BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

9th June 2016

GlaxoSmithKline

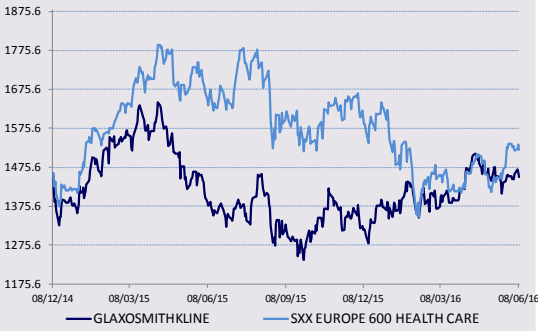
ViiV likely to impact GSK beyond dolutegravir

Healthcare

Fair Value 1740p vs. 1700p (price 1,450p) **BUY**

Bloomberg	GSK LN
Reuters	GSK.L
12-month High / Low (p)	1,510 / 1,238
Market capitalisation (GBPm)	70,642
Enterprise Value (BG estimates GBPm)	97,360
Avg. 6m daily volume ('000 shares)	8 387
Free Float	100%
3y EPS CAGR	10.7%
Gearing (12/15)	119%
Dividend yield (12/16e)	5.52%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (GBPm)	23,923	25,847	26,528	27,223
EBIT (GBPm)	5,729	7,051	7,663	7,815
Basic EPS (p)	174.32	61.33	76.54	87.89
Diluted EPS (p)	75.71	89.13	94.27	102.65
EV/Sales	4.0x	3.8x	3.6x	3.5x
EV/EBITDA	13.0x	11.1x	10.3x	10.0x
EV/EBIT	16.8x	13.8x	12.6x	12.1x
P/E	19.2x	16.3x	15.4x	14.1x
ROCE	14.7	17.3	18.4	18.7



Since we upgraded GSK to BUY in January, it has been the best performer in the large-cap pharmaceutical segment because its "self-help" profile fits well with what investors need in a more challenging environment. Now what is required for it to go further up is sustainability and visibility over this growth. We are starting with ViiV Healthcare here, which is one of the main drivers. A closer look into this has resulted in a FV upgrade.

- Not so long ago, GSK was close to exiting the HIV space after several failures and, even quite recently, some were asking the group to spin-off the joint-venture and sell part of its stake in it to extract more value. This was without clearly understanding the intrinsic value of the asset and its strong dynamic.

- Dolutegravir has become the best-in-class integrase inhibitor and is now part of several HIV treatment guidelines. In just a few years, it has become one of the biggest drugs for HIV by sales when Tivicay and Triumeq are combined. And two other fixed-dose combinations are currently in late-stage development, which should further expand the dolutegravir-based portfolio.

- But the quality of ViiV's pipeline is not limited to new FDC with dolutegravir but it also includes an interesting long-acting integrase inhibitor for maintenance therapy and/or prophylaxis, as well as two innovative compounds acquired from BMS.

- So, in the end, we see ViiV Healthcare surging from slightly more than USD3bn in sales in 2015 to close to USD6bn (non-adjusted) in 2022, i.e. from less than 10% to 14% of group's total sales. Considering that ViiV Healthcare has a core EBIT margin of around 70%, i.e. well above average (although it excludes royalty payments to Shionogi), high growth at the top-line level will also impact margins and the bottom-line.

We are introducing for the first time the risk-adjusted pipeline of ViiV to our sales forecasts. Our FV goes up by GBp40 to GBp1,740.

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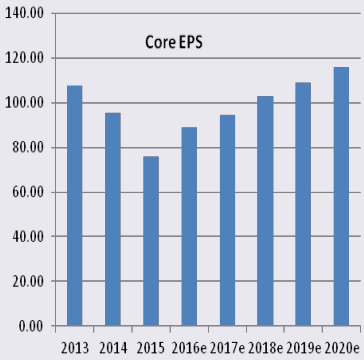

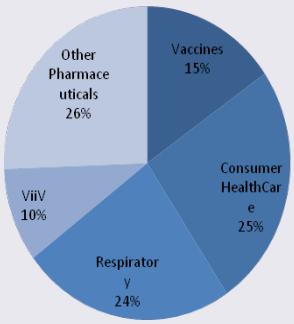

Company description

GSK was created in 2000 with the merger of UK-based Glaxo-Wellcome and Smithkline Beecham. Since then, it has faced several patent expiries and legal issues and the last couple of years were troubled ones with fraud case in China, big phase III fails and Advair sharp decrease. However, it also concluded a transforming asset swap with Novartis. This could be the base for a new start, as Pharmaceuticals is also stabilising.

