an active hepatitis C. If they did, they were asked to come on facilities on the daytime in a regular building and we offer them three months of buprenorphine and after three months they choose: they can either not to treat hepatitis C or choose to be treated for hepatitis C. If they go for HCV treatment, they can access 24 week buprenorphine taper afterwards, hoping that they will transfer to maintenance substitution program. Please, remember this a safety study.

Who can initiate HCV treatment? People who have active HCV, are interested and attendance of more than 75% of weekly education sessions (where we give them buprenorphine and the IFN injection, plus RBV for daily oral intake), regardless of any other condition.

We screened 415 people; 275 were eligible; 140 (33%) were ineligible because 94 of them didn't have viremia (23%), 29 were on methadone (7%), and 17 didn't have opioid addiction (4%).

The study sample is representative

The study sample is representative

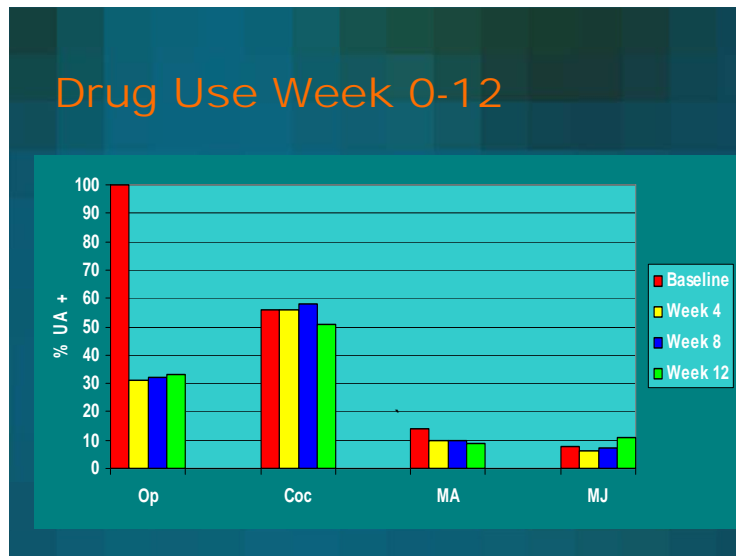
	Screened	Eligible	Enroll	Start Study Meds	P Value
n	415	275	188	146	
Age	46 (20-69)	46 (24-69)	46 (24-64)	46 (24-64)	NS
Male	70.4%	74.9%	73.9%	71.2%	NS
White	34.5%	32.0%	31.9%	33.6%	NS
Black	37.3%	40.0%	39.4%	41.8%	NS
Latino	23.9%	23.6%	23.4%	19.2%	NS

The study sample is representative

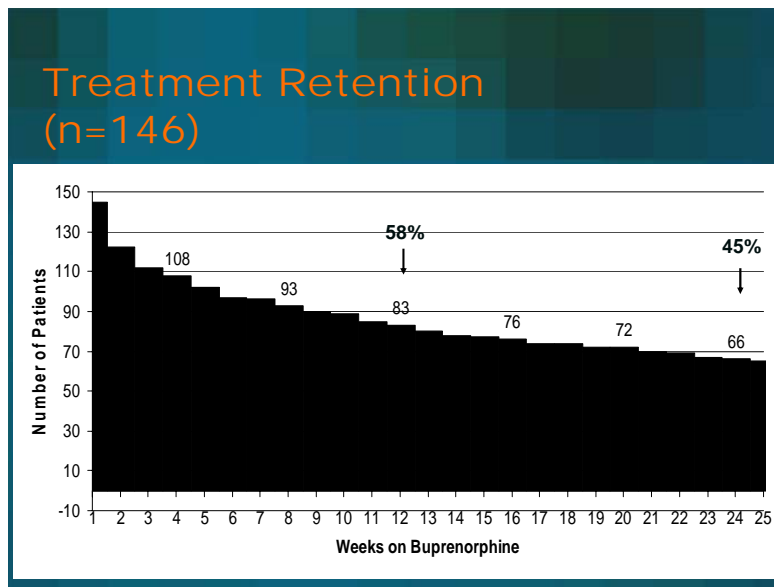
	Screened	Eligible	Enroll	Start Bupe	P Value
Yr. exposed	24	25	25	25	
ALT	46	53	55	54	<0.001*
% Cocaine	47.5	50.6	48.6	50.0	NS
% Methamp	15.6	14.9	13.5	13.2	NS
% Alcohol	58.0	50.3	60.1	55.5	NS

