

Global Production, Regulatory, and Trade Environment

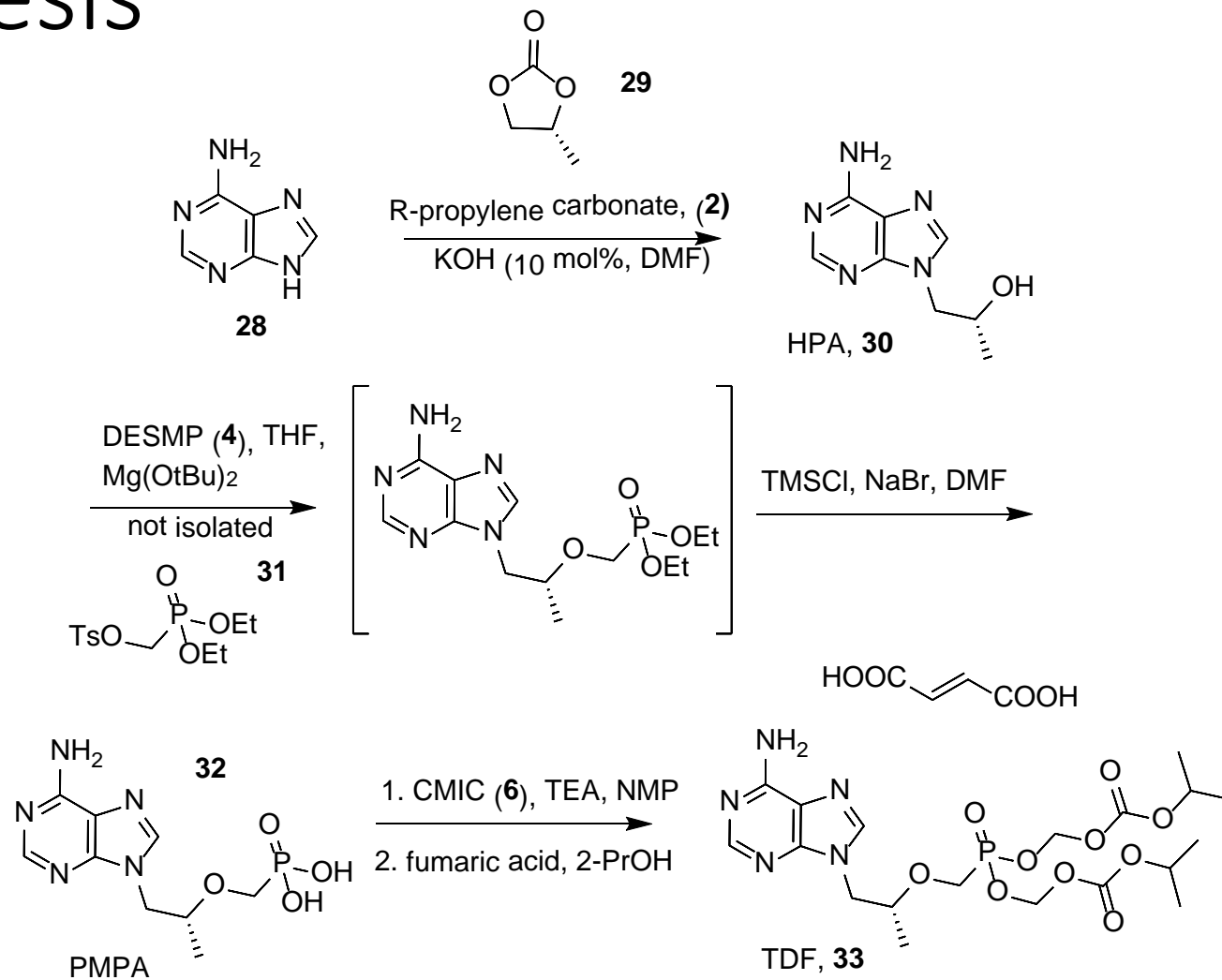
Joseph Fortunak

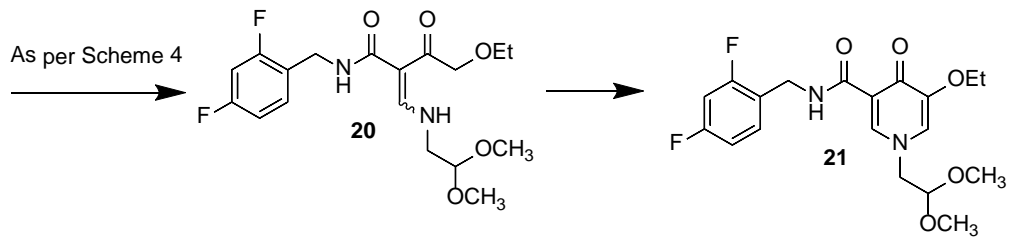
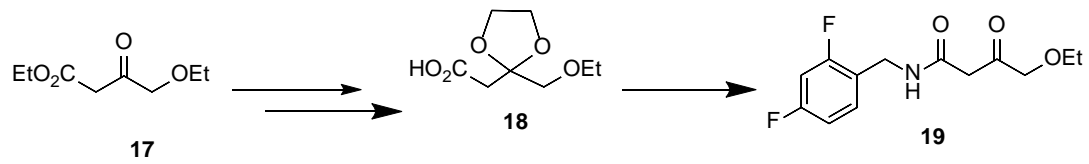
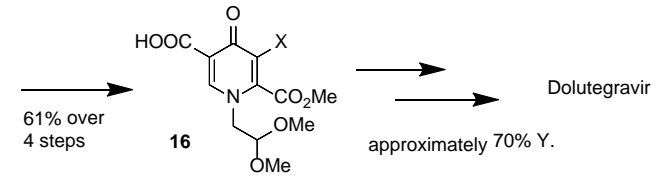
