Modeling Hepatitis Delta Virus (HDV) Dynamics During Ritonavir Boosted Lonafarnib Treatment– The LOWR HDV-3 Study

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My presentation includes discussion of off-label/investigational use of lonafarnib and ritonavir

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HDV Infection: the least common form of viral hepatitis has the worst outcomes

- 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 HBV 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

The quest for better therapies against HDV

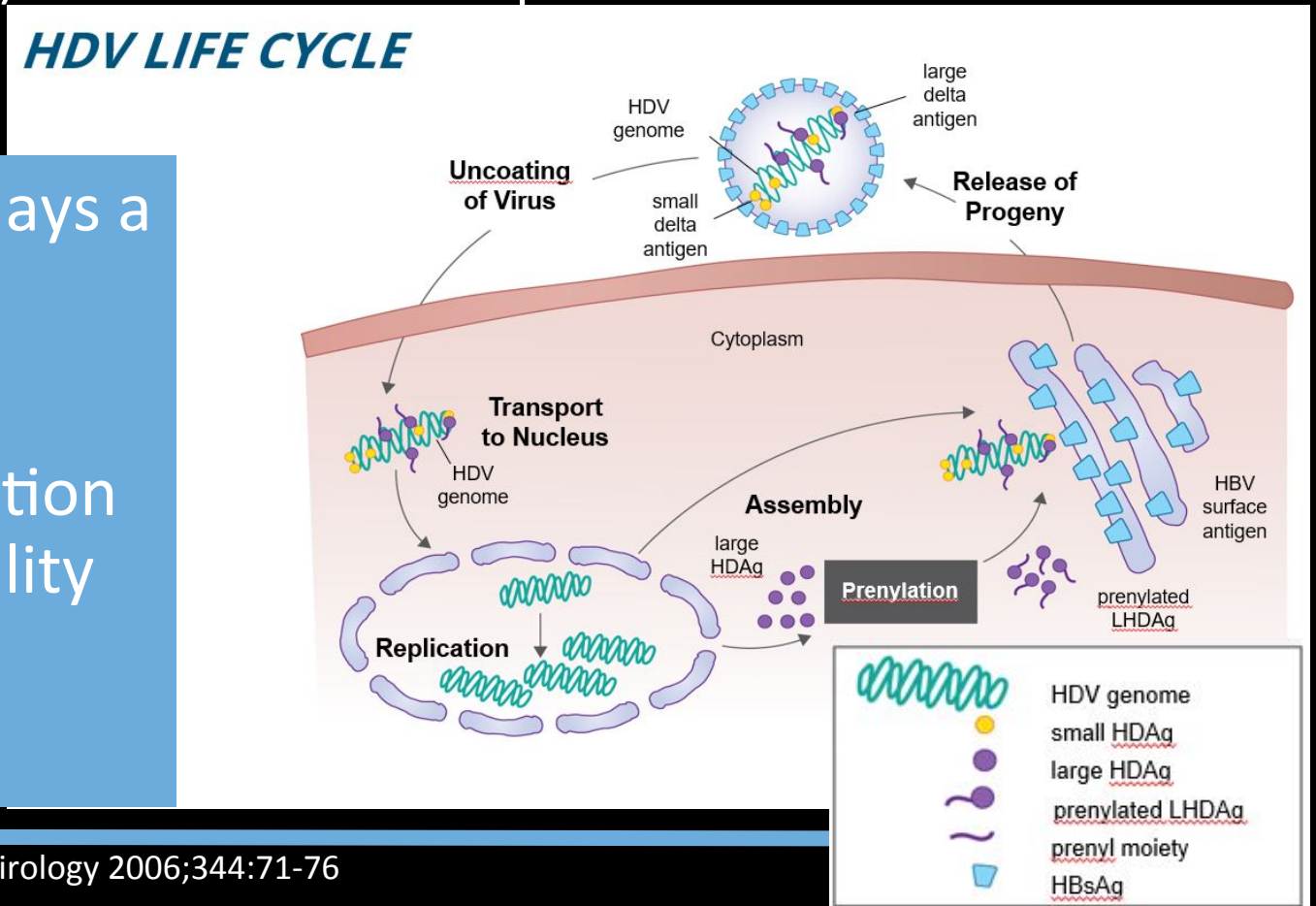
- Interferon-alpha therapy is unsatisfactory
  - <30% achieve HBsAg loss and become HDV RNA negative
  - Extended duration of therapy (>1 yr) does not improve HDV response rates
- Nucleos(t)ide analogues are ineffective
- Daily IV infusion (for 4 weeks) of silibinin is ineffective (case study)
- Investigational Therapies (in clinical trials)
  - Human sodium-taurocholate cotransporting polypeptide – Myrcludex B
  - Nucleic acid polymers – REP 2139
  - Prenylation inhibition – Lonafarnib
  - Peg-Interferon-lambda

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
Bogomolov P, et al. Hepatology 2016;65
Bazinet M, et al. Lancet Gastroenterol Hepatol 2017
Koh C, et al. Lancet Infect Dis 2015;15
Hamid et al. Hepatology abstract # 927 (AASLD 2017)
Reungoat E, et al. Hepatology 2016; 64:1(Suppl): 928A

HDV life cycle and prenylation inhibitor lonafarnib (LNF)

- HDV has a negative sense, circular RNA genome 1700 bases in length
- Encodes only one protein of its own, HDAg, in two forms, large (LHDAg) and small (SHDAg)
- Uses hepatitis B surface antigen (HBsAg) to create its envelope and to achieve secretion

- Prenylation (lipid modification) plays a vital part in the life cycle of HDV.
- Lonafarnib (LNF) disrupts prenylation of the LHDAg and prevents its ability to interact with HBsAg



Bordier et al. J Clin Invest 2003;112:407-414; Taylor JM. Virology 2006;344:71-76

The beginning of an era of HDV dynamics

- Understanding HDV dynamics is in its infancy due to limited studies with frequent kinetic data and the availability of only one medication (peg-IFN-α) with activity against HDV

- In a previous study modeling HDV and HBsAg kinetics, we provided initial insights into HDV-HBsAg-host dynamics and IFN-α's mode of action (MOA) and its efficacy against HDV

Guedj J, et al Hepatology 2014; 60(6):1902-10

Lonafarnib (LNF) phase 2 program provides important data (N>100) for viral kinetic analysis and mathematical modeling

- **Proof of Concept**
  - Monotherapy N = 14
- **LOWR HDV – 1**
  - ± RTV or PEG IFN-α N = 21
- **LOWR HDV – 2**
  - Dose Finding ± PEG IFN-α N = 58
- **LOWR HDV – 3**
  - **QD Dose** **N = 21**
- **LOWR HDV – 4**
  - Dose-Escalation N = 15

Modeling HDV kinetics during LNF-based therapy provides a novel opportunity to further characterize:

- HDV-host dynamics
- the antiviral effect of LNF and IFN-α and their MOA against HDV
- the dynamics between HDV and HBV replication