*Significant for the difference between screened and eligible cohorts

And here we have drug use till week 12.

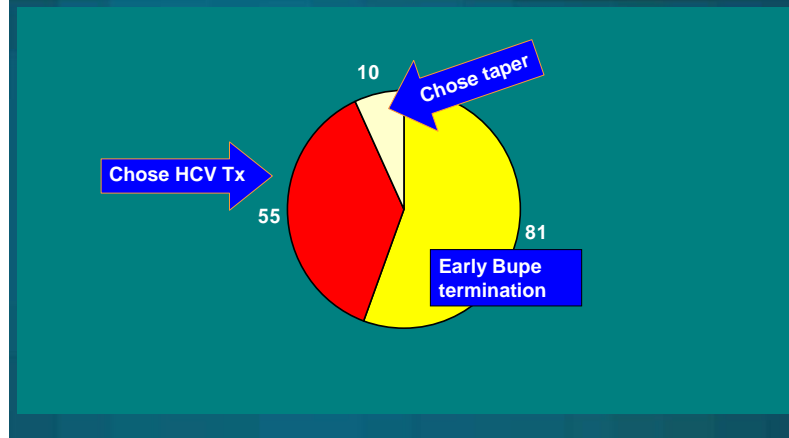


Here we have the treatment retention over the first six months.



You can see after 24 weeks 45% are still getting buprenorphine. People think that is terrible, but is actually wonderful. What per cent of them do you think would choose hepatitis C treatment? Actually most of them chose hepatitis C treatment.

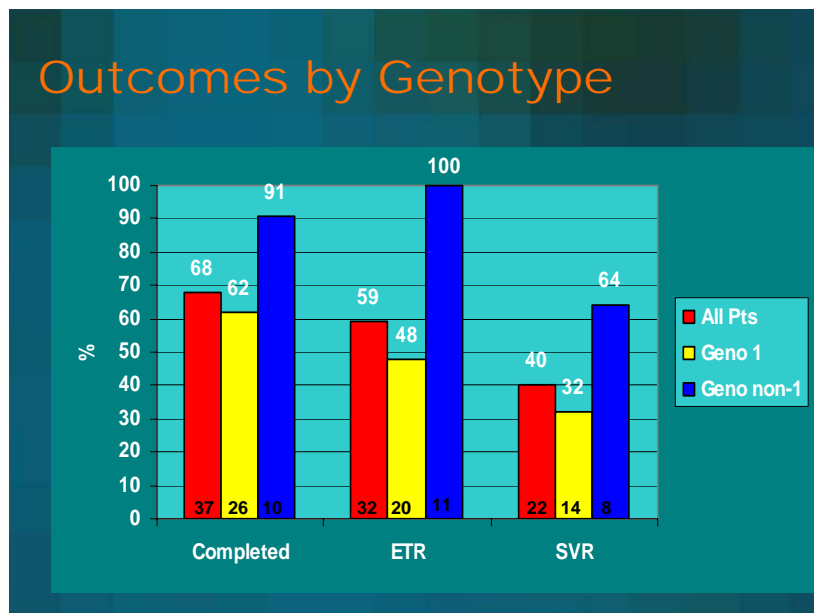
Interest in HCV Treatment



The outcomes: 37 out of 55 completed treatment; early treatment 18; 3 of them were sadly incarcerated and they are not able to receive Hepatitis C treatment; 4 medical discontinuation,; 10 of them disappeared; and one had side effects.