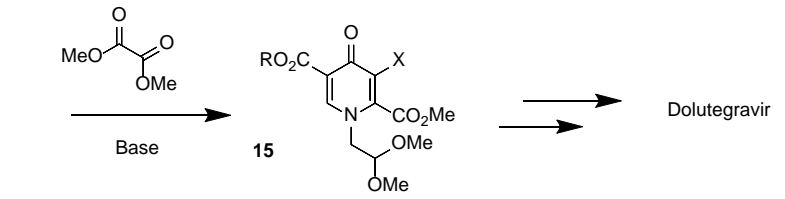
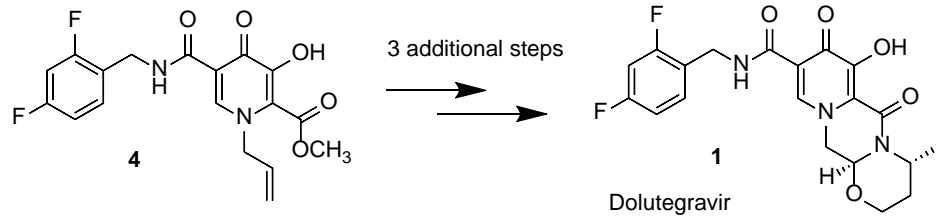
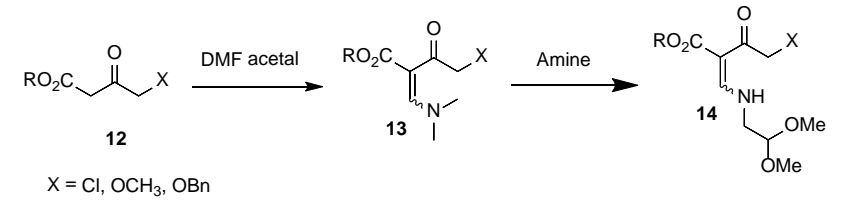
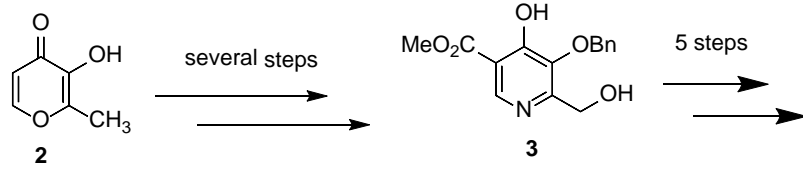
jfortunak@howard.edu

jfortunak@Comcast.net

APIs and Finished Pharmaceutical Products (FPPs)