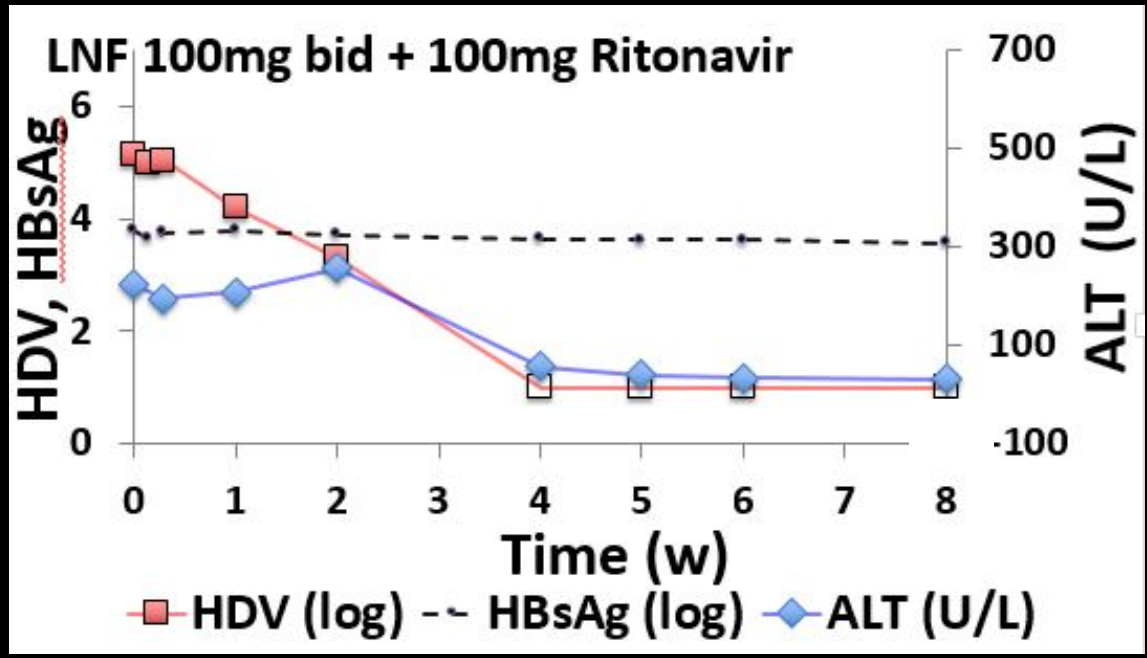
Koh et al. Lancet Infect Dis 2015;15:1167-1174;
Yurdaydin, C et al. Journal Hepatology, 2016; 64(Suppl no 2): S587

Koh et al., EASL 2017 Abstract #LBP-519
Wedemeyer et al., EASL 2017 Abstract #PS-039
Yurdaydin, C. et al, AASLD 2016 Abstract #1845

Modeling provides a strong rationale for ritonavir boosting of LNF

- PK/PD modeling predicts that a LNF monotherapy dose of 610 mg bid would achieve 99% efficacy, however, LNF maximum tolerated dose was 200 mg bid.

- LNF 100 mg bid with ritonavir (RTV) boosting exceeded the predicted 99% efficacy concentration and was associated with dramatic HDV viral load declines and better tolerability than higher doses of LNF monotherapy



Canini L & Koh C et al. Hepatology Communications 2017; 1: 288-292; Yurdaydin C et al. Journal Hepatology, 2016; 64(Suppl no 2): S587

How can modeling be used to optimize therapy ?

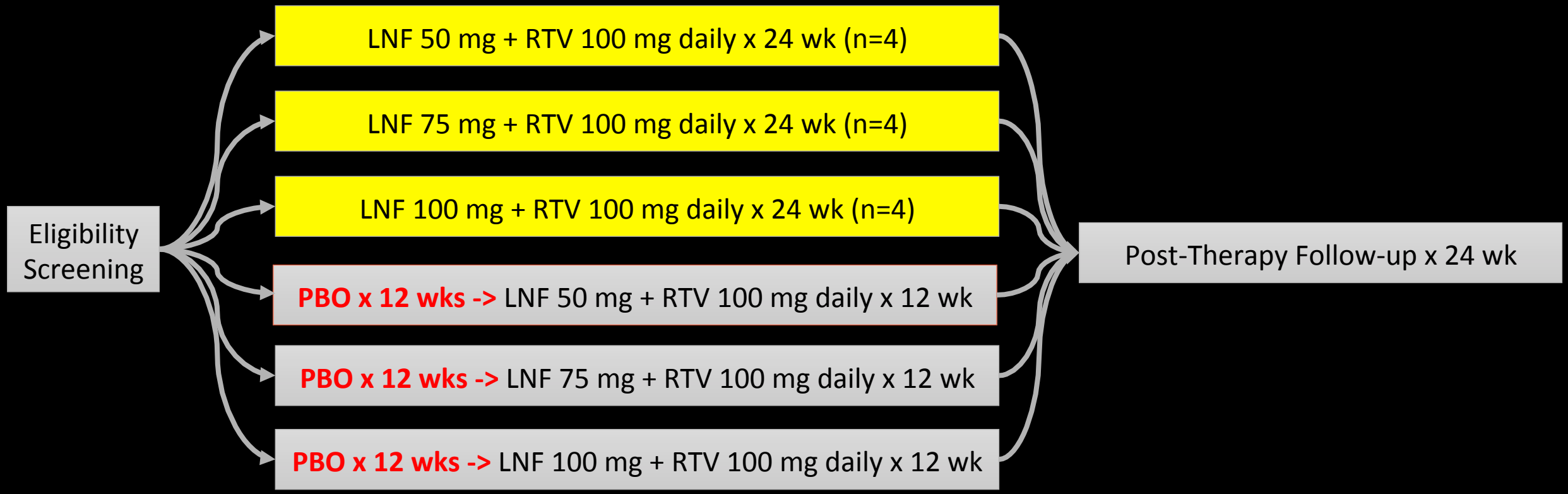
- Real-time modeling of viral kinetics can be used to individualize duration of therapy

- Modeling empowers a patient to participate in shared decision making regarding length of treatment

Dahari et al 2015; Liver International ; 35(2):289-294

LOWR-3 study design

- Phase 2a, Double Blinded, Randomized, Placebo-Controlled Study
- Lonafarnib (LNF) 50, 75 or 100 mg with ritonavir (RTV) 100 mg daily



* All eligible subjects were placed/maintained on HBV nucleos(t)ide therapy for the duration of the study