Income Statement (GBPm)	**2013**	**2014**	**2015**	**2016e**	**2017e**	**2018e**	**2019e**
Revenues	26,279	23,006	23,923	25,847	26,528	27,223	27,852
Change (%)	*1.0%*	*-12.5%*	*3.7%*	*8.4%*	*2.6%*	*2.6%*	*2.3%*
EBITDA	9,489	8,294	7,429	8,751	9,363	9,515	8,204
EBIT	7,789	6,594	5,729	7,051	7,663	7,815	8,204
Change (%)	*-1.5%*	*-15.3%*	*-13.1%*	*23.1%*	*8.7%*	*2.0%*	*5.0%*
Financial results	(588)	(307)	(650)	(618)	(567)	(441)	(349)
Pre-Tax profits	7,244	6,317	5,005	6,439	7,102	7,553	8,065
Exceptionals	(517)	0.0	0.0	0.0	0.0	0.0	0.0
Tax	1,688	1,238	976	1,320	1,491	1,586	1,694
Profits from associates	43.0	30.0	(2.0)	6.0	6.0	6.0	6.0
Minority interests	250	222	440	669	725	782	854
Net profit	5,306	2,756	8,422	2,973	3,710	4,260	4,558
Restated net profit	5,306	4,584	3,658	4,320	4,724	4,975	5,273
Change (%)	*1.1%*	*-8.5%*	*-26.1%*	*24.0%*	*9.8%*	*6.1%*	*6.4%*
Cash flow Statement (GBPm)							
Operating cash flows	8,273	5,532	4,631	7,165	8,214	9,205	9,231
Change in working capital	46.0	(91.0)	27.0	(726)	(297)	273	(186)
Capex, net	(1,142)	(1,188)	(1,308)	(1,500)	(1,500)	(1,500)	(1,500)
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	(3,680)	(3,843)	(3,874)	(4,799)	(3,839)	(3,839)	(4,223)
Other	NM	NM	NM	NM	NM	NM	NM
Net debt	12,489	13,075	10,556	11,509	10,625	8,845	7,530
Free Cash flow	5,901	2,672	1,903	3,845	4,723	5,619	5,538
Balance Sheet (GBPm)							
Shareholders' funds	7,812	4,936	8,878	9,198	10,970	13,098	15,246
+Provisions	3,437	4,178	5,171	5,171	5,171	5,171	5,171
+Net debt	12,489	13,075	10,556	11,509	10,625	8,845	7,530
=Invested Capital	23,738	22,189	24,605	25,879	26,766	27,114	27,948
Fixed assets	26,859	25,973	36,859	37,125	37,391	37,657	37,923
+ Working Capital	(298)	66.0	(101)	625	922	649	835
+ Other	(2,823)	(3,850)	(12,153)	(11,872)	(11,547)	(11,192)	(10,811)
=Capital employed	23,738	22,189	24,605	25,879	26,766	27,114	27,948
Total Balance sheet	7,812	4,936	8,878	9,198	10,970	13,098	15,246
Financial Ratios							
Operating margin	29.64	28.66	23.95	27.28	28.89	28.71	29.46
Tax rate	23.30	19.61	19.51	20.50	21.00	21.00	21.00
Net margin	20.19	19.92	15.29	16.72	17.81	18.28	18.93
ROE (after tax)	82.86	81.41	78.01	87.46	89.32	76.73	67.57
ROCE (after tax)	27.08	25.05	14.68	17.31	18.38	18.75	19.42
Gearing	160	265	119	125	96.85	67.53	49.39
Pay out ratio	72.33	140	57.36	130	105	100	101
Number of shares, diluted	4,831	4,799	4,799	4,799	4,799	4,799	4,799
Data per Share (p)							
EPS	108	57.31	174	61.33	76.54	87.89	94.04
Restated EPS	110	101	74.78	92.74	102	108	115
Core EPS	108	95.33	75.71	89.13	94.27	103	109
Change (%)	*1.2%*	*-11.3%*	*-20.6%*	*17.7%*	*5.8%*	*8.9%*	*6.0%*
Goodwill	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BV	145	88.84	107	99.32	121	149	176
Operating cash flows	171	115	96.51	149	171	192	192
FCF	122	55.68	39.66	80.14	98.43	117	115
Net dividend	78.00	80.00	100	80.00	80.00	88.00	95.00

Source: Company Data; Bryan, Garnier & Co ests.

Please see the section headed "Important information" on the back page of this report.

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1. Investment Case

Why the interest now?

The reason for writing now

ViiV Healthcare is one of GSK's fastest growing businesses but the market is focusing on the self-help angle of GSK's story which makes sense because this is how it differentiates from the crowd. But we believe it is interesting to look beyond 2016 to see if the trends are sustainable so we start here with a deep dive into ViiV Healthcare because its business can almost double in size over the next seven years.

Cheap or Expensive?

Valuation

GSK has performed very well over the last six months but after a long period of underperformance. In absolute terms, it may look expensive, but when combined with average growth rates, the PEG ratio is very reasonable. After a series of failures, the R&D pipeline was massively discounted by the market. But this journey into ViiV points to some hidden gems that we factor in for the first time.

When will I start making money?

Catalysts

GSK is expected to deliver strong core EPS growth in 2016, well above the sector average and high single-digit growth by 2020 so that each quarterly publication should prove solid. Beyond that, GSK is looking for a new CEO and we believe his name could be a catalyst as we anticipate that he will focus on R&D.

