Resistance-Driven Treatment Failure: A Challenge to HCV Elimination in Pakistan

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BACKGROUND

Global Burden of Hepatitis C

- Hepatitis C is an **inflammation of the liver** caused by the **hepatitis C virus (HCV)**[1].
- Globally, **50 million** people have chronic HCV infection, with **1million** new infections per year[1].

HCV Genotype 3 Difficult to Treat

- Genotype 3 (GT3) second most prevalent worldwide, accounting for **30%** of all HCV cases[1].
- GT3 is linked to **faster fibrosis progression**, and **less responsive to therapy**[3].
- **Pakistan** harbors the largest HCV-infected population worldwide (≈9.8 million; 4.3%), with GT3 as the dominant type[2].

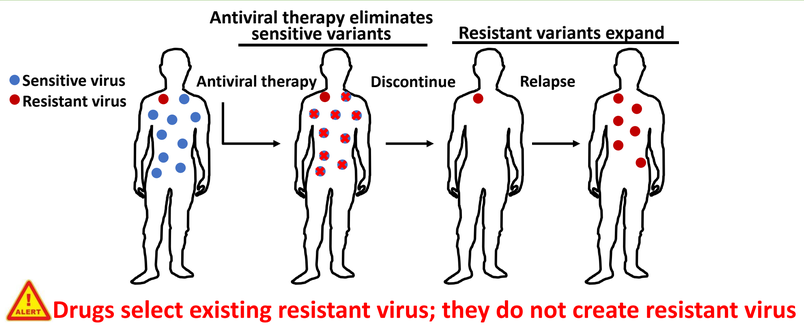
Resistance-Driven Treatment Failure

- **Direct-acting antivirals (DAAs)** target viral proteins (NS3/4A, NS5A, NS5B).Treatment failure is often driven by **resistance-associated substitutions (RASs)**, amino-acid changes that reduce drug binding[3].
- **RASs** in the **NS5A region** of HCV contribute significantly to **DAA failures**[3]. The role of **liver cirrhosis** and **GT3 subtypes** (3a vs 3b) in shaping resistance patterns not fully understood.

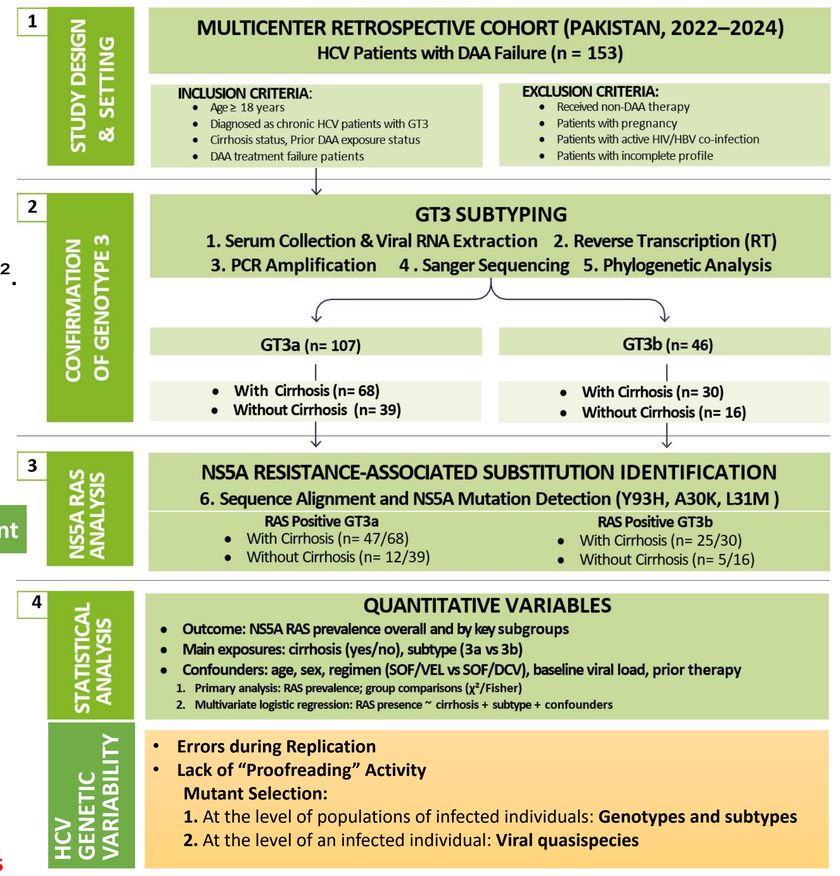
OBJECTIVE

- **To determine the prevalence and predictors of NS5A RASs among HCV GT3 DAA-failing patients and to evaluate the influence of cirrhosis and GT3 subtype on resistance patterns.**