Patient characteristics

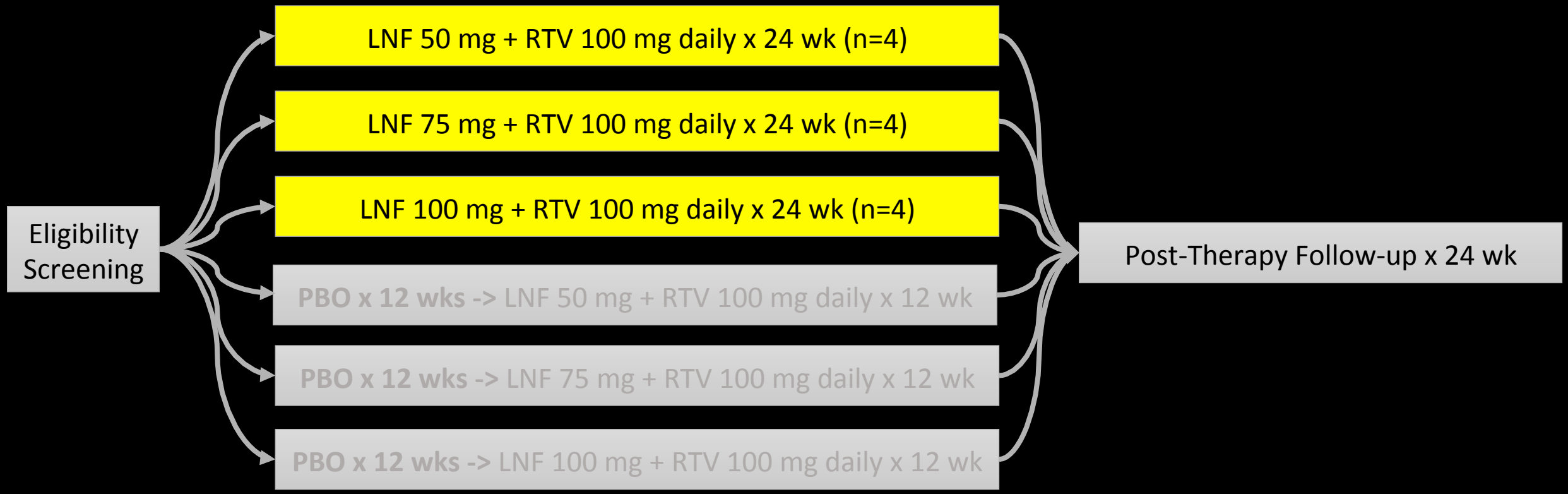
* All subjects were placed/maintained on HBV nucleos(t)ide therapy for the duration of the study

* No difference in baseline parameters between placebo and treatment groups

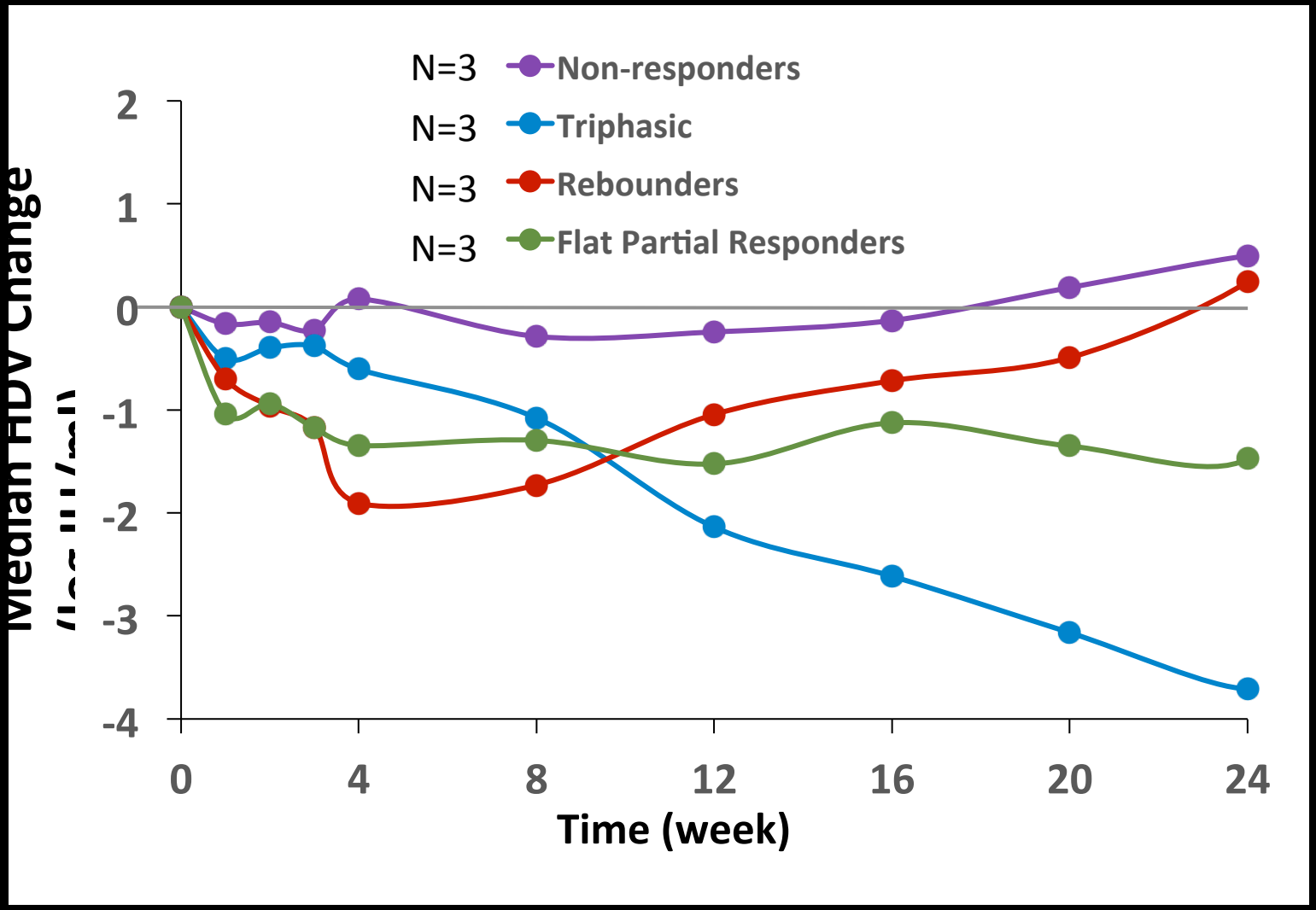
Characteristic	Result (n=21)
Male Sex (%)	13 (62)
Median Age (IQR)	40 (32, 49)
BMI	25.7 (22.5, 22.8)
Race (%)	
Caucasian	10 (48)
Asian	10 (48)
Black	1 (5)
Median Laboratory Results (IQR)	
ALT U/L	70 (45,99)
AST U/L	40 (35, 57)
HBV DNA IU/mL	<21 (<21, 23)
HDV RNA log IU/mL	6.82 (6.18, 7.25)
Fibroscan kPa	7.9 (5.4, 12.0)