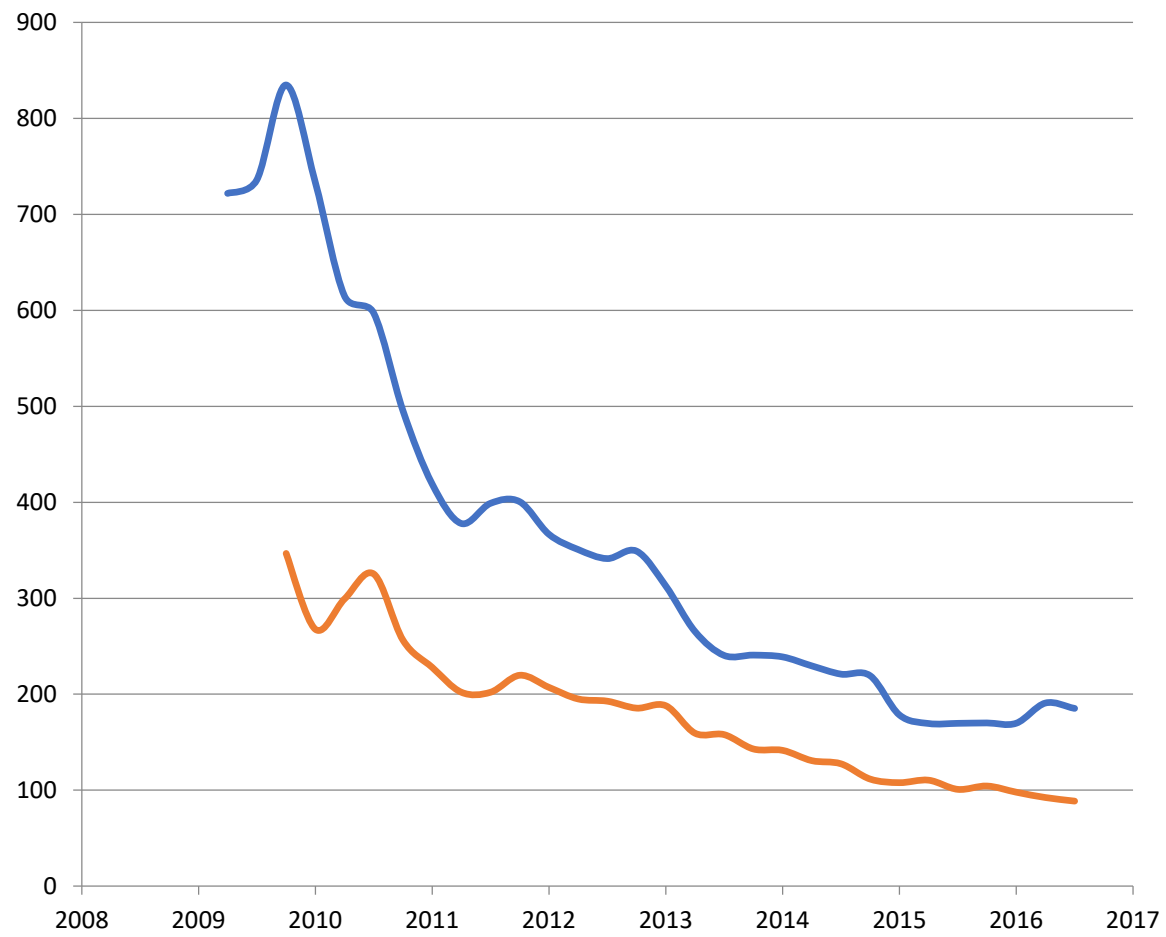
API Synthesis

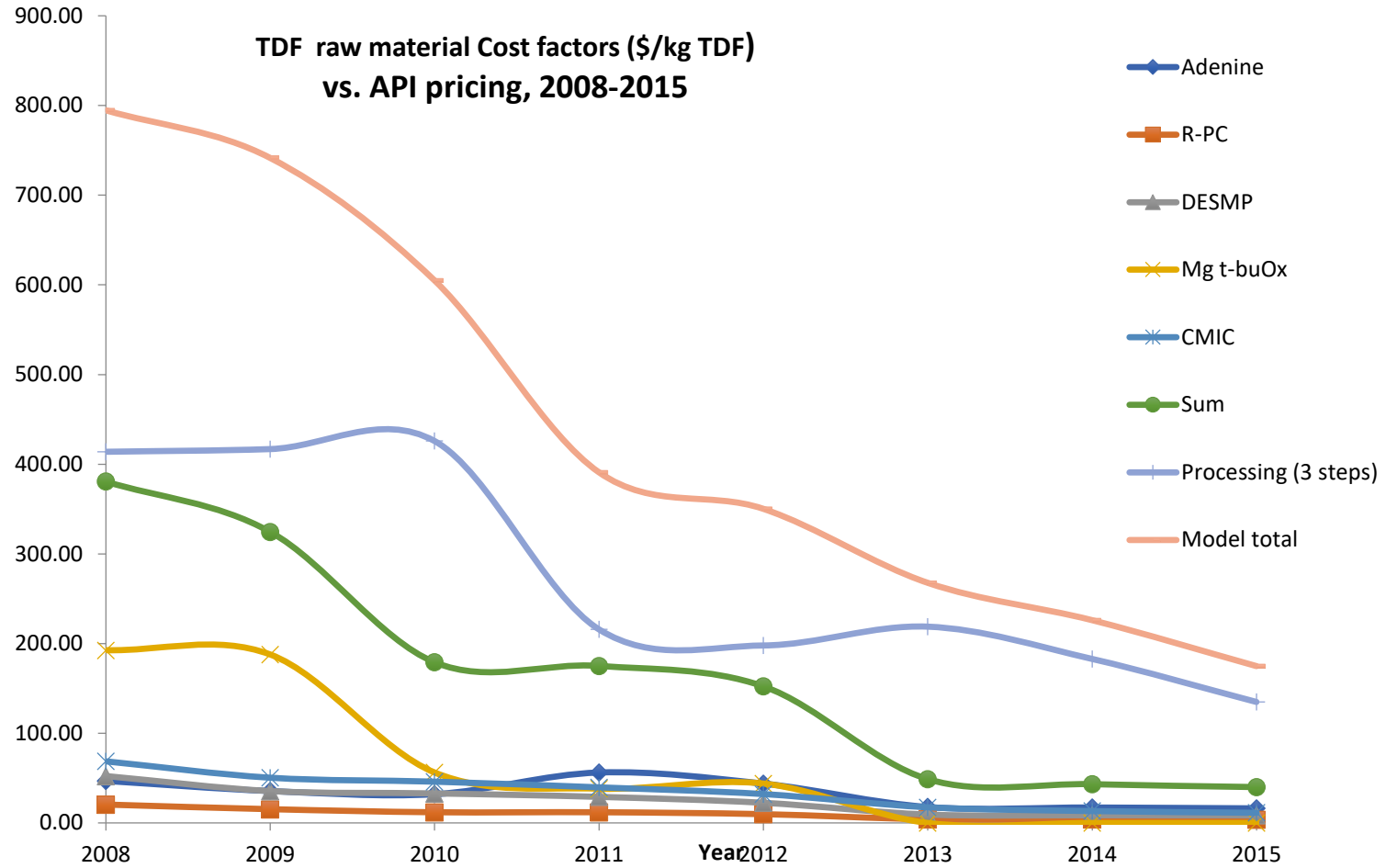




API and FPP pricing

API	FPP Pricing, US	FPP Pricing , LMICs	API pricing/kg, India/China	Generic API pricing PPPY or per treatment
Sofosbuvir	\$84,000	\$200 - \$650	\$800	\$27
Daclatasvir	\$63,000	\$45	\$850	\$4.25
Tenofovir disoproxil fumarate (TDF)	\$15,000	\$66	\$140	\$15.40
Efavirenz	\$2,600	\$48	\$105	\$24
Lamivudine (3TC)		\$42	\$135	\$15
TLE (TDF/3TC/EFV)		\$95	\$95	\$55
Imatinib	\$125,000		\$140	<\$40
Cyclophosphamide	\$27,000		\$270 - \$310	<\$20
Cholic Acid	\$312,000	N/A	\$370/kg (MP Biomedical)	\$33 - \$57





