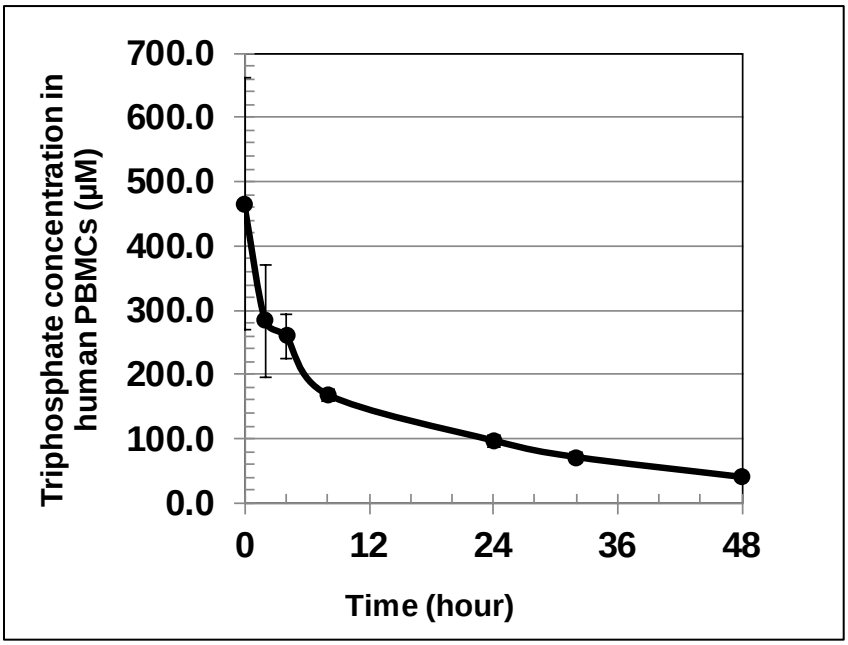
SUPPLEMENTAL MATERIAL – *Ratna et al*

FIG S1- Intracellular triphosphate levels measured by LC-MS/MS upon prodrug removal. Error bars represent SD (n = 3 replicates). Prodrug **12** was first incubated in human PBMCs at 100 µM for 24 hours. Then media was replaced with a fresh one without compound (time = 0 hour). Subsequently, time-points were taken up to 48 hours. Half-life was calculated to be 5.5 hours.



			Nucleoside 7			
	Unit	**Day**	**10 mg/kg BID**	**30 mg/kg BID**	**100 mg/kg BID**	**300 mg/kg BID**
C_{max}	µM	1	0.3	0.9	2.5	1.9
		3	0.3	0.8	1.4	2.4
AUC_{24}	µM.hours	1	2.6	7.4	22.9	24.4
		3	3.2	8.6	19.4	29.6

TABLE S1- Pharmacokinetic parameters of metabolite 7 upon oral dosing of compound 17 in the infected AG129 mouse model. The intact prodrug was not detected in plasma. Major metabolite nucleoside 7 was monitored in plasma of 3 mice. PK parameters (Cmax, AUC24) was obtained from the samples at 1, 3, 6, 24 hours post-1st-dose (day 1) and 50, 52, 55, 72 hours post 1st-dose (day 3). See Fig 6A for dosing scheme and sampling schedule. Cmax = maximum plasma concentration. AUC24 = area under the curve observed for 24 hours on the study day.

	Unit	Solution	Nanosuspension	Solid dispersion
C_{max}	µM	5.5	0.9	16.4
T_{max}	hours	0.58	0.8	0.25
AUC_{last}	µM.hours	4.4	1.5	12.2
F	%	24	8.5	68

Table S2- Pharmacokinetic parameters of compound 17 dosed orally at 15 mg/kg in different formulation to beagle dogs (n=3). Solution and solid dispersion formulation as described in Material and Methods section. Nanosuspension formulation used 1% hydroxypropyl methylcellulose and 0.2% sodium dodecyl sulfate. Intact prodrug was measured in plasma by LC-MS/MS. Cmax = maximum plasma concentration. Tmax = time to reach maximum concentration. AUClast = area under the curve (t=0 till the last measurable concentration), F = oral bioavailability. Solid dispersion formulation showed the highest oral bioavailability.

	Unit	30 mg/kg/day		100 mg/kg/day	300 mg/kg/day
Study day		1	14	1	1
C_{24}	µM	24	50	100	73
C_{max}	µM	73	98	140	150
AUC_{24}	µM.hours	1050	1558	2399	2387

Table S3- PBMC triphosphate concentration obtained from two-week repeat-dosing toxicology studies in dogs (n = 3 females and 3 males). Compound 17 was dosed orally at 30, 100, and 300 mg/kg/day for 14 days. C24 = concentration observed at 24 hours on the study day. Cmax = maximum plasma concentration. AUC24 = area under the curve observed for 24 hours on the study day.