Modelling HDV kinetics under entry-inhibitor Bulevirtide suggests the existence of two HDV-infected cell populations

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	BASELINE (Pre-treatment)																			
Pts	**Age**	**Sex**	**BMI**	**ALT (U/l)**	**PLT (x10 ^{9}/l)**	**HBsAg (IU/ml)**	**HBV DNA (IU/ml)**	**HDV RNA (log IU/ml)**	**Fibroscan (Kpa)**	**AST (U/l)**	**Bile acids (umol/l)**	**ALP (U/l)**	**T bil (mg/dl)**	**IgG (mg/dl, ULN 1600)**	**GGT (U/l)**	**PCHE (U/l)**	**Alb (g/dl)**	**IG (g/dl)**	**AFP (ng/ml)**	**sCr (mg/dl)**	**HBcrAg (logU/mL)**
#1	47	M	27.5	151	48	4891	TND	5.15	39	94	18	76	0.9	4059	47	4389	3.9	3.4	9	0.93	3.50
#2	40	M	27.8	172	217	6506	TND	5.58	8.9	89	17	90	0.6	2686	26	8378	4.2	2.3	4	0.92	3.90
#3	35	M	27.4	107	47	5299	TND	5.70	23.1	103	33	132	1.5	2121	37	5971	3.9	1.8	15	1.02	4.60
#4	39	M	23.4	79	59	5076	11	3.26	32.8	94	51	201	1.1	2506	196	3619	3.8	2.2	6	0.91	3.30
#5	62	M	24.6	99	68	6400	<10	4.64	7.8	66	15	100	1.4	1876	52	6172	3.9	1.6	7	0.98	5.10
#6	34	F	23.5	84	43	8393	15	4.39	16.3	64	28	105	1.4	2458	52	3506	3.5	2.2	9	0.65	3.70
#7	29	M	28.0	133	71	2450	15	6.32	10.9	136	18	173	1	2250	197	7234	4.2	1.9	5	0.96	3.90
#8	57	F	23.0	49	76	12344	<10	5.60	9.4	52	8	79	0.9	1047	29	2983	4.1	1	9	0.85	4.60
#9	62	M	27.0	80	60	8561	TND	6.22	39.8	86	82	174	1.4	1712	79	3964	3.6	1.6	44	0.82	4.20
#10	40	F	22.5	51	63	2407	TND	3.31	14.6	57	14	86	0.5	1600	20	5994	4.2	1.4	5	0.66	3.70
#11	40	F	20.9	113	37	9147	<10	4.34	24	214	48	176	1.5	3587	97	2037	2.9	3	8	0.82	3.80
#12	70	F	30.1	155	59	370	22	4.58	16.5	153	26	137	1	2465	13	4216	3.6	2.3	7	0.82	3.80
#13	49	M	22.2	86	73	1112	TND	3.95	11.6	89	18	100	1.7	1851	75	5875	3.5	1.7	596	0.83	3.10
#14	54	M	22.3	222	122	19266	<10	6.60	33.3	208	48	308	1	2670	362	6150	4.1	2.3	17	0.84	<2.0
#15	68	M	26.7	105	91	6701	14	6.27	15.5	113	32	79	1.5	1968	52	4554	3.7	1.9	26	0.94	4.90
#16	59	M	26.9	112	96	2708	TND	5.87	57.8	97	20	186	1.4	3713	83	3797	3.6	3.1	11	0.65	5.00
#17	47	F	20.5	32	78	5231	<10	3.74	17.4	55	306	104	1.8	1554	26	1807	4.4	1.4	4	0.84	4.50
#18	77	M	23.0	145	185	349	TND	4.39	15.2	88	11	91	0.5	2285	15	5190	4	2.1	3	0.96	3.50

Table S1. Baseline features of the 18 HDV patients treated with BLV 2 mg/day. BMI, body mass index, M, male; F, female; ALT: alanine aminotransferase; PLT: platelet count; HBsAg: Hepatitis B surface antigen; T bil: Total Bilirubin; Alb: albumin; sCr: creatinine; TND: target not detected; the Lower Limit of Quantification of the HDV RNA assay was 6 IU/ml (0.78 log IU/ml)