Goals

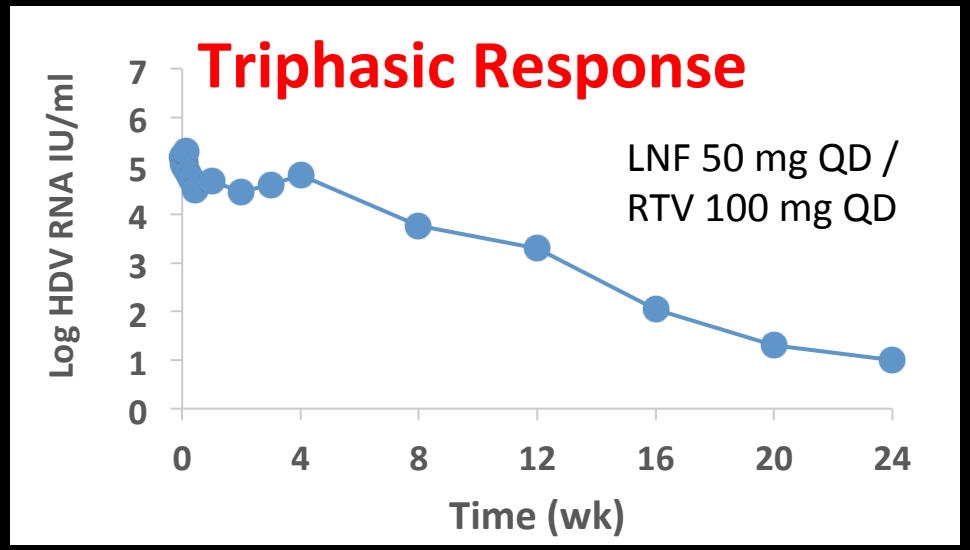
- To characterize viral kinetics and provide insights into HDV-HBsAg-host dynamics during LNF+RTV treatment using mathematical modeling
- Analysis based on 12 patients dosed for 24 weeks with frequent sampling

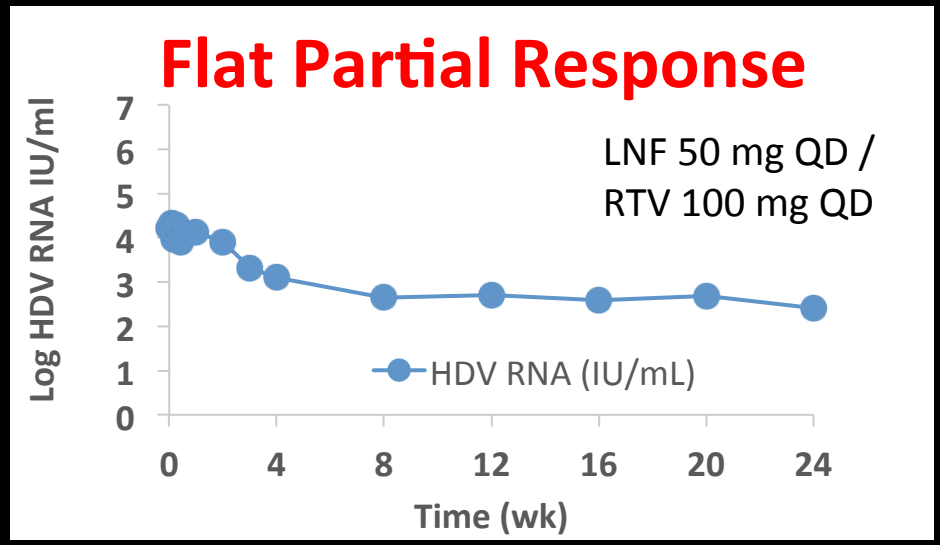


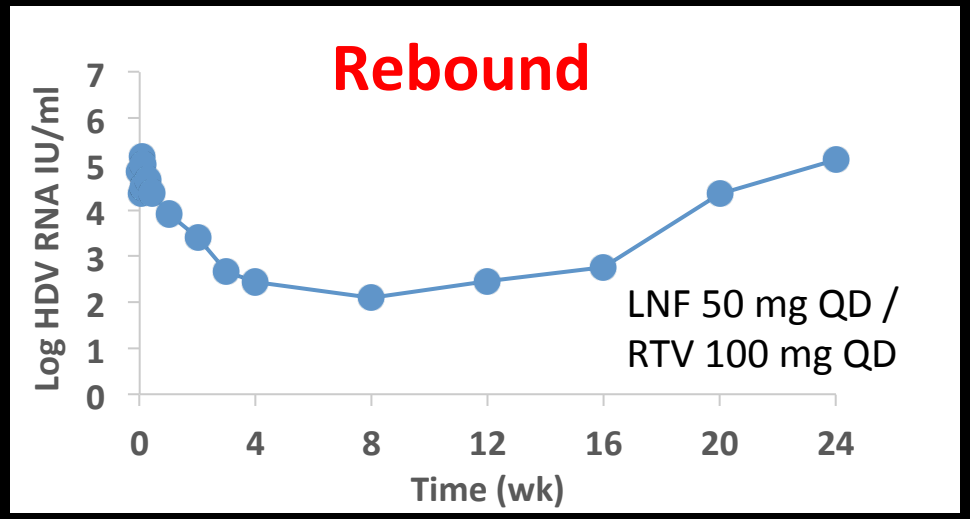
Viral kinetic analysis identified 4 distinct patterns of response

