

Is the sun setting on the era of the HIV blockbuster?



Amy Brown

Dolutegravir's approval by the FDA yesterday puts a punctuation mark on a quarter-century of HIV antiviral development. The Viiv Healthcare pill now dubbed Tivicay is forecast to achieve blockbuster sales in 2017, nipping at the heels of some of the best-selling single-agent and combination products. However, by that time, the market at large will have begun to contract - forecasts show sales of branded HIV antivirals peaking in 2016 at \$20.6bn - as older drugs like Prezista and Reyataz lose market exclusivity (see tables).

While drug developers are still attempting to innovate, much of the activity seems to be centred on new combinations of already marketed compounds - attacking resistance, improving compliance through reduced pill burden, and treating complications are the goals of many of the new agents. There still is broad interest in pushing forward with new products, and companies like Gilead Sciences, Bristol-Myers Squibb, AbbVie and the Viiv joint venture remain active. Yet with life expectancy for HIV patients who begin treatment early now nearing that of non-infected individuals, only a cure may bring new growth.

Biggest HIV antiviral companies 2008-18

	Annual sales WW (\$bn)					
	2008	2010	2012	2014	2016	2018
Gilead Sciences	4.33	6.34	8.03	9.42	10.45	9.55
GlaxoSmithKline (ViiV Healthcare)	2.81	2.53	2.13	2.41	2.70	2.72
Johnson & Johnson	0.40	1.10	1.90	2.44	2.86	2.41
Merck & Co	0.64	1.30	1.68	1.81	1.74	1.68
Bristol-Myers Squibb	1.93	1.80	1.79	1.77	1.58	0.64
Abbott/AbbVie	1.82	1.60	1.42	1.25	0.67	0.36
Boehringer Ingelheim	0.43	0.36	0.28	0.21	0.18	0.17
Roche	0.17	0.09	0.05	0.04	0.03	0.03
Pfizer	0.15	0.05	0.04	0.04	0.04	0.03
Total market	12.71	15.29	17.54	19.66	20.58	18.09

Changing times

The years since the launch of GlaxoSmithKline's Retrovir in 1987 have seen leaps in innovation, with multiple nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors coming to market, improving on the reduction in the risk of death and disease progression shown by that product. HIV "cocktails" that blocked multiple mechanisms of viral reproduction reduced disease burden and the risk of resistance, as well as extending life expectancy.

The middle of the last decade was tough for the early drugs, with Retrovir, Bristol-Myers Squibb's Videx and Glaxo's Ziagen all losing patent protection in the space of a couple of years. The pharma innovation machine continued to produce blockbusters, however - Johnson & Johnson's Prezista and Bristol-Myers Squibb's Reyataz premiered, for example.

On the other hand, there was at least one disappointment in Glaxo and Pfizer's Selzentry, which at \$203m in 2012 sales has fallen well short of initial forecasts of \$456m ([Preview - Johnson & Johnson, Pfizer results](#))

[looming, January 18, 2008](#)). Indeed, it was the struggles of Selzentry and the changing shape of the market that drove Glaxo and Pfizer into each other's arms to form Viiv ([Glaxo and Pfizer to join forces on HIV, April 16, 2009](#)).

However, those companies were left in the dust by Gilead Sciences, which focused on developing one-pill combinations. Stribild, its four-drug combination approved in 2012, is a once-daily, four-drug combination. As such, it has been the only company in the space to show impressive growth in the past five years, with 2016 anti-viral sales forecast to hit \$10.5bn in 2016, according to *EvaluatePharma*. As the table above shows, Gilead is forecast to take half the branded market in 2016, leaving five other companies to fight for the table scraps.

Top 10 HIV antivirals in 2018 and total branded market								
					Annual sales WW (\$m)			
	Product	Pharmacology class	Company	Patent expiry	2008	2012	2016	2018
1	Stribild	Nucleoside reverse transcriptase inhibitor, HIV integrase inhibitor & CYP3A inhibitor	Gilead Sciences	Sep 2021	-	58	2,543	3,573
2	Truvada	Nucleoside reverse transcriptase inhibitor	Gilead Sciences	Jan 2021	2,107	3,181	2,663	1,787
3	Complera	Nucleoside & non-nucleoside reverse transcriptase inhibitor	Gilead Sciences	May 2025	-	342	1,489	1,741
4	Isentress	HIV integrase inhibitor	Merck & Co	Oct 2023	361	1,515	1,641	1,597
5	Atripla	Nucleoside & non-nucleoside reverse transcriptase inhibitor	Gilead Sciences	Sep 2021	1,572	3,574	2,560	1,464
6	Prezista	Protease inhibitor	Johnson & Johnson	Aug 2014	334	1,414	1,984	1,369
7	Tivicay (dolutegravir)	HIV integrase inhibitor	ViiV Healthcare	-	-	-	864	1,318
8	Epzicom/Kivexa	Nucleoside reverse transcriptase inhibitor	GlaxoSmithKline	Nov 2016	818	1,053	927	586
9	Reyataz	Protease inhibitor	Bristol-Myers Squibb	Jun 2017	1,292	1,521	1,485	577
10	Intelence	Non-nucleoside reverse transcriptase inhibitor	Johnson & Johnson	Dec 2020	70	349	487	549
				<i>Other products</i>	6,159	4,536	3,941	3,533
				Total	12,713	17,544	20,585	18,095

Come 2016, only four products will be growing, the table above shows: Tivicay, Intelence, Stribild and

Complera.

It is no wonder, then, that so many of the companies with antiviral expertise have turned to hepatitis C as a growth space, although even there Gilead looks poised to take much of the spoils ([Hep C story makes Gilead impervious to bad news](#), May 3, 2013).

What is to come

The late stage pipeline does not give much cause for hope that HIV will see entry of innovative products soon. Stribild components elvitegravir and cobicistat have been knocked back by the FDA as monotherapy because of manufacturing issues, so it may be some time before those two hit the market. Behind that, only two projects in phase III have any forecasts attached to them: Gilead's prodrug version of Viread, called tenofovir alafenamid fumarate; and a combination of Prestiza with three Gilead compounds, Emtriva, cobicistat and the Viread prodrug.

That is not to say there are no innovative approaches. AbbVie and Biogen Idec both have monoclonal antibodies in phase II, while more speculative gene and cell therapies are being studied. Several companies are also trying vaccines, including Glaxo.

But given the improvements in pharmaceutical treatments for HIV patients, what is probably necessary to steal serious market share in this space is a vast improvement in efficacy – in short, a cure or something very close to one – or a way to reduce the dosing burden or side effects even more. Given that Gilead has delivered more than one one-pill, once-daily product, it will be left to competitors to see if they can deliver the cure or less toxicity if they wish to fight back.

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