Resistant variants are present before and can be selected during treatment

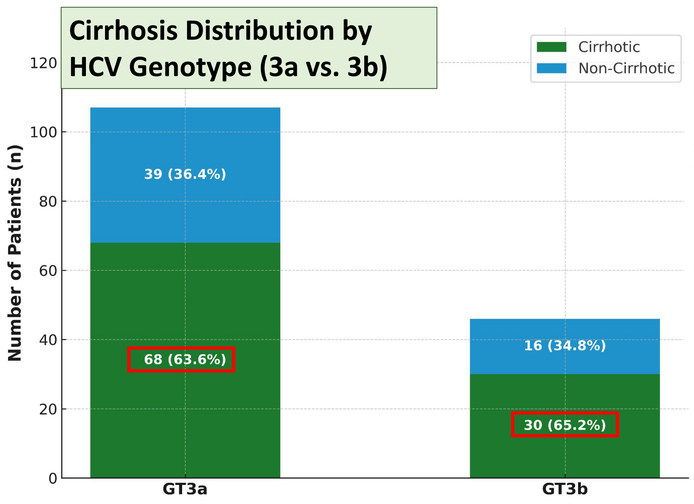


METHODS



RESULTS

Cirrhosis Distribution by HCV Genotype (3a vs. 3b)



Comparison of NS5A Y93H RAS Frequency by DAA Regimen

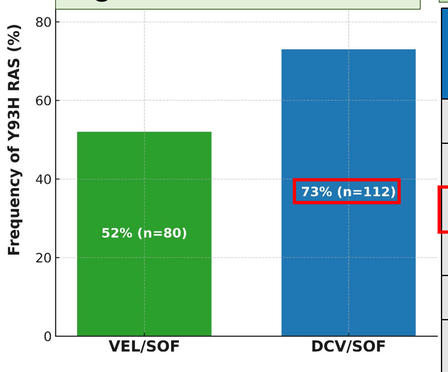


Table 1. Distribution of NS5A RASs by cirrhosis status in GT3 subtypes

GT3 Subtype	Cirrhosis Status	Total (n)	RAS Positive (n)	RAS Prevalence (%)
GT3a	Cirrhotic	68	47	69.1%
GT3a	Non-Cirrhotic	39	12	30.8%
GT3b	**Cirrhotic**	**30**	**25**	**83.3%**
GT3b	Non-Cirrhotic	16	5	31.3%
Total Cirrhotic	—	**98**	**72**	**68.8%**
Total Non-Cirrhotic	—	55	17	31.2%
Overall Total	—	**153**	**89**	**58.2%**

RAS-Positive Patients by Cirrhosis Status Across HCV GT3a and GT3b

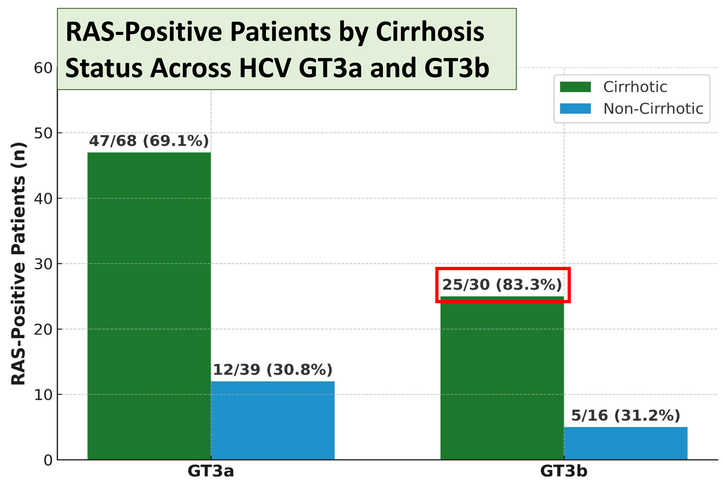


Table 2. Multivariate Analysis of Predictors for NS5A RASs Among DAA Failures

Predictor Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P value	Interpretation
Cirrhosis (Yes vs No)	**2.8**	**1.4 – 5.4**	**0.003**	**Cirrhosis independently increases the odds of resistance**
Subtype (3b vs 3a)	**3.6**	**1.8 – 7.1**	**0.001**	**Subtype 3b infection strongly predicts resistance**
Age (per 10-year increase)	1.1	0.8 – 1.5	0.45	Not significantly associated with resistance
Sex (Male vs Female)	1.2	0.7 – 2.1	0.52	No significant difference by sex
DAA Treatment Regimen (DCV/SOF vs VEL/SOF)	1.5	0.9 – 2.8	0.08	Trend toward higher resistance with DCV/SOF

CONCLUSIONS

1. **HCV Genotype 3 remains predominant in Pakistan and represents a major obstacle to HCV elimination efforts.**
2. **NS5A RASs are a key determinant of DAA treatment failure and pose challenges for effective retreatment.**
3. **Cirrhosis is strongly associated with NS5A RASs selection (68.8% vs. 31.2%).**
4. **GT3b showed the highest resistance rate in cirrhosis (83.3%), emphasizing the need for subtype-guided therapy.**

REFERENCES

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3. **Mushtaq S, *et al.*** Emergence and persistence of resistance-associated substitutions in HCV GT3 patients failing direct-acting antivirals. *Front Pharmacol*. 2022;13:894460.

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