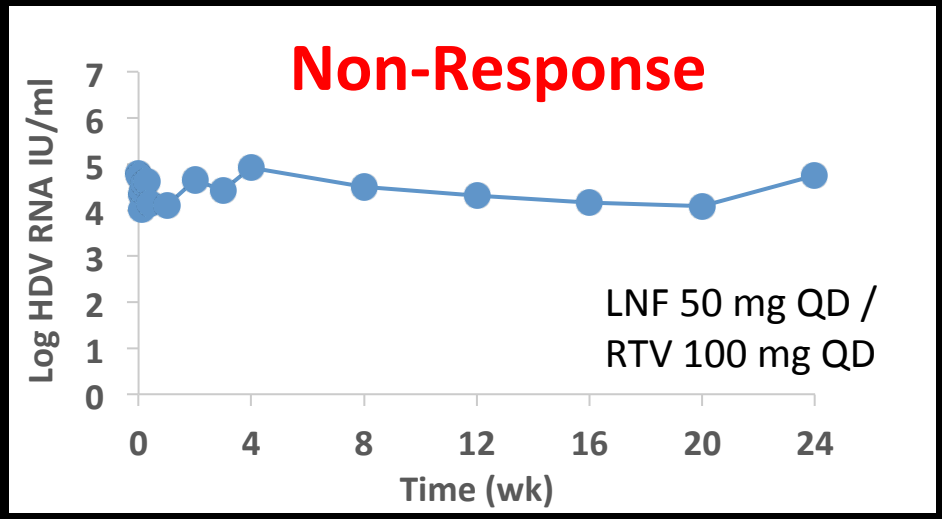


Four patterns of response seen in each LNF dosing group









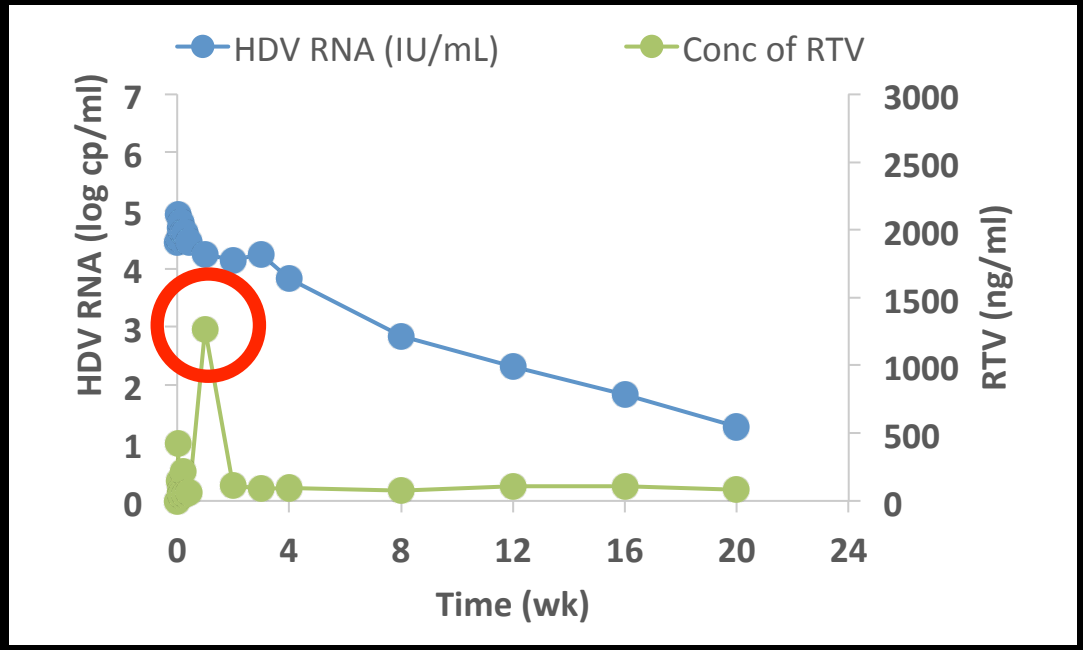
HBsAg and ALT kinetic characterization

- HBsAg levels did not change on therapy

- ALT Normalization
  - 100% of triphasic responders
  - 67% of flat partial responders
  - ALT levels fluctuated in rebounders

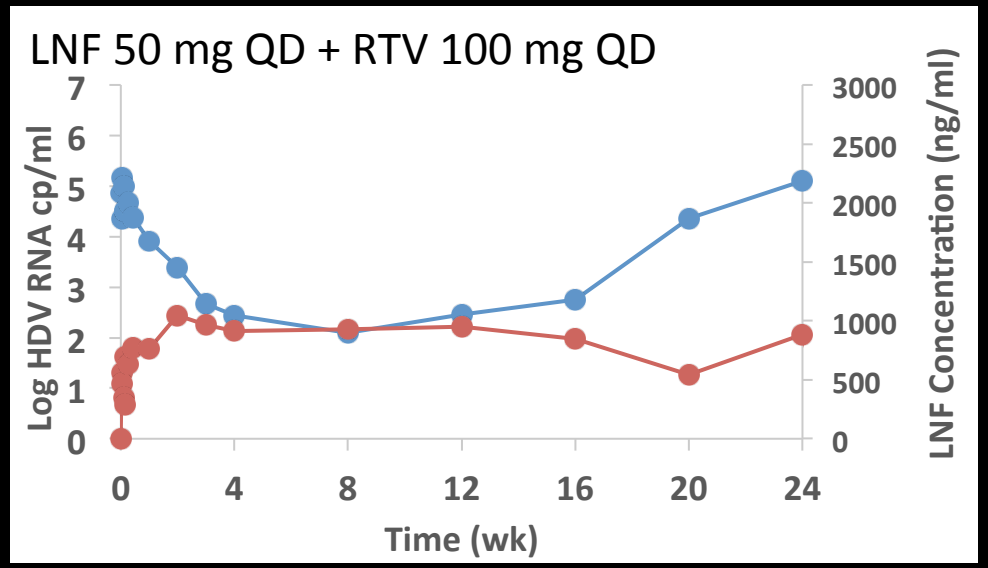
LNF and RTV kinetics

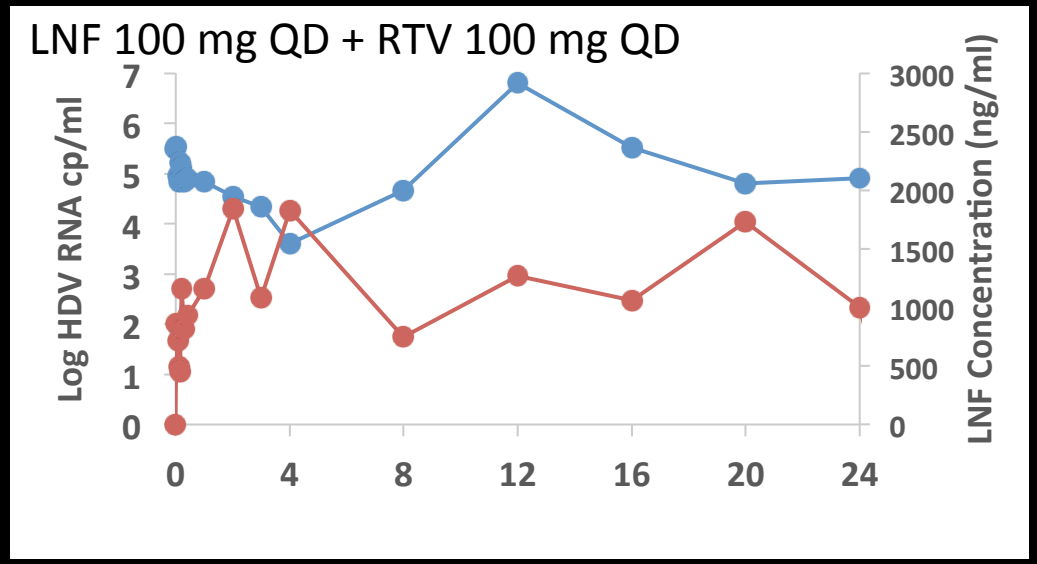
- There was no association between LNF conc. and viral response patterns
- Peak RTV levels > 1200 ng/ml were associated with a triphasic response

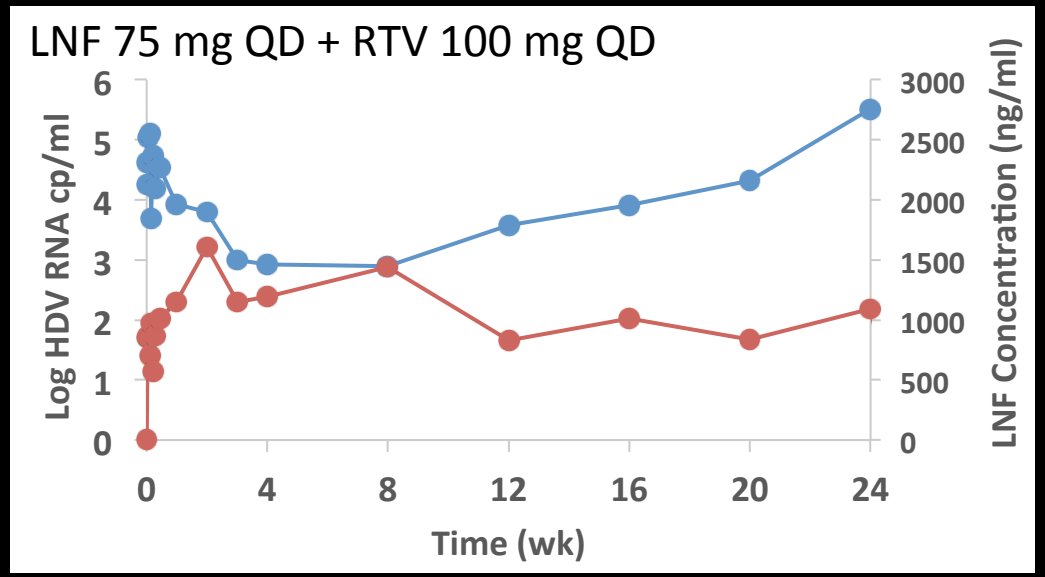


HDV rebound associated with decline in LNF conc.

