National Institute of Diabetes and Digestive and Kidney Diseases

Prenylation Inhibition with Lonafarnib Decreases Hepatitis D Levels in Humans

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Introduction

- 15-20 million people are infected worldwide with HDV
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years
- Higher risk for hepatic decompensation leading to death & development of HCC compared to mono-infected patients

Hughes SA, et al. Lancet 2011;378; Colombo M et al. Gastroenterol 1983; 85
Manesis EK et al. J Hep 2013;59; Fattovich G et al. Gut 2000; 46
Romeo R, et al. Gastroenterol 2009; 136

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The Quest For Better Therapies

- Interferon therapy is unsatisfactory
  - <30% achieve HBsAg loss and become HDV RNA negative
  - Extended duration of therapy does not help
- Nucleos/tide analogues are ineffective
- Investigational Therapies
  - HBV/HDV NTCP receptor entry inhibitor
  - HDV prenylation inhibitor

Lau DT, et al. Gastroenterol 1999;117
Wedemeyer H, et al. N Eng J Med 2011;27
Wedemeyer H, et al. Hepatology 2013;58
Heller T, et al. Aliment Pharmacol Ther 2014;40

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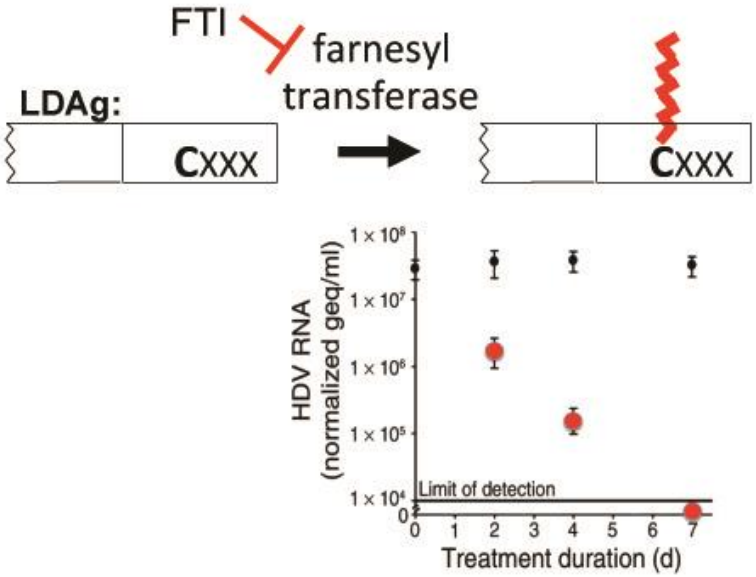
Prenylation Inhibition in HDV

- Prenylation inhibitors have demonstrated effectiveness against HDV in *in vitro* and *in vivo* models



Bordier et al. J Clin Invest 2003;112
Einav S, Glenn JS. J Antimicrob Chemother 2003; 52
Bordier BB, et al. J Virol 2002; 76

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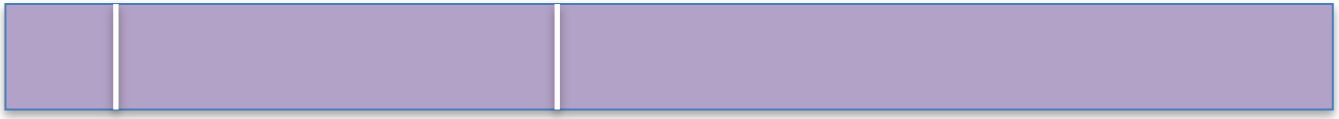
NIH HDV Lonafarnib Study

- Phase 2A, Double Blinded, Randomized, Placebo Controlled Study
- Endpoints:
  - Therapeutic: Improvement in quantitative HDV RNA levels after 28 days of lonafarnib therapy
  - Safety: Ability to tolerate lonafarnib at the prescribed dose for 28 days.