What's the value added?

Difference from consensus

We believe ViiV Healthcare is not a piece of GSK which is well-known by investors because it was not seen as strategic until recently. This report is our contribution to a better understanding not only to what it is but more importantly to what it might become in a few years' time.

Could I lose money?

Risks to our investment case

We do not see major risks to our investment case because growth is coming from in-market products for the vast majority (the largest exception being the *Herpes zoster* vaccine Shingrix which carries a low probability of failure) and from synergies with the acquired businesses of Novartis in CHC and vaccines.

Taking ViiV Healthcare more specifically, the main risk over the next five years comes from Gilead, should this be even stronger than we expect it to be.

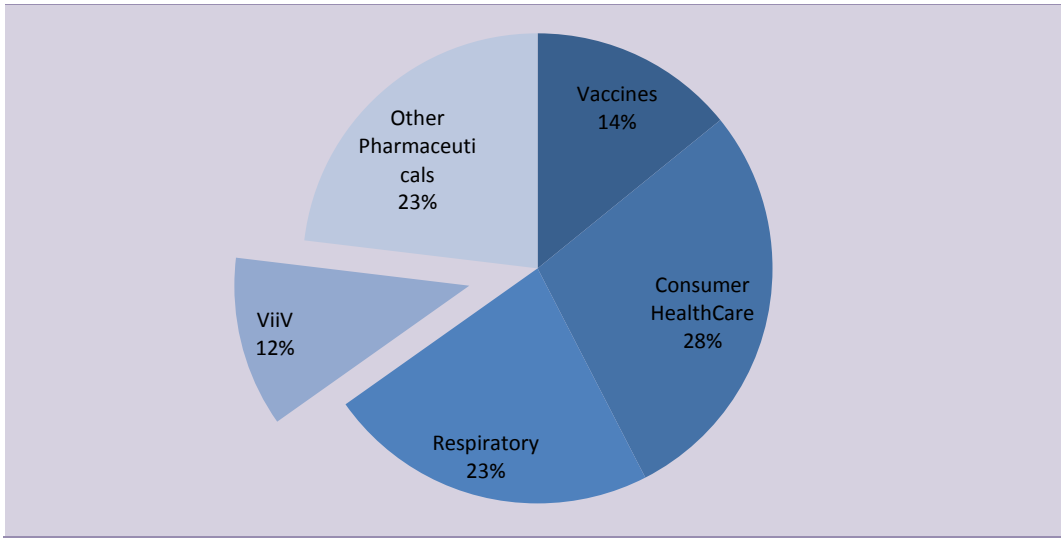
Please see the section headed "Important information" on the back page of this report.

2. Why we focus today on ViiV

2.1. ViiV is an increasing part of GSK

If there is only one good reason to spend some time on ViiV Healthcare for its influence over GSK as a whole, this is because its contribution to the group's total revenues has been increasing very consistently over the past few years to reach 12% in Q1 2016. And, of course, we were curious to dig more into this business to see how much this trend is sustainable and where ViiV might go.

Fig. 1: How GSK's total revenues split in Q1 2016



Source: Company Data;

2.2. But this is not a well-understood piece of it

Why is ViiV Healthcare so largely ignored? Well, there are various reasons for this:

HIV business almost disappeared at GSK

First could well be the history of GSK within the HIV space. Back in the '90s or even at the start of the 00 decade, GSK used to be the main and highly dominant player of the HIV market, at a time when therapies were extremely inconvenient for the patient with several pills to be taken every day. That said, the market itself was much smaller than it is today and, although GSK was a leader, revenues in absolute terms were not that high but we were compelled to keep a close eye on trends. All the more so that HIV was included in a bigger antibiotics/anti-infectives franchise (which included Augmentin and Valtrex, for instance). Since then, GSK missed the train to transform its business and maintain its positions through innovation a couple of times. First because nothing came out of its own pipeline despite years of leadership in the space and second because the combination with Pfizer to form ViiV Healthcare was to get access to a new drug called Selzentry (maraviroc), a CCR-5 receptor antagonist that was part of a class which has never been recommended in guidelines for standard use mainly because of a too limited scope of efficacy to the price of an unfavourable toxicity profile.

As a consequence, about a couple of years ago, as GSK was going through a very difficult period of its history and was considering structural changes to its portfolio of activities, alongside its asset swap with Novartis, some were arguing that it might spin off ViiV Healthcare and maybe list it as an independent company while keeping a stake in it. The idea behind this was to extract hidden value from a conglomerate.

Because the debate emerged at a time when ViiV Healthcare started to perform very well, it was as quickly closed as it opened up because it would have been dilutive and would have prevented GSK from fully benefiting from the recovery of its HIV business.