There is no evidence of virological resistance



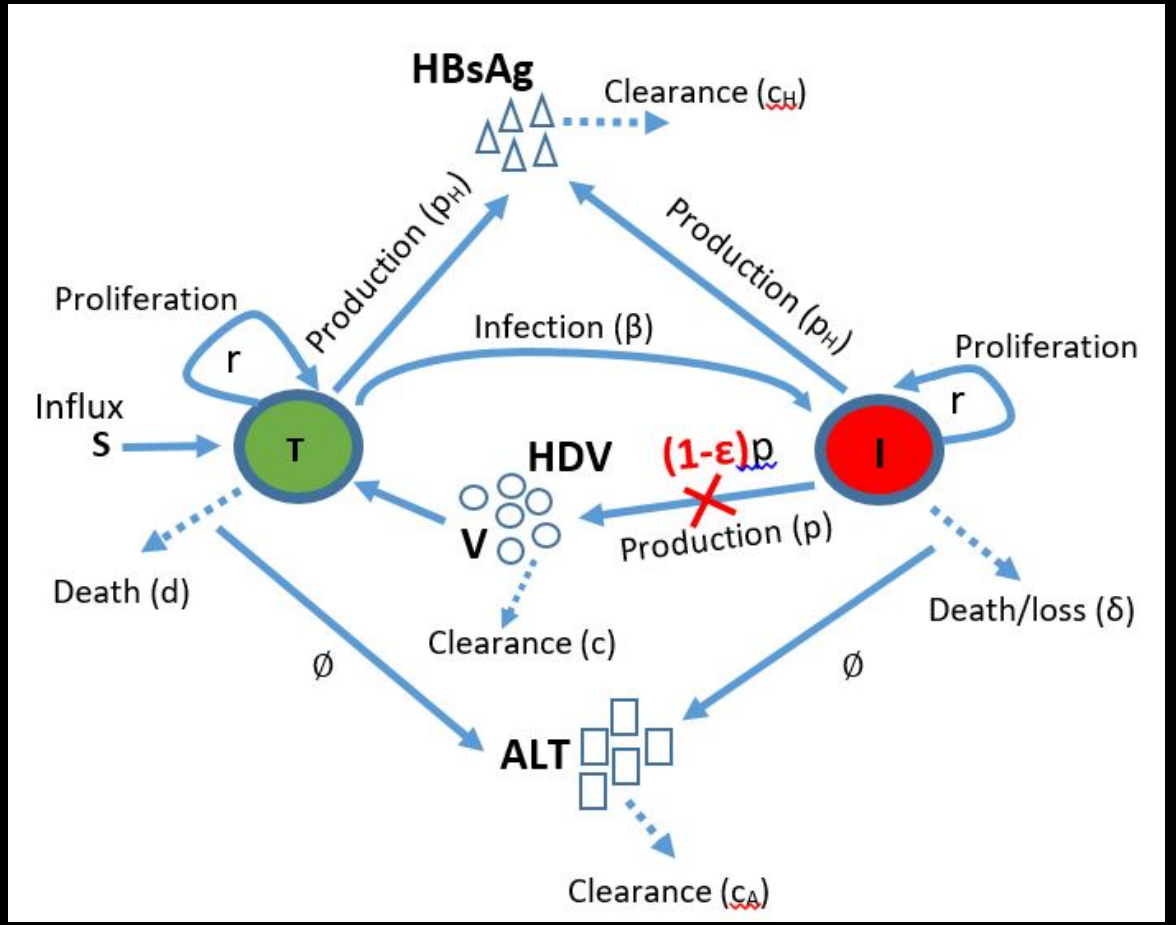




HDV RNA (IU/mL) LNF Conc (ng/mL)

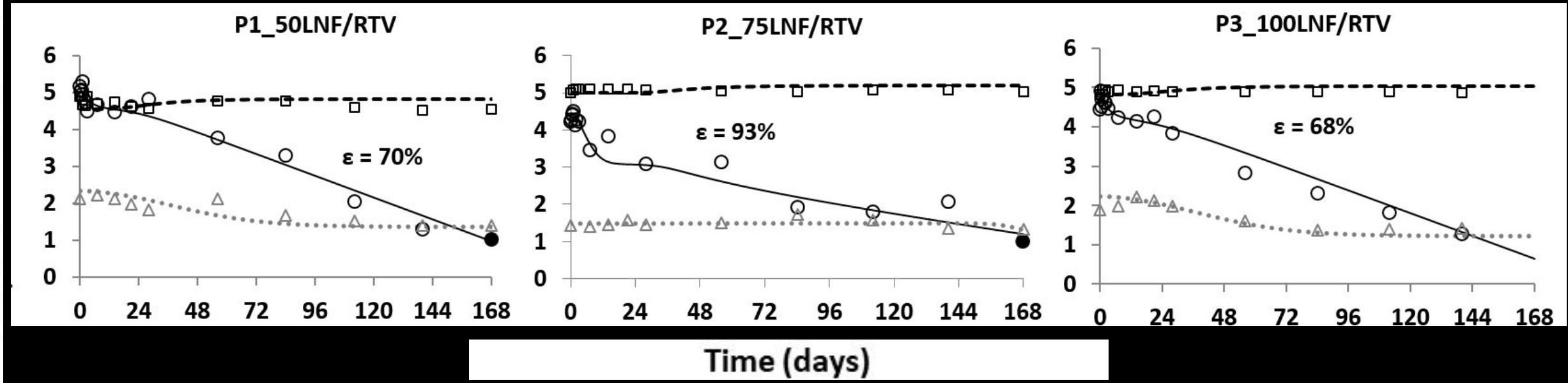
Modeling HDV RNA, HBsAg and ALT kinetics

- (T) is the number of HBsAg-productive cells that could be infected with HDV (V) to become (I)
- T+I can proliferate with maximum proliferation rate r, according to a blind homeostasis process.
- Pre-treatment steady state was assumed
- LNF efficacy (%) in blocking HDV production is represented by ε