And here you have the outcomes by genotype.

Outcomes by Genotype



Based on this experience, what would I do? These are my 5 rational directives:

Directive 1: The 20/20/20 Rule

“Special populations” that represent at least 20% of an affected population, should be represented in any Phase III studies at a minimum of 20% of the overall study population, unless this is deemed unsafe.

Directive 2: Separate or equal.

Although included in the overall study the “special populations” may be enrolled as separate cohorts, and therefore may be subjected to separate statistical analysis that does not negatively affect the overall study’s outcome. This may require that advocates assist drug companies in their interactions with regulatory authorities.

Directive 3: Flexible enrollment.

Protocols should allow a 3 months extension from the time of enrollment to medication initiation, on a per-request basis, if the investigator believes the extension will assist with patient stabilization and improve safety.

Directive 4: Relevant expertise.

Qualified experts must be included in the Phase 3 investigator clubhouse.

Directive 5: Community collaboration.

Experts and community members should provide comment in study design.

So in conclusion, because they are not really “special populations”, drug users and co-infected patients should be included in Phase 3 studies of new HCV agents. More investigator expertise and protocol flexibility should be mandated. Activists should work closely with pharma to assist with rational protocol development.

Q&A:

Q: Your experience was very interesting. My question is the duration of treatment for hepatitis C was 24 weeks?

A: 24 weeks for genotype 2 and 3, and 48 for genotype 1 and 4.

Q: Should we also design trial more adapted for that population in terms of duration of treatment to find early predictors response?

A: I think we have standard of care and I think we should offer to them.

Q: There were all mono-infected HCV infected patients?

A: We just had one co-infected person. We didn’t exclude co-infected patients, this is a very interesting geographical thing with co-infection in the US - in the West Coast we see very low co-infection in drug users, it’s about 2%. While in the East Coast and the big cities is completely different story.

Q: Did you have to change the dose of buprenorphine?

A: We actually gave a dose of 16 mg in many patients but the dose step up while on treatment - two patients were on 32 mg. That is one of the thing we have to look at.

EMA Guidelines on HCV drug development

Joan Tallada, EATG

The aim of this guideline is to provide guidance on the clinical development of compounds for the treatment of Chronic Hepatitis C (CHC) and it should be read in conjunction with updated and recognized clinical treatment guidelines. The guideline focuses on direct-acting anti-viral agents (DAAs) that should be evaluated by the EMA.

Due to the limited experience thus far with other approaches to clinical development of DAAs, this guideline is focused on studies in which new DAAs are added to the available standard-of-care (SOC) treatment for CHC where SOC comprise ribavirin plus a pegylated interferon (PEG-IFN) alpha 2a or 2b administered for a duration selected in accordance with the HCV genotype.

A special concern with respect to drug development for the treatment of CHC is the high mutation rate of hepatitis C virus (HCV) with the attendant risk of selection of drug-resistant variants leading to treatment failure. Taking into account this risk and in order to evaluate the new DAA in a stepwise fashion, the guideline discusses that initial studies should enroll subjects naïve to SOC who do not have advanced fibrosis or HIV co-infection and who have HCV genotype 1 infections. It is anticipated that sequential studies could enroll patients with genotype 1 infections who have had a sub-optimal response to SOC or relapsed. Once the effect of adding on a DAA is well described in these types of patients later studies could evaluate efficacy in specific groups such as those with other genotypes, HIV co-infected patients and null responders to SOC.

Due to the dynamics of the field and the restricted scope of this guideline, revisions and amendments are foreseen to be necessary within a short time frame.

The prognosis of HIV infection is now much improved due to modern antiretroviral therapy. Among those co-infected with HIV and HCV, however, liver failure due to CHC has become a leading cause of mortality. In co-infected patients, progression of liver disease also seems to be faster, at least for individuals with low CD4+ T-cell counts. According to biopsy studies, the proportion of patients with cirrhosis is around twice as high in HIV/HCV co-infected middle-aged patients compared with individuals of similar age who have only HCV infection.