It is worth keeping in mind that ViiV Healthcare is already a joint-venture that GSK books globally but in which it has only a 78.3% stake. And this might be another reason why the market has not been paying as much attention to ViiV as to other fully-owned parts of the group. Actually the reason why GSK owns 78.3% of ViiV Healthcare is because, after the company was formed by the merger between GSK's and Pfizer's HIV businesses with limited success, the company welcomed a third partner into the joint-venture to access one of its drugs called dolutegravir. And this time it worked very well because it is the drug that is currently changing the profile and the future of the whole company. As a monotherapy and also as part of combinations, it is by far the main growth driver. Its originator, Shionogi, which had worked with GSK since 2002 on integrase inhibitors, was proposed to transform its alliance and become part of ViiV Healthcare. It received 10% of ViiV Healthcare and is also entitled to receive between 15 and 19% royalties pre-tax on dolutegravir-based products. Note that the royalty payments to Shionogi do not hit GSK's P&L but only the cash-flow statement but we are definitely factoring them into our valuation and restating our numbers, although we do not change core numbers to remain in accordance with GSK's published numbers.

A complex agreement with Shionogi

The total cash payments to Shionogi in relation to ViiV Healthcare's contingent consideration liability in 2015 were GBP159m, recognised in two different lines of the cash-flow statement. This compares with GBP1,318m in total sales for dolutegravir-based products, resulting in a net royalty payment of 12.1%. Should we also deduct GBP159m from ViiV Healthcare's total operating income, the margin would have dropped in 2015 from 72.6% (actual) to 65.8% (restated) which remains well above the group's average and in absolute terms highly competitive within the Speciality Care pharma space.

Fig. 2: ViiV Healthcare's key numbers (excluding payments to Shionogi)

GBPm	2014	Q1 2015	Q2 2015	H1 2015	Q3 2015	9M 2015	Q4 2015	2015
Sales	1 498	446	559	1 005	622	1 627	695	2 322
Operating income	977	318	413	731	466	1 197	489	1 686
Operating margin	65,2%	71,3%	73,9%	72,7%	74,9%	73,6%	70,4%	72,6%

Source: Company Data; Bryan, Garnier & Co ests.

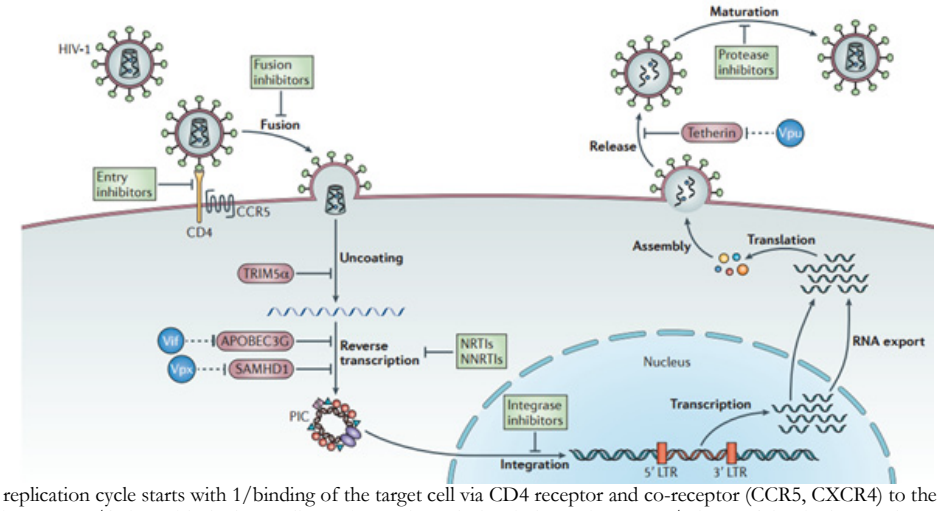
Clearly, because we suspected that ViiV Healthcare, despite patent expiries (including that of Epzicom, ViiV's second largest product), might see its sales again doubling in the next few years, and considering this major mix impact in terms of profitability, it was worth looking more closely into the division.

3. The market of HIV

3.1. From HIV to AIDS

Viruses are intracellular parasites with no metabolic capacity of their own. To initiate infection, the virus attaches to the targeted host cell through attachment/fusion proteins, enters into the cell via endocytosis, then uses the cell replication machinery to multiply its genetic code and its proteins that form the capsid, and eventually the new virions release causes host cell death and further infection in surrounding cells.

Fig. 3: Overview of the HIV-1 replication cycle



The replication cycle starts with 1/binding of the target cell via CD4 receptor and co-receptor (CCR5, CXCR4) to the viral protein gp120; 2/fusion with the host cell membrane through the viral protein gp41; 3/release of the single strand RNA and viral proteins into the cytoplasm; 4/reverse transcription of the viral RNA to DNA; 5/translocation of the viral DNA to the nucleus and integration into the host DNA, which is then transcribed and translated; 6/new viral RNA and proteins assemble, and after maturation, new virions are released.