Triphasic cases – model fits well

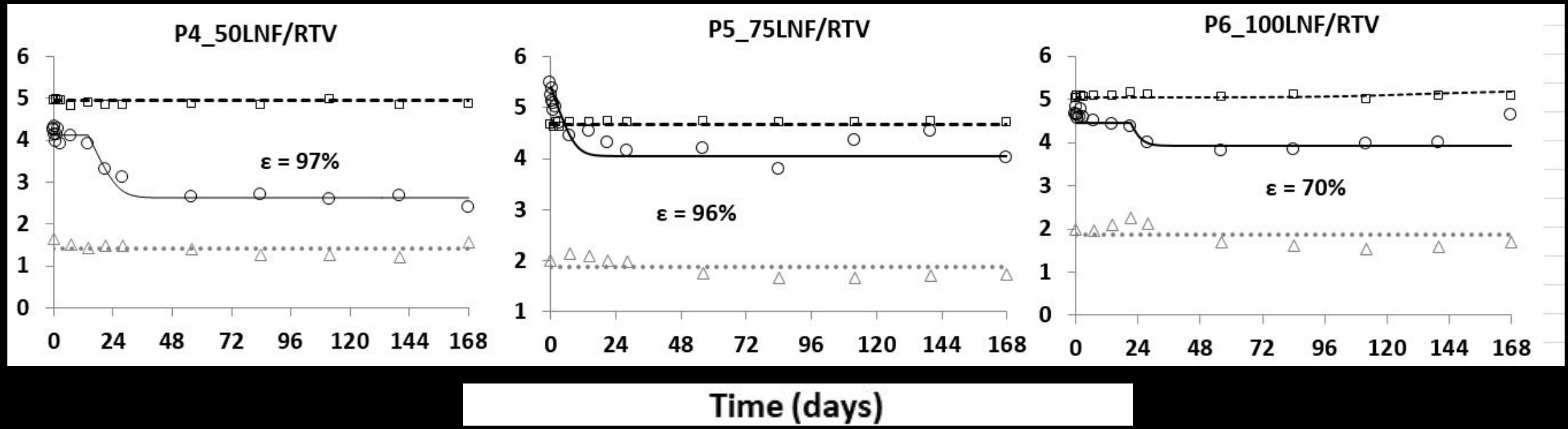
- HBsAg
- HDV RNA
- ALT



Modeling curves: HDV RNA (solid line) , HBsAg (dashed line) and ALT (dotted line)

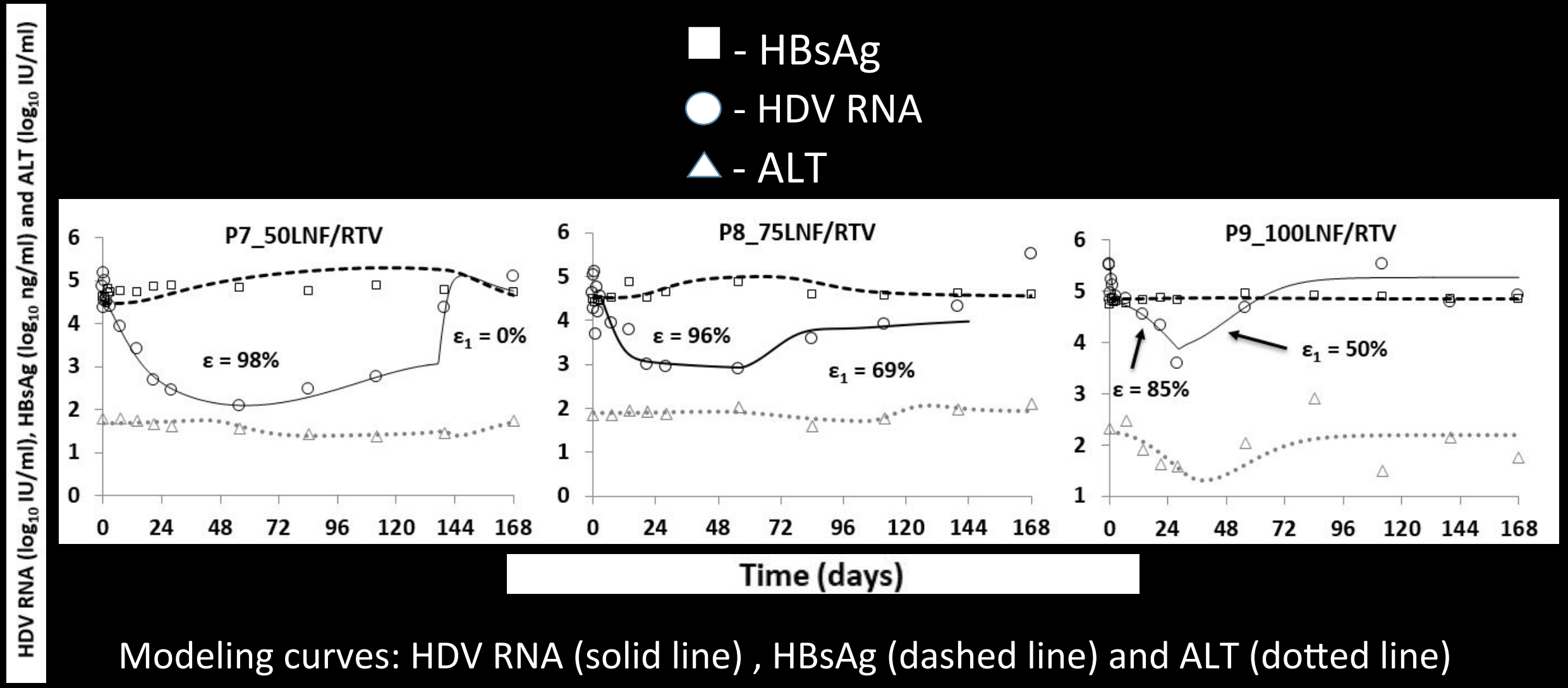
Flat partial response – model fits well

- HBsAg
- HDV RNA
- ALT



Modeling curves: HDV RNA (solid line) , HBsAg (dashed line) and ALT (dotted line)

Rebounders – model fits well



Modeling curves: HDV RNA (solid line) , HBsAg (dashed line) and ALT (dotted line)

Triphasic response is explained by drug efficacy (ε) higher than patient's critical drug efficacy (ε_c)