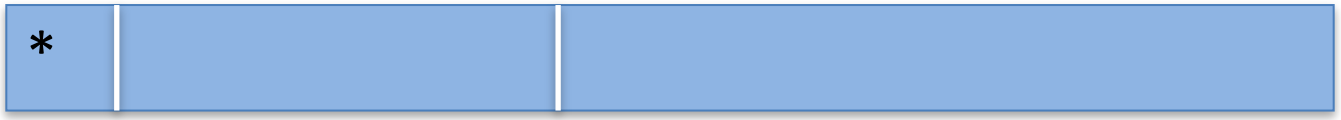
NIH HDV Lonafarnib Study Design

Group 1: Lonafarnib 100 mg BID, 6 Treatment : 2 Placebo



3 Eligibility Evaluations | 28 days of Therapy | 6 Months Follow-up

Group 2: Lonafarnib 200 mg BID, 6 Treatment : 2 Placebo



3 Eligibility Evaluations | 28 days of Therapy | 6 Months Follow-up

*Group 1 Placebo patients offered open-label Lonafarnib 200 mg

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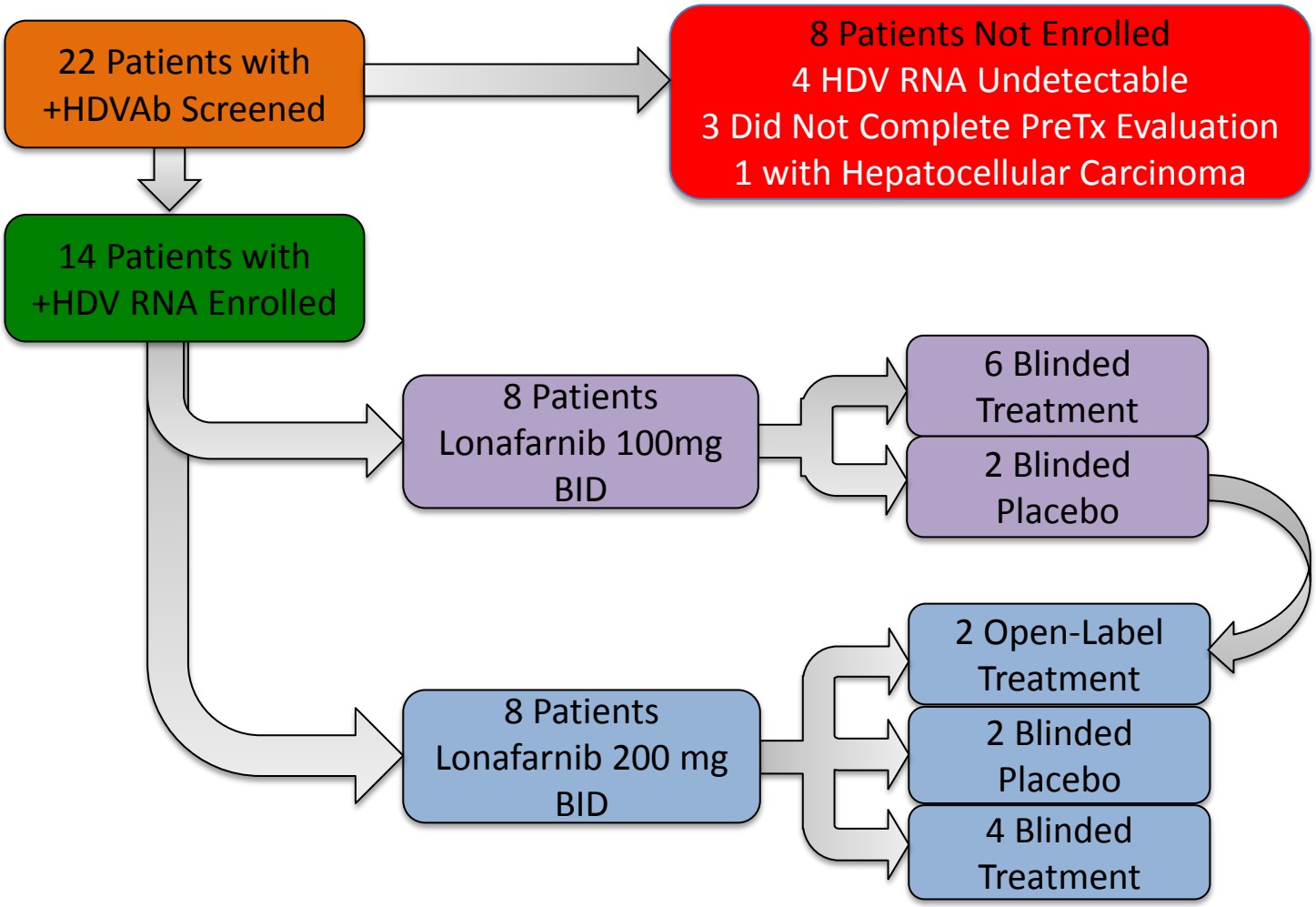
HDV Lonafarnib Study Flow