Source: (Barré-Sinoussi, Ross, & Delfraissy, 2013)

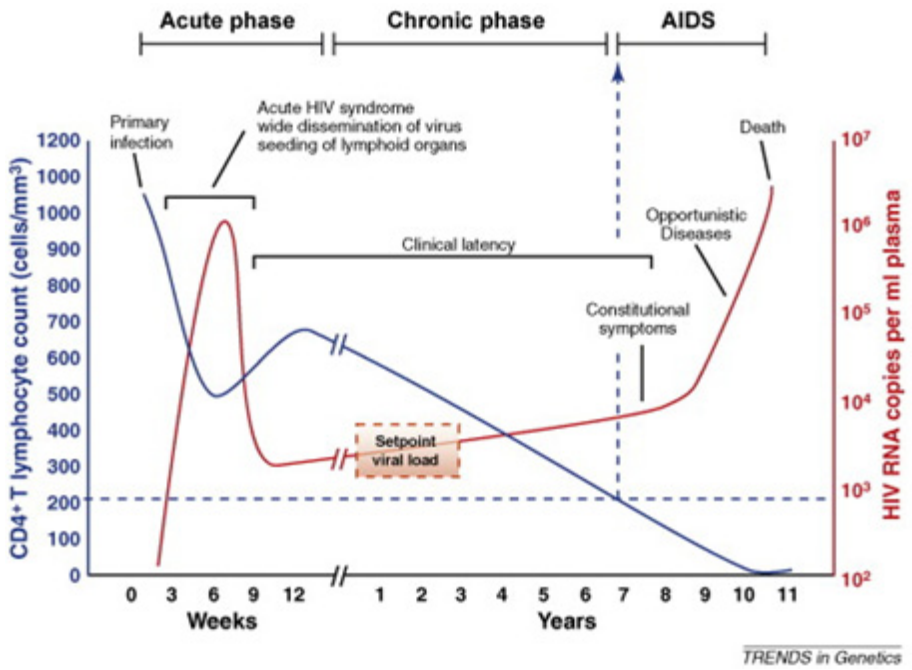
The Human Immunodeficiency Virus (HIV)'s main characteristic is its replication in helper T-cells or CD4 cells, which are central in the human innate immune system. The depletion of these key players affects the immune response that fights against external aggressions. As a result, HIV-infected individuals become susceptible to opportunistic infections or cancers and this Acquired Immunodeficiency Syndrome (AIDS) is responsible for their death.

HIV transmission occurs through the exchange of body fluids such as vaginal secretions, semen, breast milk or blood from infected individuals. Antibodies anti-HIV can only be detected after a 3-week HIV exposure, known as the window period. Antibodies anti-HIV-1/2 and/or HIV p24 antigen can be measured by serological tests (Lab or Rapid Tests) or enzyme immunoassays (EIA). The reasons why the number of newly HIV-infected people increases is due to lifestyle changes, unprotected sex, injection of drugs, lack of awareness, and transmission from mother-to-child.

HIV type-1 is dominant

Due to mutations, several HIV variants exist within a single person. However, two main HIV types exist: HIV-type 1 and HIV-type 2, each of which is subdivided into strains classified with letters. While HIV-type 1 is the major type worldwide, HIV-type 2 is concentrated in West Africa. In addition to geographical differences, HIV-type 1 is more infectious and progresses faster than HIV-type 2. When the type of HIV is not indicated, it is by default HIV-type 1 due to its predominance.

Fig. 4: Progression from HIV to AIDS



The acute phase where the body immune response is still able to fight against HIV can last years. If treated right after early diagnosis, HIV-positive people can avoid AIDS acute phase and live healthier.

Source: (Ping & Winkler, 2010)

The progression from HIV to AIDS starts with a gradual loss of CD4 cells and an increase in the viral load. Then, the viral load decreases abruptly as antibodies anti-CD4 kill both infected cells and the virions inside. Unfortunately, constant mutations occur since the HIV replication is error prone. While the production of new specific antibodies anti-HIV variants requires a minimum timespan, the virus takes advantage of a weakened immune response. Successive mutation waves deplete the body's ability to eradicate infected cells. Consequently, the viral load increases whereas the CD4 cell count continues to decrease.

3.2. How HIV is managed today

3.2.1. No cure exists so far… Prevention vs. treatment

HIV differs from other viruses in that it has the ability of remaining in a dormant state inside host cells for years without replicating itself, creating a "reservoir" of infected cells. This "reservoir" evades the immune system. Anti-retroviral therapies (ART) do not cure HIV infection and can only target cells where the virus is actively replicating. As soon as the ART therapy is discontinued, there is a risk that a dormant virus starts replicating itself in a cell and restarts the viral infection process all over again. ART therapies can be taken for prevention or treatment. ART used as prevention aims to either prevent the acquisition of HIV in HIV-uninfected people (Pre-exposure prophylaxis: PrEP), reduce the risk of HIV transmission in HIV-positive patients (prevention), or even prevent HIV infection within 72h of exposure to HIV in HIV-negative people (post-exposure prophylaxis: PEP). ART used as treatment aims at controlling the virus expansion by reducing the viral load and by increasing the number of CD4 cells.

Since 2015, the WHO recommends treating all HIV-infected people as soon after diagnosis as possible, as clinical data demonstrates additional benefits, including a decrease in the HIV transmission risk and a healthier life for patients. Secondly, the WHO recommends that populations at substantial risk of HIV infection should take an ART for prevention. Expanding ART would help prevent 21 million AIDS-related deaths and 28 million new infections by 2030 (WHO).

