People with Bleeding Disorders and HCV

Who are we?

- Informal group
- Principals are Paul Brayshaw, President HFA and Mark Antell, a longtime hemophilia advocate.
- We're in this to save our lives and those of our brothers.
- Endorsement from several hemophilia organizations including NHF and HFA.

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What are we up to?

- We call for urgency.
- Citizen Petition to the FDA calling for urgency in the development and availability of promising new drugs for people with hemophilia.
- Cited by FDA in their recent hearings on testing DAAs
- We intend to submit recommendations on the new draft FDA guidance

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Background: What facts occasion our involvement in development of DAAs for HCV?

- Bleeding disorders are dependency on clotting factor medications (Factor).
- From late 1960s till the mid 1980s, Factor was uniformly contaminated with HCV.
- Iatrogenic catastrophe
- Levels of chronic hepatitis C (CHC) among individuals who used Factor prior to 1990 are astonishingly high.
- Most adults over 30 years old with bleeding disorders have had CHC for most of their lives.
- Also high levels of HIV co-infection.

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Background: Our population has a high level of desperate need. For many SOC therapy has low success and/or contraindications.

- Various reports in the medical literature have correlated low response to SOC therapy with steatosis, insulin resistance, fibrosis, age, advanced disease, etc. All of these are related to length of time since infection. Our community is characterized by nearly lifetime infection.

- Coinfection with HIV is known to promote more aggressive progression of HCV disease, and it is associated with higher likelihood of unsuccesful treatment outcome. A double whammy.

- Due to an outrageous lapse in government and industrial surveillance, our community has an extremely high level of HIV infection. Coinfected people with bleeding disorders are more likely to have advanced disease, or to progress rapidly to advanced disease.

Background: We call for urgency for development and availability of much better therapy

- People with bleeding disorders who have CHC but no co-morbidies have needs similar to anyone with long-standing HCV infection. Better (more effective, less harmful) therapy made available in a reasonable period.

- For a very large percentage of people with bleeding disorders, a long calm process toward greatly improved therapy will not be helpful. Existing medical options are unlikely to cure (and/or are contraindicated) while the need for a good therapeutic option is severe and immediate. Our lives depend on urgency.

- Viral biology, plus experience with HIV, has taught us that a combination of DAA drugs will prove effective against HCV.

- Our community needs rapid testing and availability of DAA combinations.

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Review of Draft Guidance: Recognition of progress, suggestions for revisions.

Laudable components of the draft guidance

1. **Improved eligibility** for trials
- Biopsy requirements mitigated.
- NDA applications for DAAs should include test data for the most threatened populations.
- Early evaluation of possible interactions of DAA drugs for HCV with HAART drugs.

2. **Recognition of unmet medical needs**.
The following statements from the guidance are noted:
- "SVR rates for blacks and HIV co-infected patients with genotype 1 HCV are in the range of 20 percent to 30 percent (in some studies less than 20 percent)...." line 76
- "Pegylated interferons and RBV are difficult to tolerate and have significantly adverse event profiles that limit treatment in many patients or result in substantial morbidity." line 105
- "Also, we encourage the study of combinations of direct-acting HCV antivirals in patients with the greatest need for new agents, such as patients who cannot tolerate interferon, patients for whom interferon is contraindicated, transplant patients and patients with decompensated cirrhosis." line 254

3. **Suggestions for compassionate access**, particularly to DAA combinations. We see this as our main hope.

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Suggested areas for improvement in FDA policy and activity

1. **Testing multiple combined DAAs / Making DAAs available for testing by gov and patient-oriented curative protocols**

A. The Draft Guidance says that the 'recommended and most straight-forward' pathway for testing and developing DAAs involves single DAAs in combination with SOC. We disagree because:

- The succesful development of HAART for HIV indicates that DAAs must be combined for full effectiveness. The **FDA 'recommended' pathway is at variance** with this proven principle.

- Use of **single DAAs for HCV selects for viral resistance**. For those patients not cured, single DAA therapy (with some period of SOC therapy), will likely render those persons refractory to a whole class of DAA agents.

- While pretreatment with DAA protease inhibitors increases the efficacy of SOC therapy, there is **no certainty that this will be the case for other DAA classes**.

B. We must learn how to test combination DAA agents early in development. FDA should identify and suggest means to improve this serious deficiency in the drug testing process.

C. We cannot identify where the draft guidance calls for access to DAAs for government or private sponsored testing of multiple DAAs

In response to our request for suggestions on how to move toward much better HCV therapy for the most threatened patients, Dr. Carl's Dieffenbach, Director of the AIDS Division of the National Institute for Allergies and Infectious Diseases, stated:
" My suggestion for a pathway is not novel or new — put combinations that are safe and provide quality blood levels in HepC patients with genotypes that are not responsive to IFN/Ribovirin or people that IFN has failed to help. In terms of help, you can make sure that the community voice is loud and clear on access. Without the agents donated to future studies, we all should be pessimistic."

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Suggested areas for improvement in FDA policy and activity

2. **Additional information on the cost / benefit of SOC therapy**
The HALT-C study found that unsucessful INF therapy was associated with more adverse events than non-treatment. This effect was large, but just below statistical significance.

FDA should encourage further statistical review of published literature, perhaps by NIH, to follow up on the HALT-C suggestive findings about the consequences of non success.