Drug (indication)	Dose	Pricing/dose, US	Pricing /dose, LMICs
Cefuroxime (anti-infective)	500 mg, 20 count	\$1.815 - \$2.15	\$0.368
Atazanavir (AIDS)	300 mg, 30 count	\$29.74 - \$52.77	\$0.5213
Atenolol (cardiovascular)	50 mg/30 count	\$0.133 - \$0.3787	\$0.0059
Atorvastatin (lipid-lowering)	20 mg/30 count	\$0.3327 - \$2.933	\$0.0714

Representative pricing of medicines in the US versus median pricing in LMICs.

Full Disclosure

Journal of Virus Eradication 2015; 1:000-000

ORIGINAL RESEARCH

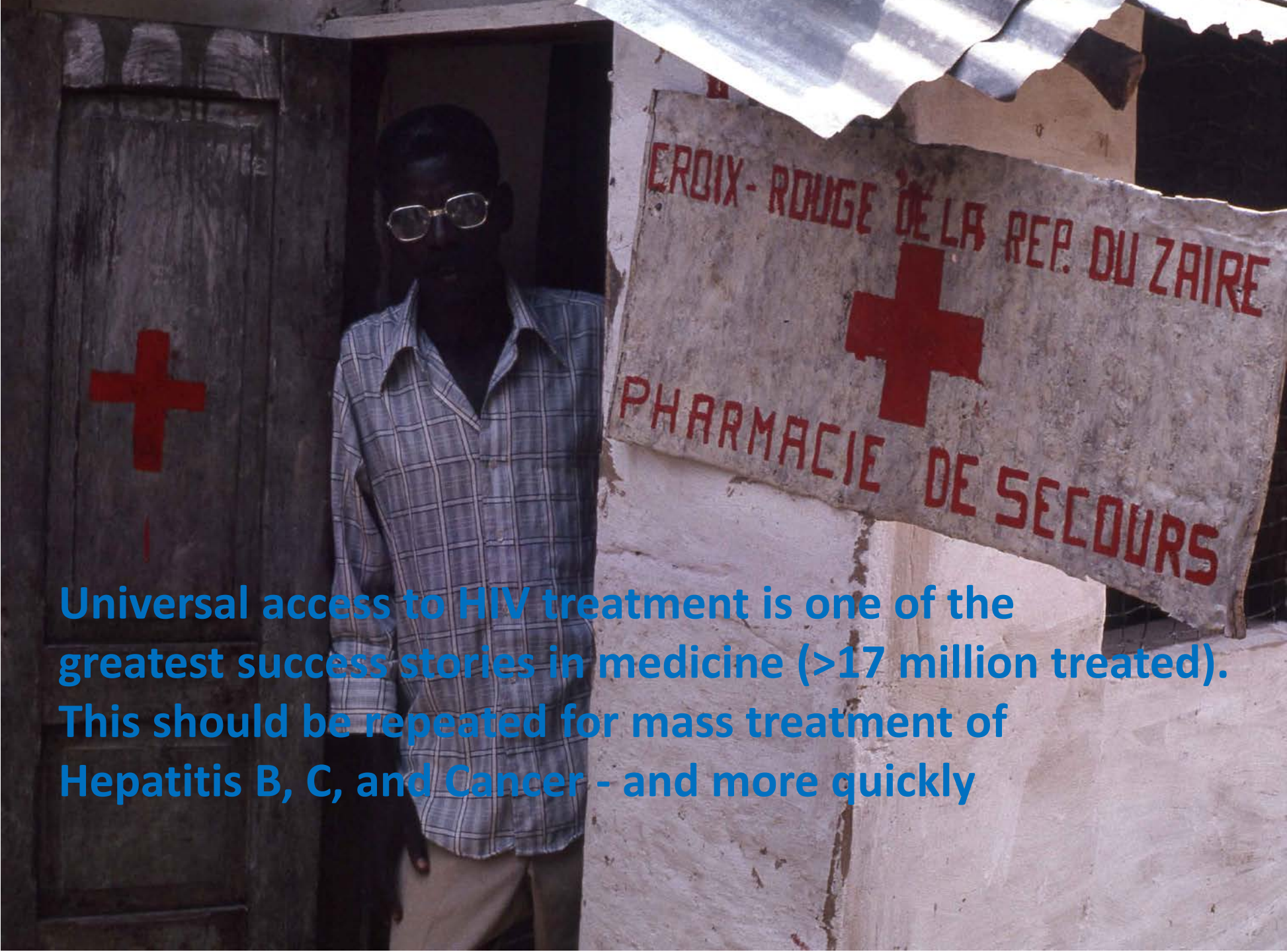
Analysis of minimum target prices for production of entecavir to treat hepatitis B in high- and low-income countries