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Patient Characteristics

Feature	Result
Males	71%
Median Age (range)	38 (29-61)
Nucleoside Analogues	31%
Race	
Caucasian	43%
Asian	50%
African	7%
Median Laboratory Results (IU/mL)	
ALT	89
AST	61
HDV RNA	1.01E+06
HBV DNA	<21
Median Histology	
Ishak Fibrosis	3

*No difference in baseline parameters between placebo and treatment groups

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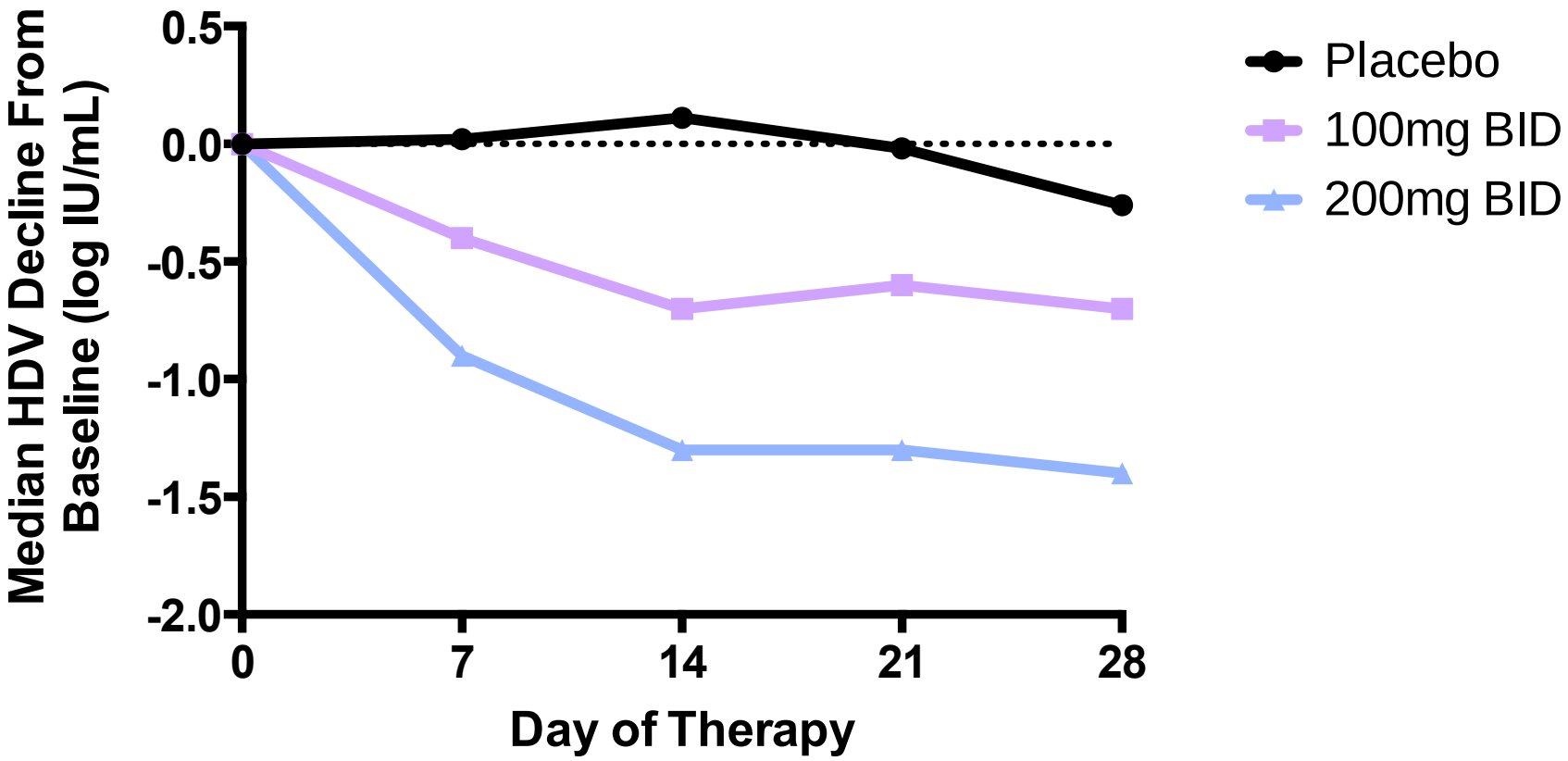
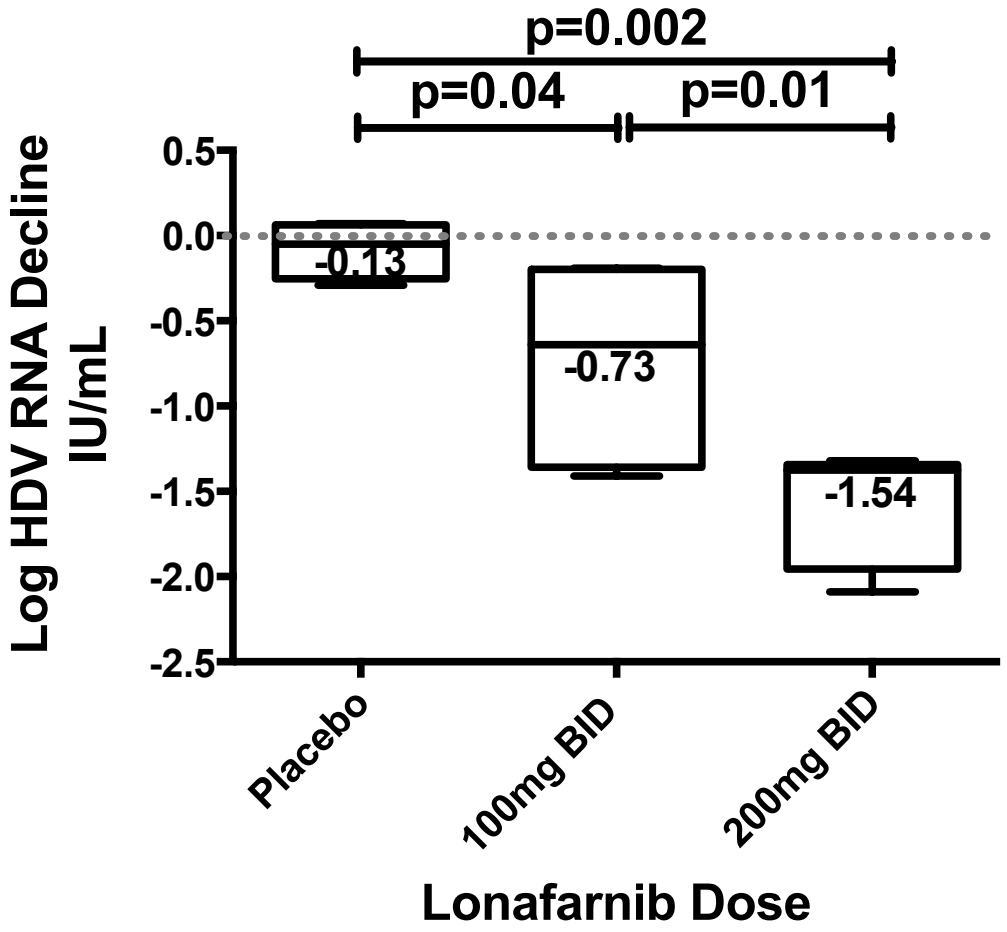
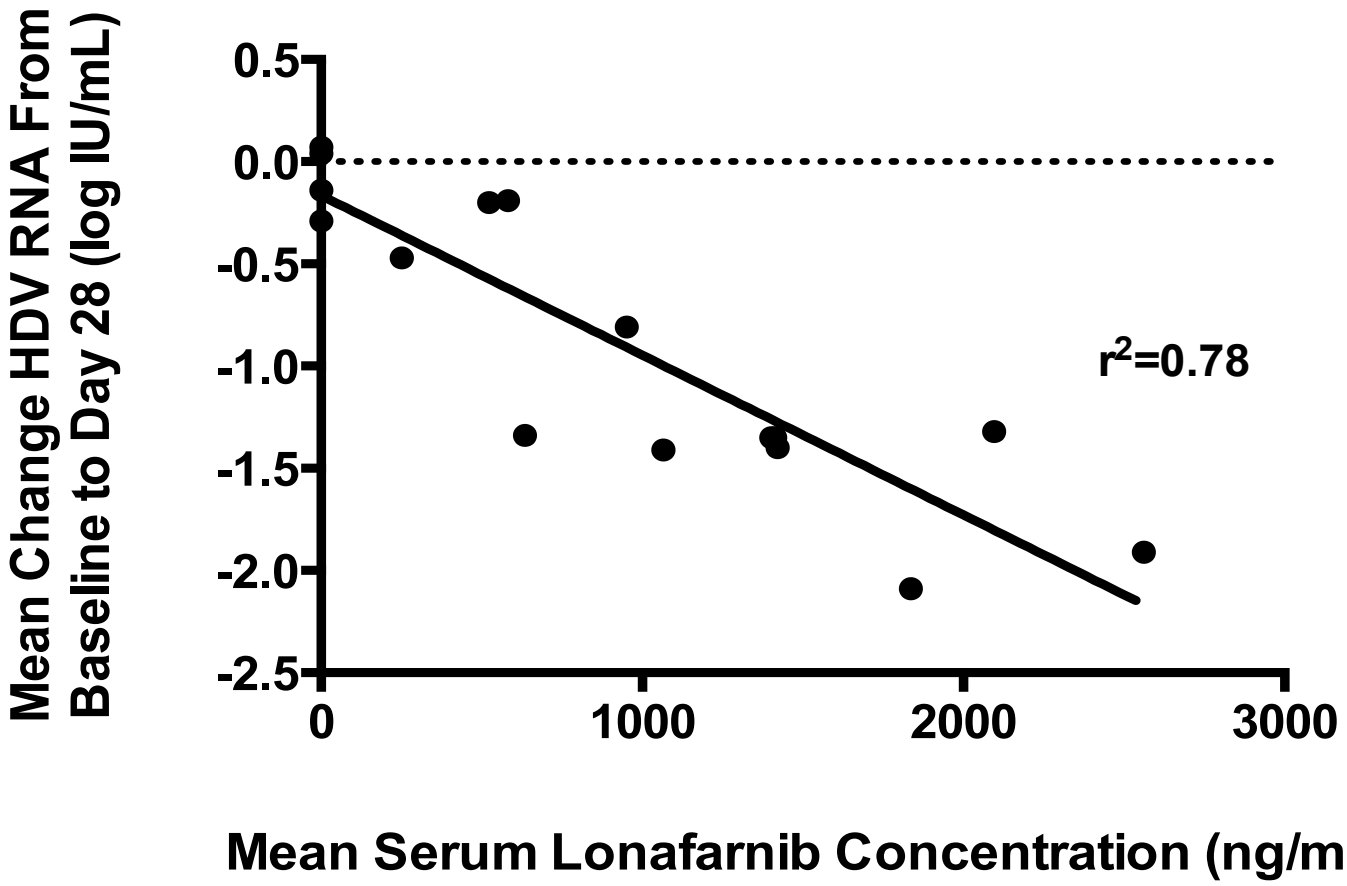
HDV Decline During Therapy