With current standard-of-care (SOC), i.e., pegylated interferon-alpha 2a or 2b (PEG-IFN) and ribavirin, around 70-85% of patients infected with HCV genotype (GT) 2 and 3 achieve SVR after a 6-month treatment course. In contrast, only half of patients infected with HCV GT 1 and 4 reach SVR despite treatment for one year. Even lower SVR rates are reported in some sub-populations such as those with HCV/HIV co-infection. Therefore there is a particular need for development of new treatments that can improve on these SVR rates. Tolerability and safety is also a concern with current SOC and a shortened duration of SOC is a worthwhile objective for drug development in the treatment of CHC.

HCV is a RNA virus with a high mutation rate and variants that demonstrate reduced sensitivity to polymerase and protease inhibitors associated with specific viral mutations have been obtained in the laboratory and from treated patients. Available data indicate that within class cross-resistance is likely to occur. When HCV was co-exposed to two DAAs of different classes *in vitro*, however, the rate of selection of drug-resistant variants was significantly lower. This observation raises the possible advantage of combining more than one DAA with SOC for optimal treatment of CHC.

The impact of resistance on subsequent treatment attempts is unknown. It is also not known how long resistant variants may persist after stopping therapy in cases of virological failure. However, resistant variants, and not wild type HCV were recovered from patients who relapsed after achieving an end-of-treatment response (ETR) following treatment with a DAA (protease inhibitor) in combination with SOC. The development of drug resistance should therefore be regarded as potentially harmful and must be taken into account in the design of clinical studies and in the benefit-risk assessment of DAAs.

This guideline acknowledges the constraints put on clinical drug development imposed by the high rate of mutations of HCV and therefore emphasizes the importance of taking the risk of selecting for resistant variants into account in the design of clinical studies, including the possible use of adding more than one DAA to SOC. **Once sufficiently encouraging data are available from treatment naïve subjects, drug development is encouraged in difficult-to-treat patient populations, such as HCV/HIV co-infected patients and null-responders to SOC.**

Subject characteristics and selection of subjects

With respect to diagnostic criteria, indications for therapy and clinical follow-up, adherence to up-dated and generally acknowledged clinical treatment guidelines is recommended.

It is anticipated that the initial clinical development program will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection, do not have advanced fibrosis and are not co-infected with HIV.

Once the DAA has been evaluated in the population above, with a preliminary assessment made of the likely safety and efficacy to be expected, risk of treatment failure and selection of resistant variants, suitable agents should be studied in a larger range of patient populations.

Thus, it is anticipated that later studies (which may precede or follow an initial approval for use in the above mentioned patients) should evaluate use in:

- Patients with advanced fibrosis or cirrhosis and candidates for SOC.
- Patients with a documented response (e.g., > 1 log reduction at week 4 or > 2 log reduction at week 12) to a prior course of SOC who did not achieve undetectable HCV-RNA
- Patients with relapse during or after completion of SOC.
- Patients infected with virus of GT 2/3 and 4.

- **HIV/HCV co-infected patients.**
- Liver transplant patients.
- Patients with a documented null-response to SOC defined as, e.g., < 1 log reduction of HCV-RNA at week 4-12.
- Patients who did not achieve SVR with therapy that included an approved DAA.

Clinical pharmacology studies

Pharmacokinetics

It is foreseen that some new DAAs will have an extensive drug interaction potential. As an important target population is HIV/HCV co-infected patients, an extensive interaction program is likely to be needed. The prioritization of clinical drug-drug interaction studies (e.g., performed pre- or post-initial approval) should take into account the possible mechanisms of interactions and the clinical need for co-administration of specific agents with the DAA.

