Paper #86

Evaluating Strategies to Mitigate the Potential Impact of Resistance-Associated Substitutions on HCV Treatment Programmes:

A Cost-Consequence Modelling Study

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Introduction

- Hepatitis C Virus (HCV) is a global public health threat, with over 50 million people living with current chronic HCV infection[1]
- Although Direct Acting Antivirals (DAAs) are highly effective (>95%) at treating HCV infection, approximately 2 - 12% of those treated with DAAs fail to achieve cure (SVR12)[2]
- There is growing evidence that resistance-associated substitutions (RAS) may negatively impact DAA efficacy
- RAS may be present in high levels in certain HCV[2,3] subtypes, which are highly prevalent in regions of Africa, such as Ethiopia (genotype 4r) and Cameroon (genotype 1l)[3]

Aims

1. Estimate the cost and treatment implications of RAS on HCV treatment programmes across six different genotypes settings.
2. Evaluate the outcomes and costs of different diagnostic strategies for mitigating the impact of RAS on HCV treatment programmes.

Methods

- We developed a decision tree model comparing diagnostic strategies to guide HCV treatment and retreatment programmes across six different genotype settings. Strategies included:

Strategy	Description
Simplified (status quo)	All patients receive the same treatment and retreatment, regardless of genotype, subtype and the presence of RAS. No genotype or RAS testing is performed at any stage.
Genotype-led	All patients undergo HCV genotype testing prior to starting initial treatment. Treatment and retreatment are tailored by genotype.
Subtype-led	All patients undergo subtype testing prior to starting initial treatment. Treatment and retreatment are tailored by subtype.
Baseline RAS-led	All patients are tested for RAS prior to initial treatment. Treatment and retreatment are guided by the presence of baseline resistance.
Decision Rule	Treatment and retreatment for all patients is based upon the most prevalent genotype as assessed by a population seroprevalence study.

- Model outcomes were measured as HCV months averted and healthcare costs (in USD), showing the baseline impact of RAS and the effects of personalised approaches.
- The model was run using two treatment scenarios: suboptimal (SOF/DAC; SOF/VEL) and European Association of the Liver (EASL) recommended (SOF/VEL; SOF/VEL/VOX).

Discussion

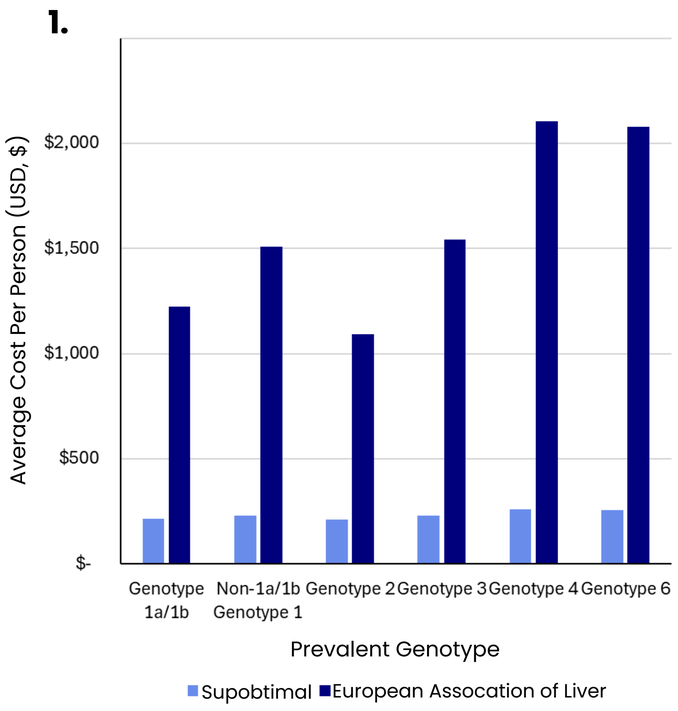
- **High cure rates with variable costs:** All tested strategies achieved high SVR12 across genotypes, but costs were higher where the most prevalent genotype is 'uncommon'.
- **Personalised strategies:** Personlised strategies performed better but incurred higher costs, which may limit affordability.
- **High parametric uncertainty:** There is limited data on the prevalence and impact of RAS on HCV treatment outcomes, which contributes to uncertainty in the model output.
- **Key drivers of outcomes:** Our results indicate that both the prevalence of NS5A RAS and their effect on treatment outcomes strongly influence model results, highlighting the need for further research to clarify the relationship between RAS and SVR12 rates.
- **Public health relevance:** Optimizing cost-effective regimens can contribute to HCV elimination, while helping prevent the emergence of resistance and safeguarding the long-term efficacy of existing DAAs.