HDV RNA Decline After 28 Days of Therapy



Correlation of Serum Drug Concentration and Change in HDV RNA



HDV Resistance Testing

- Population-Based Sequencing of LDAg (codons 115-215) from Serum
  - Baseline
  - End of Therapy (Day 28)
  - End of Study (24 weeks post-therapy)
- Lonafarnib 100 mg BID
  - Completed
- Lonafarnib 200 mg BID
  - Baseline and End of Therapy (Day 28): Completed
  - End of Study (24 weeks post-therapy): Pending

→ NO RESISTANCE SEEN

Symptoms & Side Effects

Lonafarnib 100 mg BID

Symptom	Patients
Nausea	2
Loose Stools	3
Decreased Appetite	1
Abdominal Bloating	1

Lonafarnib 200 mg BID

Symptom	Patients
Nausea	6
Diarrhea	6
Anorexia	5
Dyspepsia	6
Vomiting	3
Weight Loss (mean)	6 (4 kg)

No Subject Experienced a Grade 3 or 4 Adverse Event
No Subject Experienced a Serious Adverse Event

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Summary

- After 28 days of therapy with lonafarnib, serum HDV RNA was significantly lower in both treatment groups compared to placebo
- A dose dependent reduction in serum HDV RNA was seen with lonafarnib therapy
- Serum lonafarnib concentrations correlate with HDV RNA decline

Summary

- No HDV resistance was identified during population-based sequencing of LDAg
- Lonafarnib was generally well tolerated at the prescribed doses for 28 days

Conclusion

- This is the first demonstration that treatment of chronic HDV with the prenylation inhibitor lonafarnib significantly reduces virus levels in patients
- The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV

Future Directions

- Single and Multi-National confirmation studies evaluating
  - Dosing
  - Duration
  - Efficacy

Acknowledgements

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