Andrew Hill*¹, Dzintars Gotthardt², Graham Cooke², Sanjay Bhagani³, Isabelle Andrieux-Meyer⁴, Jennifer Cohn⁵, Joseph Fortuna⁶

¹Department of Pharmacology and Therapeutics, Liverpool University, UK, ²Faculty of Medicine, Imperial College London, London, UK

³Department of Infectious Diseases/HIV Medicine, Royal Free Hospital, London, UK, ⁴Division of Infectious Diseases, Geneva University Hospital, Switzerland

⁵Division of Infectious Diseases, University of Pennsylvania, Philadelphia, US, ⁶Chemistry and Pharmaceutical Sciences, Howard University, Washington DC, US



Universal access to HIV treatment is one of the greatest success stories in medicine (>17 million treated). This should be repeated for mass treatment of Hepatitis B, C, and Cancer - and more quickly

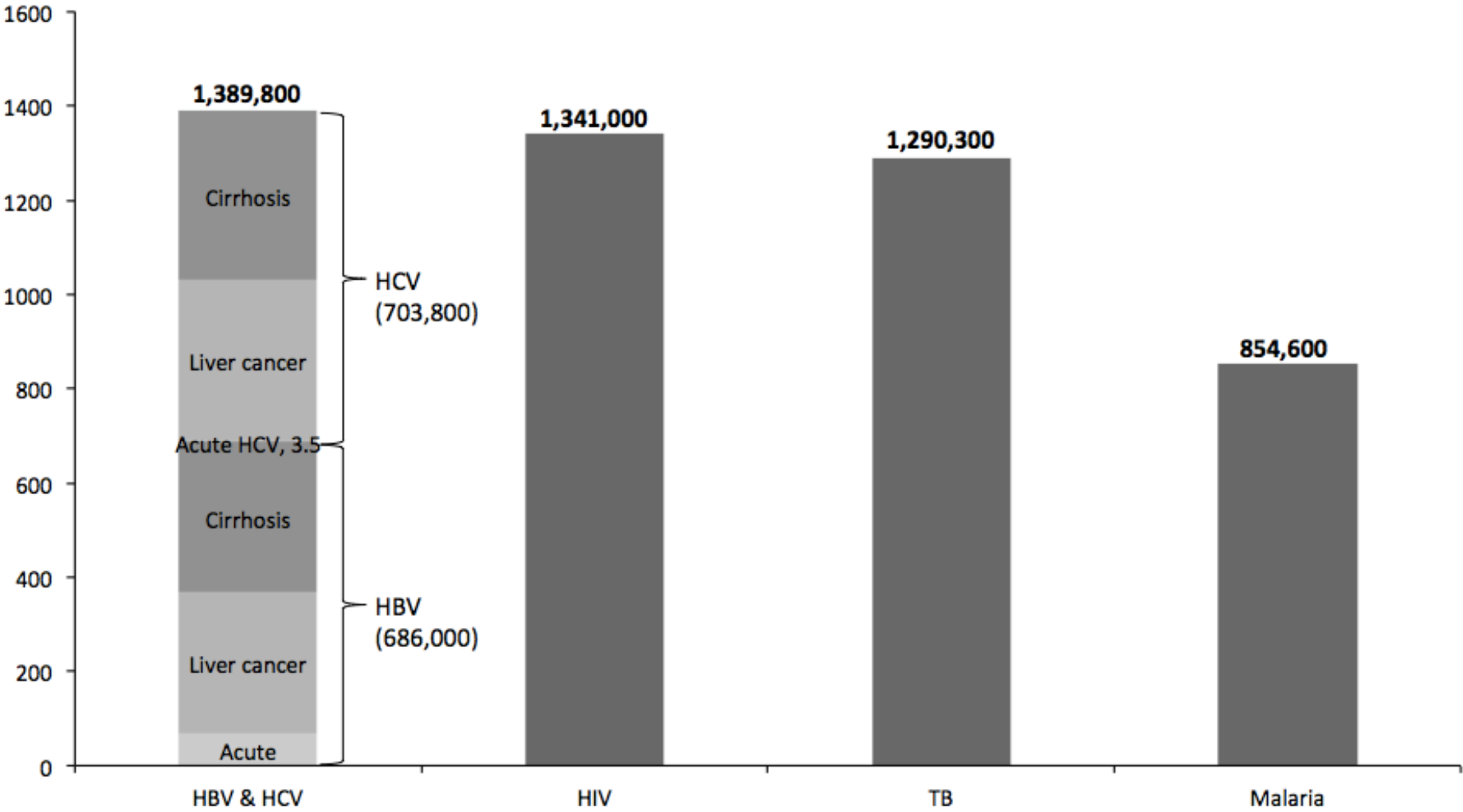
Impact of Global Access Campaigns Upon the Indian and Chinese Pharma Industries

Priorities in LMICs?