Key Message

The optimal diagnostic strategy to guide HCV treatment programmes depends on the prevalence of clinically significant resistance-associated mutations. This highlights the importance of context-specific solutions rather than a 'one-size-fits-all' approach

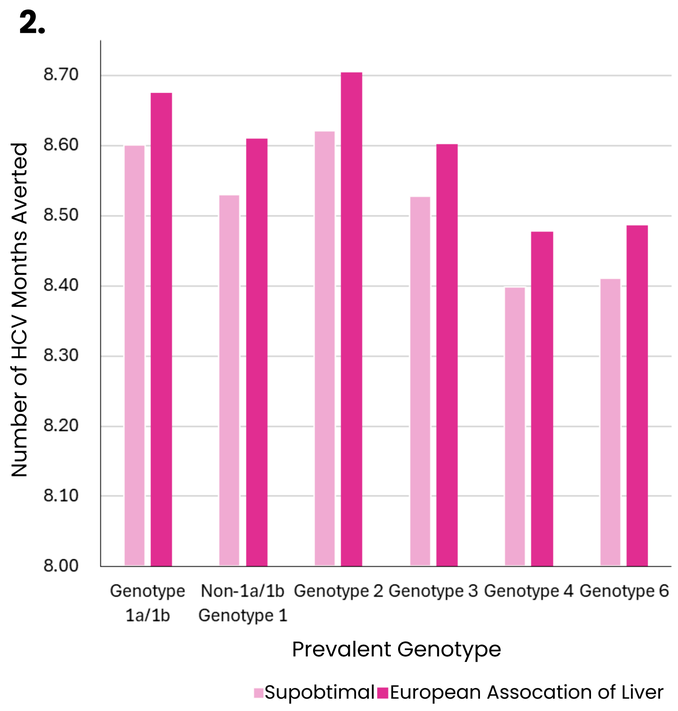
HCV treatment costs are higher in settings with more 'uncommon' genotypes reflecting higher rates of treatment failure

1.



1. The average costs required to treat HCV per patient, using suboptimal and EASL-recommended treatment regimens, in different HCV genotype settings