	WEEK 24				WEEK 48			
Pts	**ALT (U/l)**	**HBsAg (IU/ml)**	**HBV DNA (IU/ml)**	**HDV RNA (log IU/ml)**	**ALT (U/l)**	**HBsAg (IU/ml)**	**HBV DNA (IU/ml)**	**HDV RNA (log IU/ml)**
#1	18	4997	<10	2.55	15	4252	TND	2.02
#2	29	6342	TND	2.59	24	5610	TND	2.11
#3	22	5429	TND	3.58	27	4838	<10	3.38
#4	52	4183	<10	1.96	57	4001	<10	TND
#5	41	7274	<10	<0.78	35	6481	TND	<0.78
#6	32	11774	TND	1.56	53	8630	TND	2.90
#7	76	2791	<10	5.77	86	2674	21	5.99
#8	46	13729	<10	2.56	38	14793	<10	1.30
#9	51	11501	<10	5.28	53	10607	TND	6.02
#10	26	3107	<10	1.26	28	2778	<10	<0.78
#11	78	12091	<10	<0.78	51	8474	TND	<0.78
#12	20	417	TND	1.26	17	355	TND	0.95
#13	22	1209	TND	1.68	23	820	TND	2.34
#14	82	19821	<10	3.90	55	18239	<10	2.98
#15	28	7327	<10	4.02	33	5344	<10	4.45
#16	36	2595	<10	2.92	34	1974	TND	2.46
#17	45	7424	<10	1.62	36	7414	<10	2.37
#18	19	311	<10	1.20	22	284	TND	<0.78

Table S2. **Measurements during therapy of the 18 HDV patients treated with BLV 2 mg/day**. ALT: alanine aminotransferase; HBsAg: Hepatitis B surface antigen; TND: target not detected; the Lower Limit of Quantification of the HDV RNA assay was 6 IU/ml (0.78 log IU/ml)