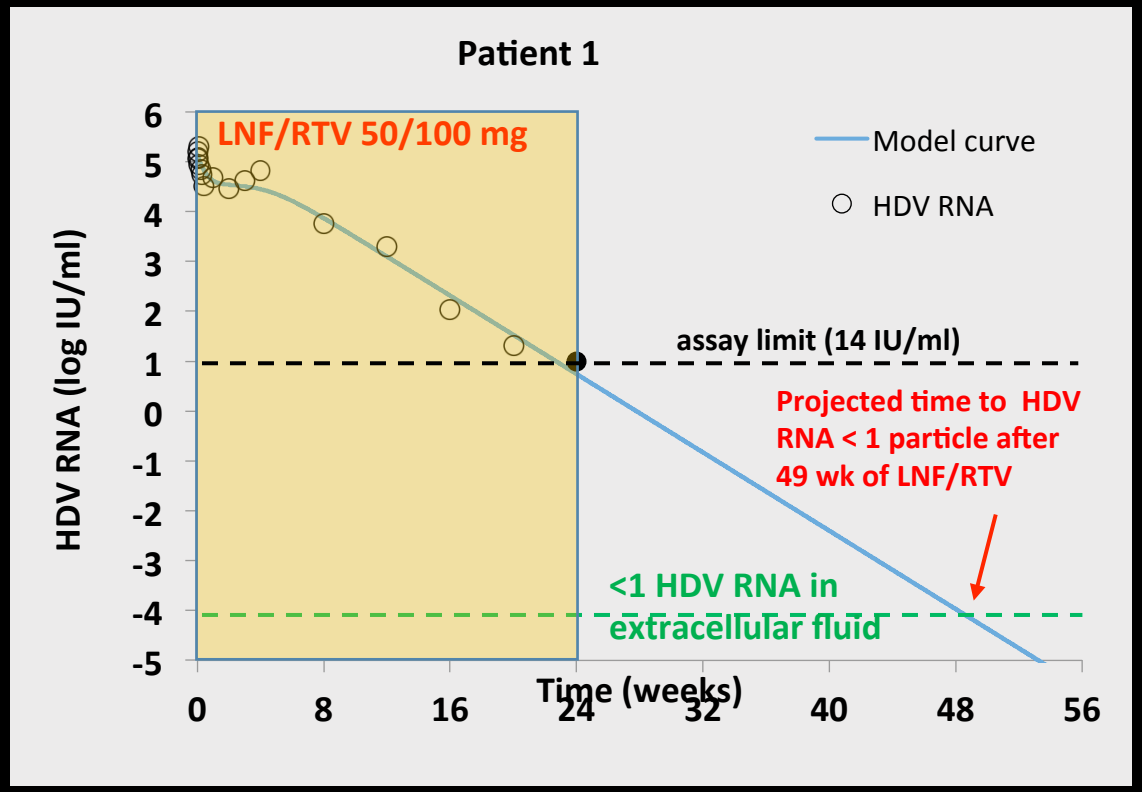
Pt	Viral kinetic pattern (LNF dose)	Estimated LFN +RTV efficacy in blocking HDV production (ε)	Estimated critical drug efficacy in each patient (ε_c)
1	Triphasic (50)	0.70	0.50
2	Triphasic (75)	0.93	0.92
3	Triphasic (100)	0.68	0.42
4	Flat partial (50)	0.97	0.98
5	Flat partial (75)	0.96	0.98
6	Flat partial (100)	0.70	0.77
7	Rebound (50)	0.98	0.99
8	Rebound (75)	0.96	0.97
9	Rebound (100)	0.85	0.66

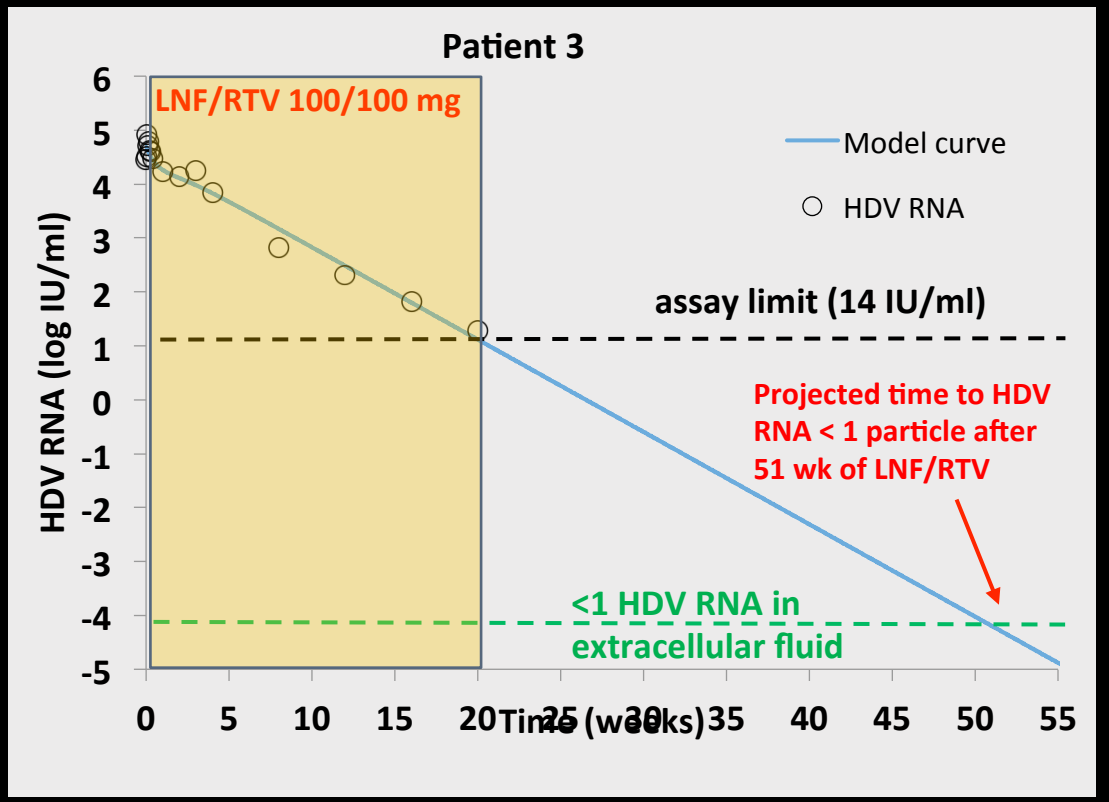
When $\varepsilon > \varepsilon_c$ viral load is predicted to decline in a triphasic manner

When $\varepsilon < \varepsilon_c$ viral load is predicted to decline in a flat partial response manner.

estimated ε before viral rebound

Predicting time to < 1 HDV particle in the entire extracellular-body fluid





Summary

- LNF+RTV was safe and generally well tolerated
- The kinetic analysis indicates that there is no association between ritonavir boosted lonafarnib dosing (50, 75 or 100 mg daily) and viral response pattern (i.e., triphasic response, flat-partial response and rebound)
- The model was able to reproduce the observed viral, HBsAg and ALT kinetics in each patient and provided insights into viral-host-drug dynamics
- Modeling results show high antiviral efficacy (95%) with ritonavir boosted lonafarnib

Discussion

- The results suggest that on treatment (real time) modeling may help individualize the length of lonafarnib-based therapy that is needed to achieve HDV clearance

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EIGER
Leader in HDV

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Adverse Events

Nausea	Diarrhea	Anorexia	Abdominal Bloating	Vomiting	Headaches	Fatigue	Significant Weight Change
8 (38%)	12 (57%)	12 (57%)	13 (62%)	2 (9%)	3 (14%)	10 (48%)	0 (0%)

Symptom	Group Significance	Score Difference (100 pt scale)	P value
Nausea	50 vs 100 mg LNF	8.5	0.001
Abdominal Bloating	75 vs 100 mg LNF	10.7	0.0003

No significant changes in weight in all subjects
No Grade 3 or 4 adverse events
No discontinuations due to adverse events