In designing the program, priority should be given to studies of co-administration with other drugs used in the management of HCV, HIV, liver transplantation, depression and substance abuse. Within these areas, essential drugs without reasonable therapeutic alternatives and a potential for interaction should be prioritized for study and the aim should be to provide sufficient data to support recommendations for adjustment of dose and/or dose intervals as necessary for the experimental compound and for essential drugs.

For DAAs that are nucleoside analogues, the potential for interaction to occur at the level of intracellular activation by phosphorylation should be explored. If an interaction cannot be excluded based on knowledge of phosphorylation pathways, *in-vitro* interaction studies should be conducted. If the possibility of a relevant interaction cannot be excluded *in vitro*, then *in vivo* studies should be undertaken with an appropriate range of compounds measuring possible effects on activated compounds.

This guidance document foresees that DAAs are used as add-on to SOC which includes the nucleoside analogue ribavirin. The very long T_{1/2} and the toxicity of ribavirin have to be considered in the design of interaction studies.

Pharmacodynamics

It is anticipated that an initial application dossier should include an extensive evaluation of the *in-vitro* activity of a new DAA including exploration of the mechanism of action, activity against viruses other than HCV, and the risk of selection for drug-resistant variants, with assessment of the potential for cross-resistance to occur.

Whenever there is a suspicion based on theoretical considerations that a certain combination of compounds could be antagonistic, combination studies *in vitro* should be performed. The results need to be cautiously interpreted, however, and the full spectrum of mechanisms of activity for anti-HCV activity *in vivo* should be known.

Clinical efficacy studies

Studies are expected to be randomized and, whenever possible, double-blind.

Adherence to therapy is of vital importance for treatment outcome and major efforts to encourage and document compliance should be undertaken.

Patients included in efficacy studies and achieving SVR should be followed for at least one year post treatment. Any late post-treatment relapses (or re-infection) should be carefully documented.

Patients exposed to DAA(s) and not achieving SVR should be monitored with frequent sampling of HCV-RNA (e.g., every three months) and assessment of genotypic and phenotypic resistance for at least one year. Reversion to wild type virus and long-term persistence of drug-resistant variants should be documented.

Exploratory studies

Dose finding, monotherapy studies

Currently, 5-(7) days duration of monotherapy is considered acceptable. If there is a strong scientific rationale to prolong this period of monotherapy and if the compound is foreseen to have a high genetic barrier to resistance, 10-14 days might be acceptable. In this context, i.e., when no *in vivo* data are available, a high genetic barrier may be defined as the need for > 2 likely key mutations to achieve IC₅₀ values higher than expected free drug exposure *in vivo*.

It is expected that these studies initially would be performed in patients naïve to SOC, without co-infection and without advanced fibrosis. Depending on degree of cross resistance, as evident from *in vitro* studies, it could be appropriate to study patients with viruses that show reduced susceptibility to an approved DAA of the same class as the experimental DAA.

Early exploratory studies of combination therapy

In these studies it is anticipated that regimens with different dosages and durations of the new DAA will be added to SOC and compared to SOC alone in treatment naive patients.

Consideration could be given to employing a lead-in-phase of SOC before randomization to identify those patients that might derive most benefit from addition of another agent to SOC. In this way patients with detectable HCV-RNA, but with e.g., ≥ 1 log HCV-RNA decrease after 4 weeks of SOC may be randomized to remain on SOC or to receive DAA + SOC. At the same time the lead-in phase could serve to avoid randomization of the following groups of patients:

1. Null-responders to SOC (e.g., <1 log decrease at week 4). If randomized, these patients might in practice receive functional monotherapy with the DAA, with a high risk of treatment failure and selection of resistant variants.
2. Rapid virological responders (HCV non-detectable at week 4). These patients have a high chance of SVR using SOC. Excluding these patients in early trials enriches the population for patients likely to benefit from add-on therapy to SOC.

The results obtained on adding a DAA after a lead-in SOC phase may be different from the effect of adding the DAA from the outset, depending on the control of viral replication achieved by SOC alone.