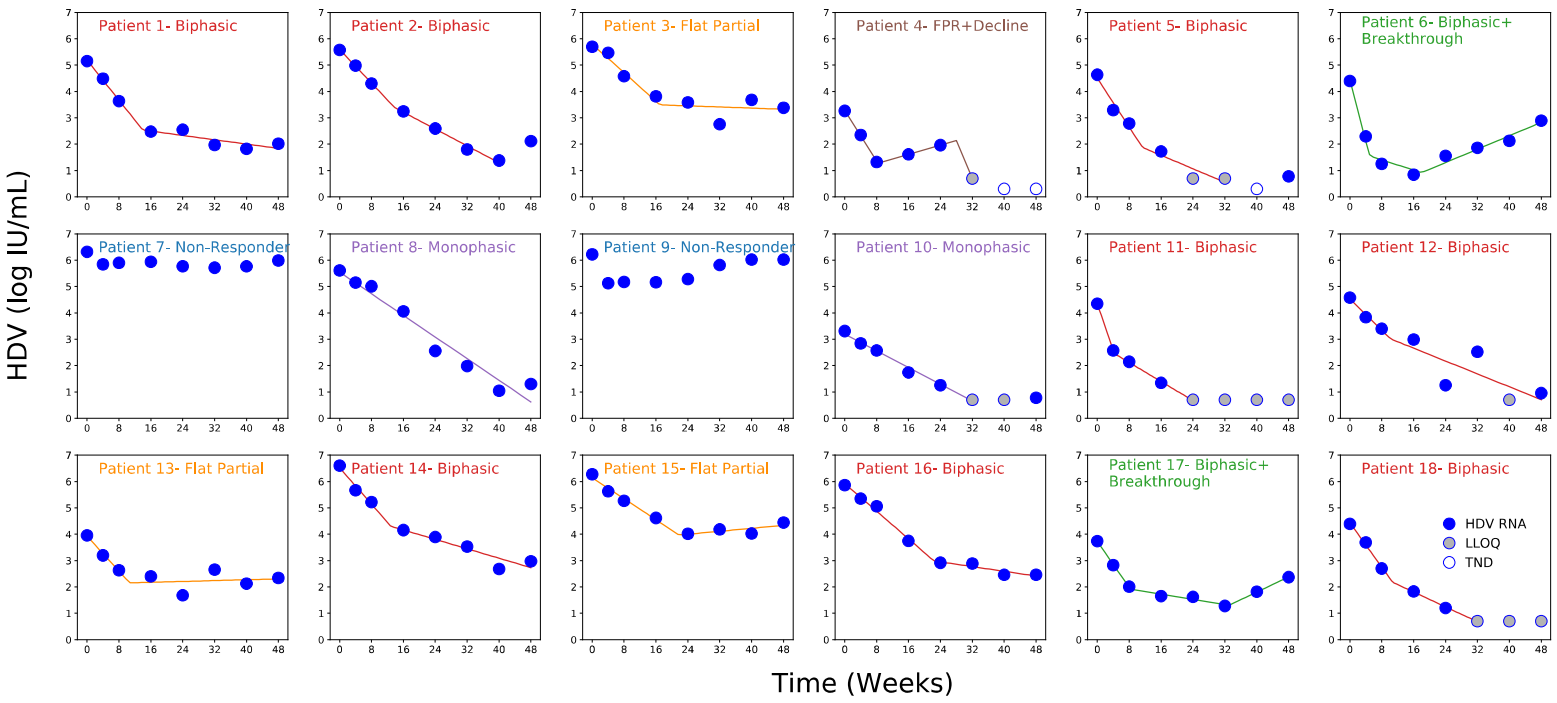

Fig. S1. Patient kinetic fits using piecewise linear fits.

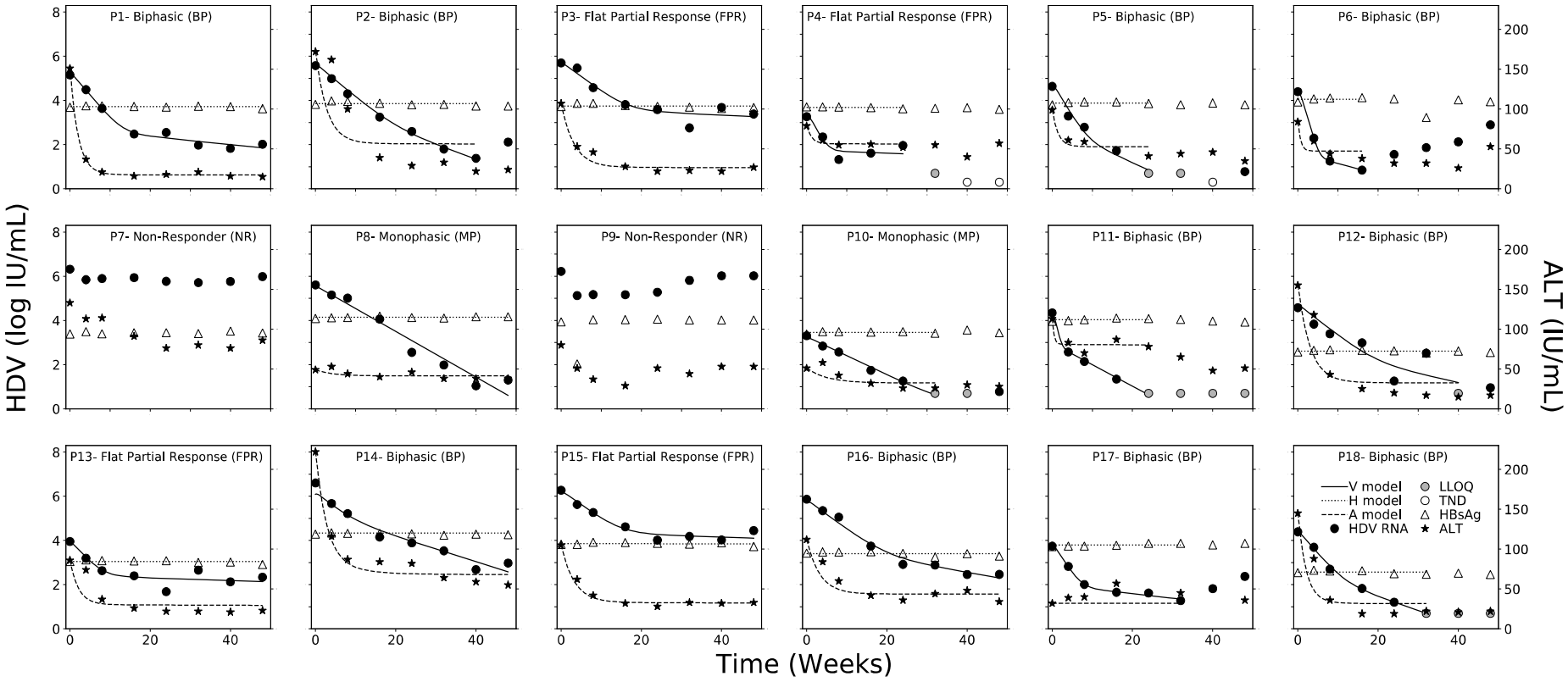

Fig. S2. Fit curves of all patients (including 2 NR patients – without modeling curves)