3.2.2. Anti-retroviral drugs classification

Current ART active compounds fall into six distinct groups, based on their mechanism of action:

- Entry Inhibitors: Attachment Inhibitors & CCR5-antagonists
- Fusion Inhibitors
- Nucleoside Reverse Transcriptase Inhibitors (NRTI)
- Non-Nucleoside Reverse Transcriptase Inhibitors (nNRTI)
- Integrase Strand Transfer Inhibitors (INSTI)
- Protease Inhibitors (PI)

Fig. 5: Six distinct classes of ART drugs

	CCR5-antagonists	Fusion inhibitors	NRTI	nNRTI	INSTI	PI
MoA	Prevents the virus attachment to the target cell by interfering with the CD4 cell's co-receptors CCR5 and/or CXCR4	Prevents the virus attachment to the target cell by interfering with a protein on the viral envelope (gp41)	Binds to the active site of the Reverse Transcriptase enzyme inhibiting the viral DNA production from RNA	Binds to the Reverse Transcriptase enzyme, not at its active site, inhibiting the viral DNA production from RNA	Blocks the integrase enzyme, responsible for the integration of the virus genetic material into the host DNA for transcription and replication	Prevents the cleavage of the viral proteins crucial for viral maturation, thus blocking the virions production
Side effects	Cough, pyrexia, diarrhoea, upper respiratory tract symptoms, rash, abdominal pain, dizziness	(Grades 2-4) : local injection site reactions, gastrointestinal, fatigue	(Grades 2-4) : headaches, gastrointestinal, fatigue, cough	(Grades 1-4); neuropsychiatric disorders, headaches, dizziness, insomnia, rashes, abdominal pain	(Grades 2-4): very well tolerated. Headaches, insomnia	(Grades 2-4): headaches, rash, abdominal pain, gastrointestinal
Use	Does not offer a complete solution to the inhibition of HIV entry Indicated in CCR5-tropic HIV-1 detectable who have evidence of viral replication and HIV-1 strains resistant to several ART drugs	Twice-daily subcutaneous injection + high cost = only for patients resistant to other classes of drugs Salvage role, Indicated in HIV-1 treatment-experienced	"Preferred" regimen option. Recommended in combinations for treatment-naive and experienced patients	"Alternative" regimen option. Recommended in combinations for treatment-naive patients	"Preferred" regimen option. Recommended in combinations for treatment-naive and experienced patients	"Preferred" and "alternative" regimen options. Recommended in combinations for treatment-naive and experienced patients
Single-drug	Selzentry/Celsentri (maraviroc, ViiV)	Fuzeon (enfuvirtide, Roche), the only one approved in this class	Zidovudine (Retrovir, GSK)	Intelence (etravirine, J&J)	Isentress (raltegravir, Merck)	Reyataz (atazanavir, BMS)
			Viread (tenofovir, Gilead)	Sustiva (efavirenz, BMS)	Vitekta (elvitegravir, Gilead)	Prezista (darunavir, J&J)
			Epivir (lamivudine, ViiV) Emtriva (emtricitabine, Gilead) Ziagen (abacavir, ViiV)	Viramune (nevirapine, Boehringer) Edurant (Rilpivirine, J&J)	Tivicay (dolutegravir, ViiV healthcare)	Norvir (ritonavir, Abbott)

Source: (Max, 2014)

3.2.3. Guidelines for HIV treatment-naive adolescents and adults

The Department of Health and Human Services (DHHS) provides HIV guidelines classified as "Preferred" and "Alternative" treatments options (AIDSinfo). The DHHS recommends for initial therapy, the combination of three active antiretroviral drugs, including 2 NRTI:

- nNRTI-based regimen: 1 nNRTI + 2 NRTI
- PI-based regimen: 1 PI + 2 NRTI
- INSTI-based regimen: 1 INSTI + 2 NRTI

Preferred drugs combine efficacy and low resistance

Currently, "Preferred" regimens comprise a 4 INSTI-based regimen and a 1 PI-based regimen for initial therapy, as INSTI-based therapies have proven to be highly effective, safe, very well tolerated with a high genetic drug resistance barrier and low drug-drug interactions. The boosted PI-based regimen is another preferred option, as it is also recognised for its high drug resistance barrier but it is not well tolerated. NB the nNRTI-based regimen is not one of the DHHS's "Preferred" options as it has a low genetic drug resistance barrier and lower efficacy compared to dolutegravir.

Boosters can be used to prolong certain ART drugs' half-life so that the serum level is "boosted", in order to reduce the dosing frequency and the number of pills. Ritonavir (Norvir) and cobicistat (Tybost) are the main boosters on the market, and they prolong PI's (darunavir, atazanavir) and INSTI's (elvitegravir) half-life. Yet, both boosters have dangerous drug interactions, in particular with recreational/party illicit drugs, which could be of importance to be aware of in a context of "chemsex" or in gay populations (Bracchi, Stuart, & Castles *et al.*, 2015).