Causes of Death: USA, 2014

All Causes	2,626,418
Cardiovascular Diseases	614,348
Malignant Neoplasms	591,699
Chronic Lower Respiratory Diseases	147,101
Accidents	136,053
Cerebrovascular Disease	133,103
Alzheimer's Disease	93,541
Diabetes Mellitus	76,448
Influenza, pneumonia	55,227
Nephritis	48,146
Suicide	42,773

Worldwide deaths from HCV, HBV, HIV, tuberculosis, and malaria in 2013



Causes of Death - Africa

- ***BUT: This does not even count the incalculable burden of cardiovascular diseases and diabetes...***
- (Rob Ridley) Approximately 14 million deaths per year occur in sub-Saharan Africa because of ***preventable or easily treatable diseases:***
 - Diarrheal diseases
 - Simple Infections
 - Malaria
 - Tuberculosis
 - HIV/AIDS
 - Hepatitis B and C

	LE Sales	Units	Units	G%	Units	G%	Units	G%	LE Sales	LE Sales	G%	LE Sales	G%	LE Sales	G
	Rank	MAT/02/2012 (Absolute)	MAT/02/2013 (Absolute)		MAT/02/2014 (Absolute)		MAT/02/2015 (Absolute)		MAT/02/2012 (Absolute)	MAT/02/2013 (Absolute)		MAT/02/2014 (Absolute)		MAT/02/2015 (Absolute)	
Pharma market		1,678,724,286	1,879,809,426	12%	1,889,000,369	0%	2,025,931,360	7%	19,321,756,510	23,018,465,849	19%	24,855,001,290	0	28,464,898,532	15
AUGMENTIN	1	5,672,894	7,139,100	7%	7,646,917	7%	8,446,074	10%	234,255,131.00	301,282,679.00	29%	331,398,377.00	10%	383,364,252.00	16
CEFOTAX	2	15,535,228	18,712,976	6%	18,648,982	0%	22,517,438	21%	176,098,848.00	211,882,976.00	20%	214,656,672.00	1%	261,212,480.00	22
CATAFLAM	3	10,741,137	11,983,641	15%	13,833,146	15%	15,741,697	14%	157,189,424.00	185,895,360.00	18%	215,429,936.00	16%	254,210,608.00	18
FLUMOX	4	19,083,946	20,521,558	-3%	20,064,919	-3%	22,830,485	14%	180,519,932.00	197,372,840.00	9%	195,242,248.00	-1%	229,468,160.00	18
AMARYL	5	6,062,062	5,959,519	-18%	4,878,933	-18%	5,278,000	8%	182,915,184.00	190,549,312.00	17%	186,981,104.00	-2%	203,738,896.00	9
CONCOR	6	7,883,438	10,109,245	8%	10,891,693	8%	10,297,149	-5%	108,741,360.00	138,177,744.00	28%	149,290,416.00	7%	193,026,560.00	29
VOLTAREN	7	8,901,812	10,914,605	8%	11,826,481	8%	13,667,980	15%	124,834,576.00	146,992,320.00	18%	160,319,658.00	9%	190,011,344.00	19
CATAFAST	8	4,735,016	6,388,183	17%	7,460,022	17%	9,860,638	32%	85,230,288.00	114,987,296.00	35%	134,280,400.00	17%	177,489,680.00	32
CURAM	9	4,377,980	4,879,127	11%	5,516,985	11%	6,130,988	11%	105,729,082.00	126,038,737.00	19%	154,147,308.00	22%	175,983,148.00	14
INS MIXTARD 30 HM	10	5,286,024	5,398,533	3%	5,557,747	3%	6,435,482	16%	125,099,952.00	133,140,632.00	6%	145,106,266.00	9%	164,029,744.00	13
CONTROLOC	11	982,457	1,101,646	77%	1,954,033	77%	2,512,686	29%	65,895,246.00	87,071,952.00	32%	127,483,448.00	46%	161,973,320.00	27
PLAVIX	12	451,232	564,462	12%	632,065	12%	783,655	24%	92,502,560.00	116,712,656.00	25%	129,573,328.00	12%	160,649,280.00	24
DIAMICRON	13	7,201,537	7,766,258	-5%	7,415,780	-5%	7,833,418	3%	132,712,864.00	148,033,856.00	12%	145,825,440.00	-1%	155,200,592.00	6
BRUFEN	14	9,993,193	11,748,957	19%	14,035,053	19%	14,811,014	6%	92,090,067.00	118,885,812.00	29%	145,557,440.00	23%	150,049,280.00	3
VIRECTA	15	6,295,725	7,029,428	7%	7,553,141	7%	7,803,024	3%	113,022,486.00	127,130,944.00	12%	139,038,176.00	8%	149,185,104.00	7
ZANTAC	16	5,133,917	6,783,327	14%	7,744,629	14%	7,619,594	-2%	97,256,144.00	127,880,912.00	31%	146,319,280.00	14%	145,128,480.00	0
EREC	17	6,846,281	7,065,115	-27%	5,165,673	-27%	3,891,289	-25%	118,825,040.00	175,330,512.00	48%	182,899,520.00	4%	136,399,696.00	-21
HIBIOTIC	18	2,645,420	2,656,489	2%	2,721,837	2%	2,717,476	0%	113,994,472.00	125,004,560.00	10%	130,366,880.00	4%	130,349,152.00	0
FERROTRON	19	1,374,927	2,345,157	28%	3,006,912	28%	3,839,299	21%	45,372,592.00	77,389,184.00	71%	99,228,096.00	28%	120,096,864.00	21
DEPOVIT B12	20	12,812,744	19,895,356	-17%	16,482,672	-17%	18,821,424	14%	77,899,984.00	114,904,072.00	48%	163,419,104.00	-10%	119,896,480.00	14
CLEXANE	21	1,116,682	1,198,849	20%	1,439,410	20%	2,154,116	50%	58,730,912.00	86,434,560.00	13%	77,285,512.00	16%	118,435,464.00	51
CEFAXONE	22	3,727,432	5,458,467	-11%	4,879,796	-11%	6,979,265	43%	60,980,380.00	94,673,224.00	55%	82,808,828.00	-13%	115,548,640.00	40
PANADOL	23	3,890,605	6,293,269	25%	7,867,318	25%	10,139,507	29%	44,153,352.00	70,761,562.00	60%	87,033,620.00	23%	115,071,984.00	31
GYNERA	24	3,036,951	3,558,049	7%	3,890,329	7%	4,454,498	17%	51,628,168.00	60,486,832.00	17%	90,339,312.00	49%	111,362,448.00	21
EPICEPHIN	25	0	2,408,524	50%	3,611,777	50%	5,729,028	59%	0	43,637,724.00	NDIV/01	87,164,712.00	54%	106,489,632.00	56
VIAGRA	26	226,618	1,381,773	4%	1,437,434	4%	2,256,557	57%	25,076,988.00	57,296,800.00	128%	60,714,018.00	6%	103,180,352.00	70
														4,331,557,61	17