Additional exploratory studies

Before progressing to confirmatory studies it may or may not be considered necessary to perform further exploratory studies. This decision can only be made after review of the data from the first studies and with knowledge of the properties of the DAA in question and other DAA under development or licensed. Issues to be addressed include:

- Is there a need for further exploratory studies in order to optimize the dose and/or duration of DAA treatment?
- Is shortened duration of SOC meaningful to study in identifiable groups of patients, e.g., rapid virological responders to lead in SOC, or SOC + DAA?
- Have proper stopping criteria been identified for the experimental regimen?
- Is a lead in phase with SOC likely to be overall beneficial?
- Is the use of more than one DAA as add-on likely to be needed to optimise benefit – risk taking resistance development into account?
- Is an exploratory trial warranted in patients with documented responsiveness to prior SOC, but without SVR despite proper adherence with respect to dosages and duration?

Exploratory studies in specific patient populations

In order further to document the safety and efficacy of the experimental compound, additional exploratory studies are likely to be needed and should be considered in the following groups of patient:

- *HCV/HIV co-infected patients*: The primary aims of exploratory studies in co-infected patients include safety and confirmation that doses predicted from interaction studies result in proper exposure to the experimental compound and interacting HIV medicinal products. **If not otherwise justified, these data should be available at time of drug approval.**

Confirmatory studies

The objectives of add-on trials would be to demonstrate enhanced efficacy and/or an overall reduction in the duration of therapy that might confer improved tolerance of a treatment regimen compared to SOC. The final risk-benefit analysis would have to take into account the degree of enhancement of efficacy in the light of the safety profile of the regimen and the risk of selecting for drug-resistant variants, with implications for the possible success of further therapeutic regimens.

In most cases, it is foreseen that first confirmatory studies are conducted in treatment naïve patients infected with HCV genotype 1. The range of patients to be included in further confirmatory studies must be decided on a case by case basis depending on accumulated data with the new DAA. Target populations may encompass patient populations as detailed in section 4.1 of this guideline.

Prior to the initiation of confirmatory trials, preliminary stopping rules for insufficient viral response for DAA containing study arm(s) should have been identified.

The various scenarios envisaged for the design of confirmatory studies include:

- A comparison with SOC demonstrating superiority of the DAA+SOC regimen over the SOC regimen.
- When at least one DAA has been approved, consideration will need to be given to comparison of the new DAA with an approved DAA, each added to SOC, in a study intended to demonstrate at least non-inferiority of the experimental agent.
- If exploratory studies indicate a need for combination therapy including more than one DAA (licensed or under development), the most informative design is SOC vs. SOC+A vs. SOC+B vs. SOC+AB. However, data from exploratory studies may indicate that one or both of SOC+A or SOC+B would be sub-optimal and so reduce the number of treatment arms.

In HIV/HCV co-infected patients, the activity of SOC, including use of weight-based ribavirin dosing, is currently poorly documented with respect to effect size. Therefore randomized SOC comparative trials are considered necessary in order to document the add-on activity of DAA.

Clinical safety evaluation

It is expected that mechanism-related toxicities (such as mitochondrial toxicity for nucleoside analogues and the impact on glucose transport for protease inhibitors) will have been well characterized in non-clinical and clinical studies. Any signals that emerge from the non-clinical studies should be followed in the clinical development program.

Discussion

It was agreed that different stakeholders will take the opportunity of the public consultation period by the EMEA to advocate for the *Sitges I Declaration* spirit and ideas to influence the final European Guidelines. More precisely, the EATG will collect community view points and send them to the EMEA liaison representatives.

Issues in Clinical Trial Design

Tracy Swan, TAG

I am going to be brief in my presentation. One of our key questions is what is the optimal time for studies in HIV/HCV co-infected people? And also, what do we need to know before performing these studies?