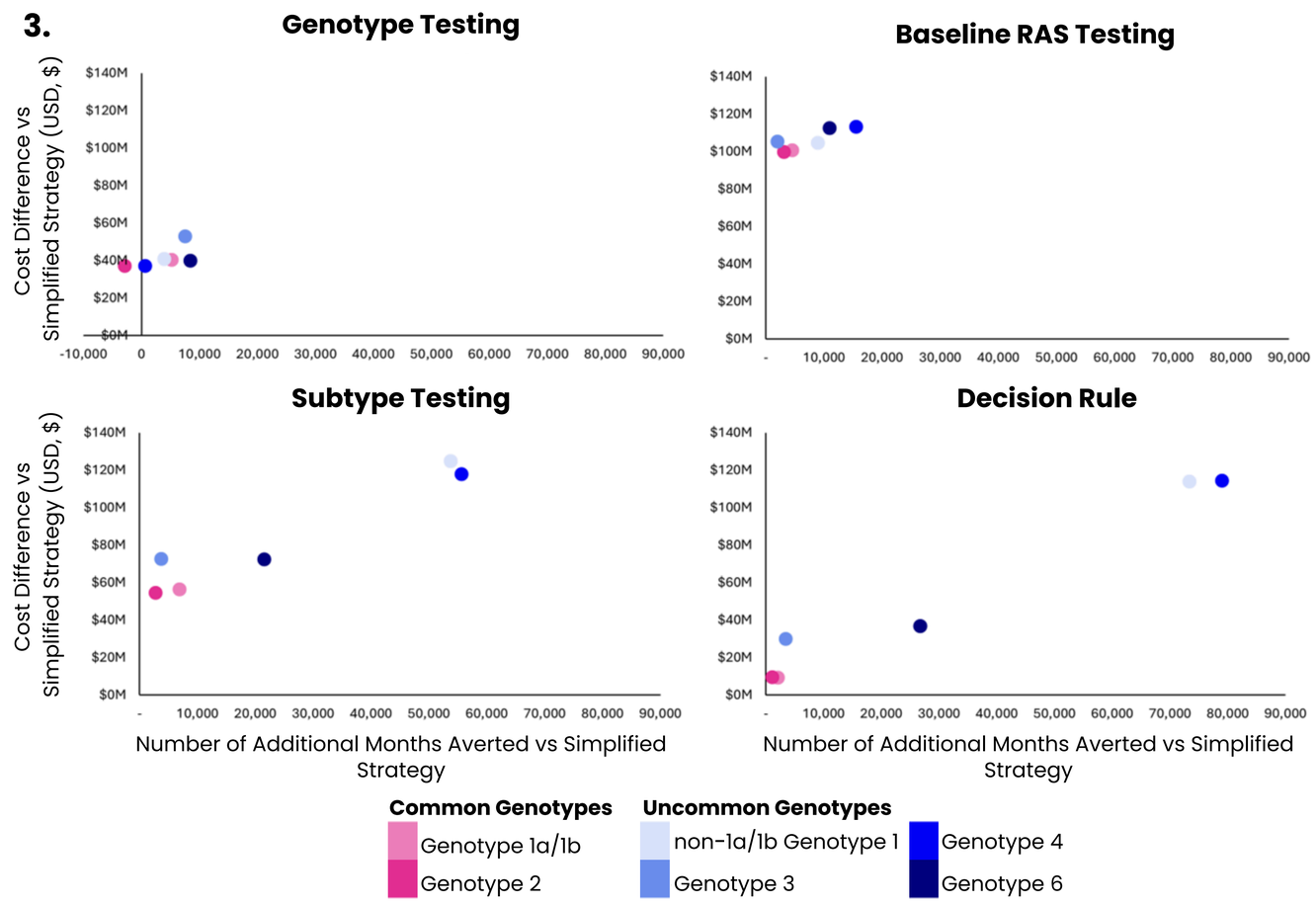
2.



2. The average number of HCV months averted over three rounds of HCV treatment, per patient, using suboptimal and EASL-recommended treatment regimens, in different HCV genotype settings

Personalized strategies worked better than the simplified strategy, especially for uncommon genotypes, but they cost more.

3.



3. Comparison of HCV treatment strategies relative to the simplified approach for a population of 400,000 people living with HCV, showing the difference between additional months of HCV infection averted and incremental costs. Results are stratified by genotype, with common genotypes (1a/1b and 2) in pink and uncommon genotypes (non-1a/1b genotype 1, 3, 4, and 6) in blue.

Note on definitions: We use the current standard definitions of HCV genotypes, referring to "uncommon" genotypes as those subtypes other than the widely studied "epidemic" subtypes (1a, 1b, 2a, 2b, 2c, 3a, 4a). These uncommon subtypes, sometimes referred to as "endemic subtypes", are underrepresented in European and North American cohorts but can be regionally prevalent in certain areas of Africa, Asia, and other parts of the world. Therefore, we acknowledge that this term can be misleading.

References

1. WHO. 2024. 'Hepatitis C Fact Sheet'. WHO. https://www.who.int/news-room/fact-sheets/details/hepatitis-c.
2. Inzaule, S. et al. 2024. 'Prevalence of Drug Resistance Associated Substitutions in Persons With Chronic Hepatitis C Infection and Virological Failure Following Initial or Re-Treatment with Pan-Genotypic Direct-Acting Antivirals: A Systematic Review and Meta-Analysis'. *Clinical Infectious Diseases*. 79(6): 1437-46.
3. Vo-Quang, E. and Pawlotsky, JM. 2024. '"Unusual" HCV Genotype Subtypes: Origin, Distribution, Sensitivity to Direct-Acting Antiviral Drugs and Behaviour on Antiviral Treatment and Retreatment. *Gut*. 73(9): 1570-82.