All preferred and alternatives recommendations are based on 2 NRTI, including three recommended combinations: Tenofovir Disoproxil Fumarate (TDF)/ emtricitabine (FTC); Tenofovir Alafenamide Fumarate (TAF)/emtricitabine (FTC); Abacavir (ABC)/lamivudine (3TC).

Lately, Fixed-Dose Combinations (FDC) have been developed as they reduce the burden pill, enhancing a patient's adherence.

In 2013, adults' 1st-line was ART of 2NRTI+ 1 nNRTI, such as TDF/3TC combined to efavirenz (EFV). Adults' 2nd-line ART consisted of 2NRTI+1 PI such as TDF/3TC + ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r). Since 2013, the DHHS guidelines have changed and 1st-line ART guidelines 2015 are summarised in the table below:

Fig. 6: DNSS guidelines 2015 for initial therapy

Recommended options	
2 NRTI	1 INSTI
Tenofovir DF/emtricitabine (TDF/FTC)	Dolutegravir (DTG)
Abacavir/lamivudine (ABC/3TC)	Dolutegravir (DTG)
Tenofovir DF/emtricitabine-cobicistat boosted (TDF/FTC/COBI)	Elvitegravir (EVG)
Tenofovir AF/emtricitabine-cobicistat boosted (TAF/FTC/COBI)	Elvitegravir (EVG)
Tenofovir DF/emtricitabine (TDF/FTC)	Raltegravir (RAL)
2 NRTI	1 PI
Tenofovir DF/emtricitabine (TDF/FTC)	ritonavir-boosted darunavir (DRV/r)
Alternative options	
2 NRTI	1 nNRTI
Tenofovir DF/emtricitabine (TDF/FTC)	Efavirenz (EFV)
Tenofovir DF/emtricitabine (TDF/FTC)	Rilpivirine (RPV)
2 NRTI	1 PI
Tenofovir DF/emtricitabine (TDF/FTC)	cobicistat-boosted atazanavir (ATZ/c)
Tenofovir DF/emtricitabine (TDF/FTC)	ritonavir-boosted atazanavir (ATZ/r)
Abacavir/lamivudine (ABC/3TC)	cobicistat or ritonavir-boosted darunavir (DRV/c-r)
Tenofovir DF/emtricitabine (TDF/FTC)	cobicistat-boosted darunavir (DRV/c)

Source: (AIDSinfo)

Fig. 7: Fixed Dose Combinations are becoming popular

NRTI	nNRTI	INSTI	PI	Drug name	Company	FDA approved
			Lopinavir-*ritonavir*	Kaletra	Abbvie	2000
Tenofovir DF+ Emtricitabine				Truvada	Gilead	2004
Tenofovir DF+ Emtricitabine	Efavirenz			Atripla	Gilead	2006
Tenofovir AF+ Emtricitabine		Elvitegravir-*cobicista*t		Genvoya	Gilead	2015
Tenofovir AF+ Emtricitabine				Descovy	Gilead	2016
Tenofovir DF+ Emtricitabine		Elvitegravir-*cobicistat*		Stribild	Gilead	2012
Tenofovir DF+ Emtricitabine	Rilpivirine			Complera/Eviplera	Gilead, Janssen	2011
Tenofovir AF+ Emtricitabine	Rilpivirine			Odefsey	Gilead, Janssen	2016
			Darunavir-*cobicistat*	Prezcobix	Gilead, Janssen	2015
Abacavir+ Lamivudine				Epzicom/kivexa	ViiV	2004
Abacavir+ Lamivudine+ Zidovudine				Trizivir	ViiV	2000
Zidovudine+ Lamivudine				Combivir	ViiV	1997
Abacavir+ Lamivudine		Dolutegravir		Triumeq	ViiV	2014

Source: Street Account

The choice of the third ART agent is a matter of debate and patient's factors such as viral load, CD4 cell count, HIV genotypic drug resistance, patient's preferences, and HLA-B*5701 status. The latter is of main importance before prescribing an ART regimen containing abacavir, since it represents a genetic factor of an abacavir allergic reaction. This hyper-sensitivity reaction (serious and sometimes fatal) is frequent and leads to the withdrawal of ART. A high level of drug-resistance may develop faster with nNRTI (rilpivirine), NRTI (emtricitabine, lamivudine), INSTI (raltegravir, elvitegravir), whereas this may takes longer with other NRTI, ritonavir-boosted PI and dolutegravir. Also, the PI-based regimen and efavirenz are known for their higher adverse events levels. Factors such as tolerability, pill burden, drug interactions, and patient's comorbid conditions should guide the choice of the ART therapy.

When achieved, the two primary endpoints are: 1/ the proportion of patients with HIV viral load of under 50 copies per ml, and 2/ an increasing CD4 cell count, often measured at weeks 48 and 96. The secondary endpoints include time to viral suppression, the patient's safety and tolerance and no viral drug resistance. Viral failure is usually defined as two consecutive HIV viral load measures of over 50 copies per ml on or after week 24.