There are HCV- specific issues for trial design, like the limitations of surrogate markers: drugs will be treating the virus, not the liver disease. The point is then that we need trials that test treatment strategies, not just the drug potency, but also how to use it.

We can borrow some of the lessons from HIV drug development. We need a lead-in period, because by week 4 we will see if the treatment is working, and if not you don't want to give a new drug to them as a magic bullet. Furthermore, we may need to add one more week in the lead-in period to allow for return of the viral load results.

We need to enhance the understanding of resistance, and trials with more than one agent. There may be interactions with other anti-HCV drugs, and we have to make sure that there are no significant interactions with antiretroviral agents and commonly-used medications.

Other issues to be considered: no additive toxicities, complimentary resistance profiles (to avoid cross-resistance) and assess anti-HIV activity thoroughly.

I think that a good design for anyone entering a study could be this one from a community perspective:

Factorial Trial Design

A + B + SOC

A + C + SOC

A + B + C &/or

A + B + C + SOC



You avoid anyone being in SoC -that may be failing. plus only one drug. The problem with this is that we will need at least 3 drugs, and this means companies collaborating with each other and convincing regulatory agencies that this is the best option for people.

Regarding study populations, Diego already covered it, so I going to skip it.

Then, there is the issue of Expanded Access Programs, that can be a good idea if drugs are going to be as good as we expect them to be. There should be pre-approval access to life-saving drugs: they will allow sponsors to gather valuable safety data and increase the number of physicians with experience in using new treatments – therefore creating a market before approval. The big question here is WHEN to open EAP? Also how these programs will be designed and how they are going to work.

I am proposing here an activist checklist:

- Eligibility criteria: who is excluded, and does this make sense?
- Is the study too inclusive (i.e. any degree of liver damage, “treatment experienced”). Are the results going to make sense?
- What is the risk/benefit ratio for particular trials for particular populations: treatment-experienced vs. treatment naïve people, both mono and co-infected? What are the arguments for each?
- What are the long-term implications of HCV treatment trial designs? How many questions can we put in one single trial?

Panel discussion with drug company representatives

Facilitation: Joan Tallada

Each company is invited to offer formally their perspective on the issues that have discussed.

Schering-Plough

There are so many questions unanswered, that is very difficult to know how to go forward. Plus, doing a trial takes at least 3 years each: recruitment, trial implementation, data interpretation. Sometimes we learn new things while we are doing the trial that would have changed the design if we have known before. Another problem we have, and we need the support of the community for, is participant enrolment and retention, because we have abandon problems, but still studies are worth to be done. Issues are so complex that we need a multi-disciplinary approach: hepatothologists, HIV specialist, mental health specialist. We need to understand not only the drug and the best trial design, but also the best setting to do the trials.

On the other hand, we have already met with community to discuss co-infection trial design. As we committed, we have decided to start the co-infection trial as soon as Phase III is ongoing. The discussion was very fruitful about CD4 threshold and other design aspects. We are open to go on with this positive collaboration.

Q: What about including people in maintenance-substitution (methadone, buprenorphine) therapy in your studies?

A: We are open to it, but unfortunately usual doctors to do trials are not used to work with this population, and we may need to look for special risk-management , controlled settings to achieve this. We also have to be careful with how to interpret AE when people are using substitution therapy.

Gilead

I want to say first how much I appreciate I had to opportunity to be here and how much I have learnt. Where is Gilead in this field? We have one drug in phase I trial, a non-nucleoside polymerase inhibitor, that had a QT prolongation problem that we have overcome. To illustrate the challenges with substitution therapy, you have to consider that methadone, for instance, also have QT issues.

We are looking to go to Phase II trial soon. Other drugs are behind, but we are committed in different targets for HCV. And we are already starting drug interactions to move this drug forward. We also have a license for an anti-fibrosis drug, for a condition that is affecting HIV-HCV co-infected people a lot.