Do we compare/contrast
India and China?

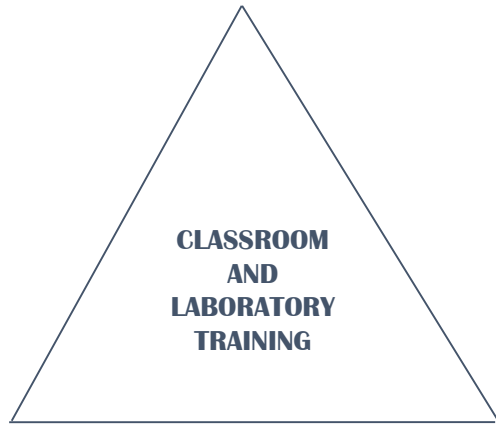
Local Pharmaceutical Manufacturing - Africa







INDUSTRY



ACADEMIA



Regulatory





Patents

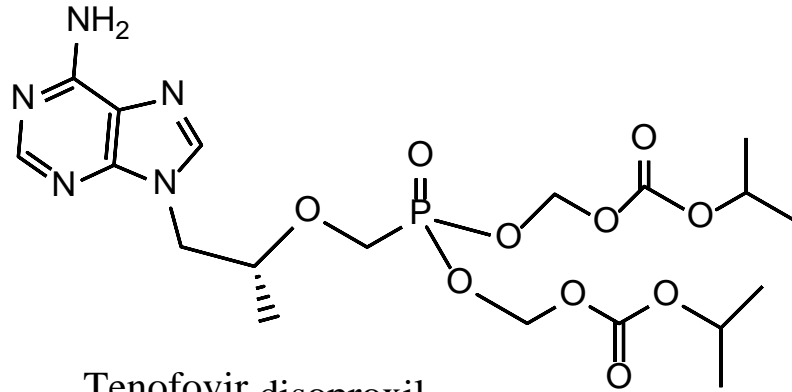
The Patent Estate - Evergreening

- Pharmaceutical companies represent nearly every aspect of drug development and delivery as containing patentable innovation:
 - Composition of matter
 - Method of use
 - Combinations with other drugs
 - Pharmaceutical compositions (formulations)
 - Processes and Intermediates (not listed in the Orange Book)
 - Crystalline forms (salts, polymorphs, hydrates, solvates, co-crystals, dispersions)
 - Latter-day “improvements”