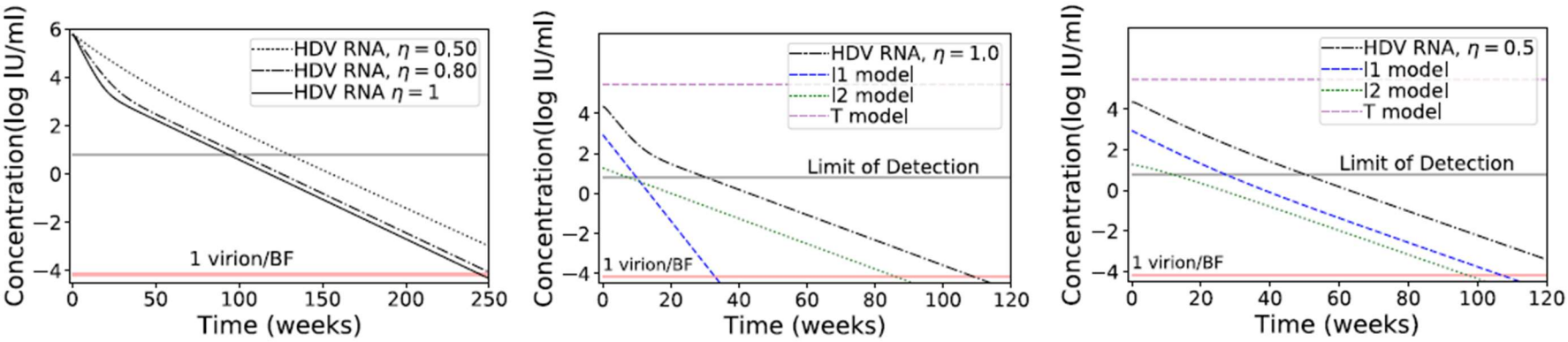

Fig. S3. **Robustness of results to variations in BLV effectiveness in blocking infection**. (a) Here we show how reducing the BLV effectiveness in blocking production from η=1 to η=0.8 and η=0.5 changes the HDV RNA dynamics. We show the difference based on estimated parameters for Patient 18 (Table 1, main manuscript) and find minimal changes to the HDV RNA dynamics until η=0.5, at which point the viral dynamics curve becomes monophasic and is considerably higher. (b)-(c) We show the dynamics of I_1, I_2 and T during treatment for (b) η=1 and (c) η=0.5 to explain how the lower η allows for cell infection to occur and thereby delays the crossover point at which I_2 becomes dominant to well beyond the point where the virus becomes undetectable.

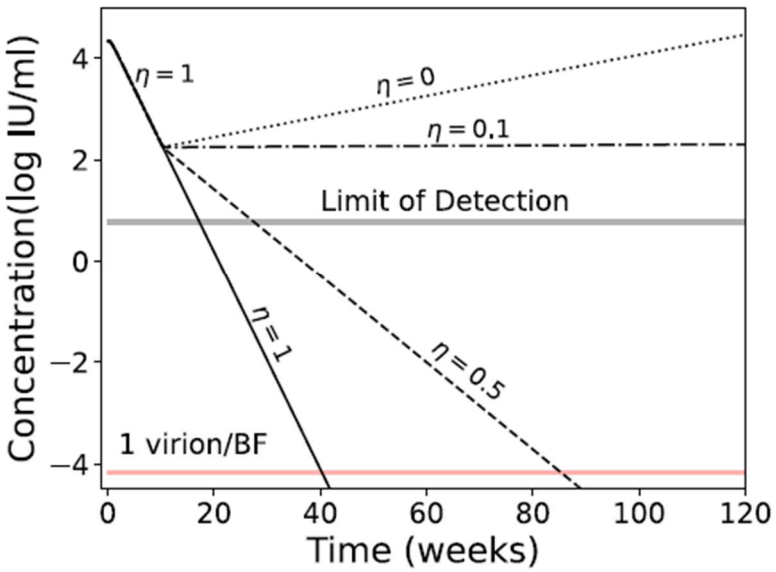

Fig. S4. HDV RNA Concentration as a function of time for different values of blocking of infection. We find that reducing blocking of infection from 100% effectiveness ($\boldsymbol{\eta}$=1) to lower levels can explain the biphasic pattern (if $\boldsymbol{\eta}$=0.5), the flat partial response (if $\boldsymbol{\eta}$=0.1) and a potential rebound (if $\boldsymbol{\eta}$=0). Other parameters correspond to the fit results for Patient 18 (Table 1, main manuscript).