Abbott

We are pretty active but like an iceberg, under the water, because we have not tested any drug in humans yet. We have however disclosed two big research programs for HCV. We are working with a small biotech to develop them. We have learnt from HIV that

combination therapy it is the best option, but first we have to understand how each particular drug works.

This meeting has been very helpful to go back with a lot of points and questions we have to plan in advance. We need the help of the community to prioritize research, particularly in drug interaction studies. These decisions are difficult, I know now how many things are needed, but we have to discuss what to study first if we cannot do it at the same time. And this is where you, the community, tell us what the priority is from your point of view.

The reason why we haven't gone that far is because drug development is full of challenges, and any obstacle may force you to stop and go back to try and understand what went wrong. Plants are ready for product manufacturing that will be started once we have made it sure with a good, safe candidate that can go to clinical trials.

Tibotec

Our lead compound is telaprevir being developed together with Vertex, moving to Phase III. From Phase II trials we need to understand better the drug, safety, efficacy, and particularly resistance, and especially for the co-infection program. We have a quite large resistance program, including long follow-up for participants. We have also discussed internally and with the regulatory agencies how to reduce resistance emergence both for naive and for treatment-experience people.

The company is committed to develop its compounds in co-infected people. We are running drug-drug interactions, including ARV's. We are already discussing with Vertex how to deal with co-infection trials, which is a key issue for us.

We also recognize that we need interaction studies with substitution therapies. Also the importance of community networks we can work with. The factorial design that Tracy mentioned is a good starting point to address multi-drug trials. Other important topics are when to start and which populations to start with.

We have other HCV drugs in much earlier stage, but I cannot give you details right now.

Q: Should we tell people at the community that the Tibotec compound won't be available in clinical practice before 3 years?

A: For mono-infection we expect to have it by then. We recognize that once approve for mono-infected, it will be used in co-infected, and by then we have to have at least the safety data - and we are committed to it.

Roche

We have 3 compounds in human testing. The most advanced is our polymerase inhibitor that has shown good efficacy results, presented in EASL 3 weeks ago. We are very excited about that. We have however a problem with neutropenia with this drug, that emerged in combination therapy not in mono-therapy - it seems to be a synergy with interferon. It won't be a problem if we can go to interferon-free drugs.

We don't have a dose yet, even for mono-infected, so we cannot move to co-infection yet. We are doing interaction tests, and we hope to be able to do co-infection trial in parallel to Phase III, and have data by the time the drug is approved.

We have collaboration with Pharmasset and with Intermune. We have compounds of different classes, and we are looking specifically into doing combination trials.

Regarding relations with the community, what I hope is that I can put together European and US activists and engage them in discussing trial concepts. It is a bit of an educational process internally, also.

Pfizer

I would echo the things that other companies have said. We have a polymerase inhibitor in Phase I, and we are already doing drug-drug interaction with ritonavir. The only data published so far was preclinical. If you want information from us, you have to ask for a presentation to avoid to be seen from a regulatory point of view as promotional.

Among several issues, one important is which population do you want when you say "special population"? There other groups also pushing to be tested first. Also, how many conditions do you allow in with a single person: co-infection, maintenance therapy, etc.?

We want community people input when it is about discussing Phase IIb and Phase III trials, and we are not yet there. For each drug we have asset teams, where I sit, and my job is to caution people in the company when something does not make sense from an advocate point of view. Fortunately, we have researchers in the HCV section who have experience in the HIV field, and they understand community issues and they do care about co-infection.

Towards a consensus in clinical trial design

All participants

Note: the result of this section is the Sitges II Declaration, a text that has been discussed by community and company representatives after the actual meeting, and is still pending final approval. Once adopted, it will be incorporated herein.

Closing remarks

Tracy Swan & Joan Tallada

It has been a very fruitful and intensive meeting. Thank you very much to the presenters, the participants, and the sponsors and everyone who participated. Special thanks to Gonzalo as logistic assistant. We look forward to keep working in a collaborative way.

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