Tenofovir Alafenamide – Patent Applications

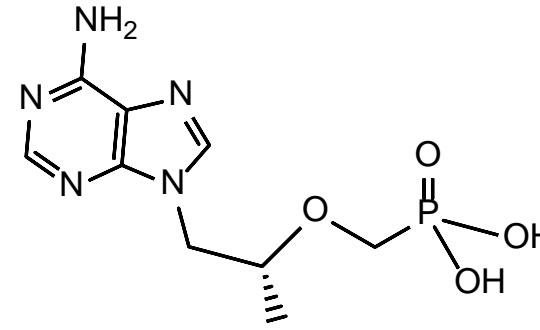


Tenofovir, Tenofovir Disoproxil, Tenofovir Alafenamide



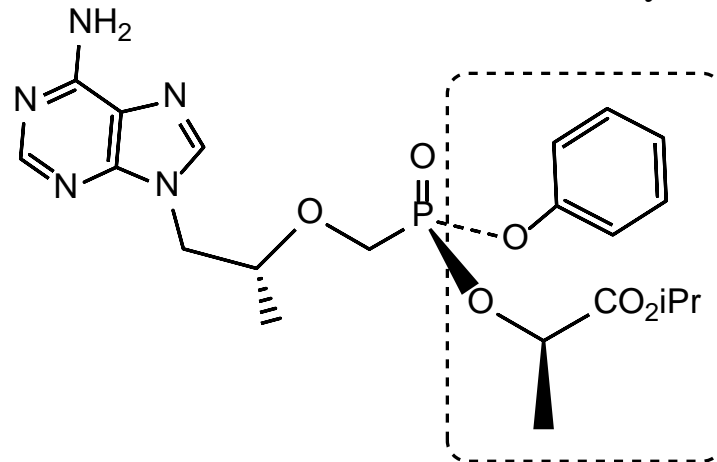
Tenofovir disoproxil

Prodrug selected by Gilead Sciences
(John Martin)



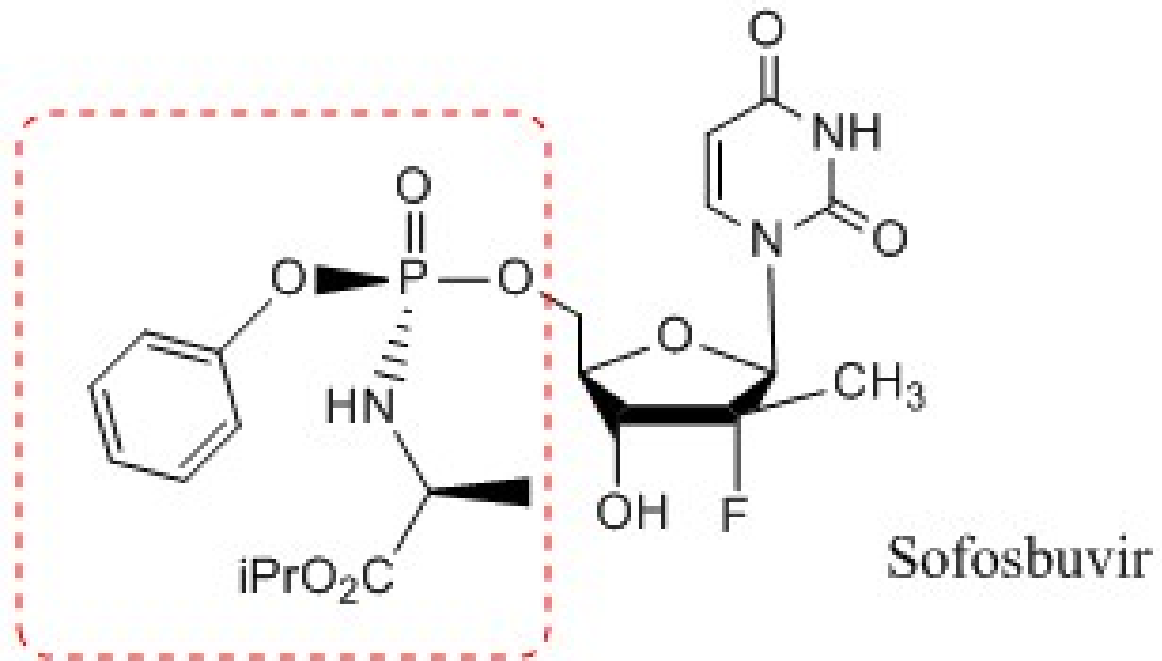
Tenofovir (API)

Synthesized by Antonin Holy and
tested by Eric de Clerq



First published by
McGuigan et. al.,
(1989) and applied
to hundreds of
antiviral compounds

Sofosbuvir



Emerging Issues

- Alternative salts of tenofovir disoproxil fumarate (citrate, phosphate) from Indian generics have been approved by the EMA (March, 2017) and the tartrate is expected to be approved this month
- This provides a means for getting around originator patents, but it also creates new patent issues... (DTG, TDF, solvates and new crystal forms of important APIs (aripiprazole/abilify)
- Tenofovir disoproxil fumarate is presently taken by an estimated 12MM people in LMICs
 - Patent coverage on the drug molecule theoretically expires in 2017/2018
 - Gilead Sciences seeking to extend this to 2020 in US and Europe with a 2015 application covering solid state forms of tenofovir disoproxil, preventing generic companies from