HIV-positive patients can be stratified depending upon their viral load (> or <100,000 copies/ml), their CD4 cell count (> or <200 cells/ml), or their HIV mutations.

3.3. Future challenges in HIV

Fixed-dose combinations are now the treatment of choice for their convenience

For two decades, ART therapies have markedly improved, resulting in a significant decrease in mortality and comorbidities. Nowadays, fixed-dose combinations have become popular as they offer the possibility of taking a single daily pill instead of a plethora of different pills/doses. The shift from a lethal infection to a manageable chronic disease brings new challenges to overcome.

1/ As ART is taken for decades, adverse effects (AE) are of greater importance for patients' tolerability, a key factor for ART's success; 2/ drug interactions are becoming another concern since complications and poly treatments increase with age; 3/ as the WHO's recent recommendation of "treat them all" extended substantially the number of eligible HIV-positive subjects for treatment, new drugs prices and reimbursements will face budget pressure. Consequently, proof of therapeutic improvement will have to be more rigorously demonstrated. New expensive fixed-dose combinations will have to prove that they bring clinical benefits compared to standard of care or matched generics, despite their advantage of a single daily-dose; and 4/ reducing ART failing therapies due to drug resistance caused by virus mutations continues to be a challenge. One way to overcome drug resistance to commonly prescribed ART regimens is to explore drugs with new mechanisms of actions such as HIV entry inhibitors.

In other words, a new antiviral drug has to demonstrate a significantly better AE profile and/or a greater viral suppression/less resistance, along with a better patients' adherence (longer-lasting effect, fewer daily pills). Once-daily regimens and fixed-dose combinations (FDC) are preferred due to their simplification, convenience and adherence.

Technical and scientific advances led clinical studies to: 1/ investigate new active compounds that they hope will be safer and longer-lasting, 2/ develop optimised combinations to reduce the pill burden, and 3/ study the possibility of switching from a three-drug to a dual-drug regimen in HIV-suppressed individuals for HIV maintenance in order to reduce toxicities, drug interactions and to address cost-effectiveness health concerns.

3.4. How the HIV market evolves

■ Epidemiology

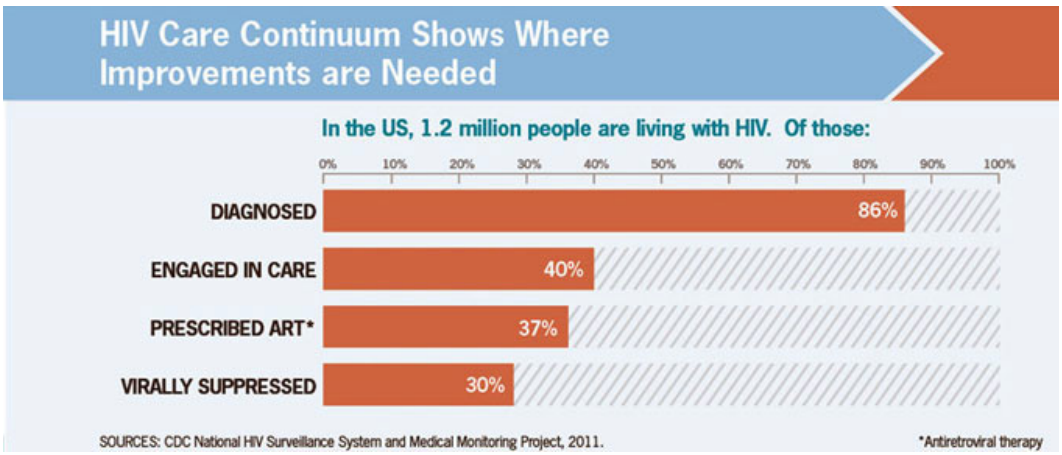
According to the WHO 2015, 37 million people were infected with the Human Immunodeficiency Virus (HIV) in the world, causing 1.2 million deaths per year?. The global prevalence of adults aged from 15 to 49 years old living with the HIV was estimated to 0.8%. However, regions are markedly uneven in terms of prevalence: 4.5% in Africa, 0.4% in Europe and 0.1% in western Pacific. Although the number of new infections has decreased by 35% and AIDS-related mortality by 41%, the incidence still represents 2 million of newly HIV infections diagnosed each year globally, with 70% located in Sub-Saharan Africa.

In March 2015, only 15.8 million (40%) people were receiving an anti-retroviral treatment (ART), and 54% were aware of their infection, highlighting the potential progress to increase both awareness and the portion of HIV-infected individuals under ART therapies. Children are affected as well, and 2.6 million children worldwide live with HIV, due to their HIV-positive mothers. While 41% of the HIV-infected adults received a treatment, only 32% of children in need received an ART therapy, pointing out the medical need for more treatment options for children (WHO).

Halting and reversing the HIV spread goals have been reached and the next step is to end the HIV epidemic by 2030, as part of the Sustainable Development Goals (Unaids.org, 2015).

The market growth is no longer driven by newly HIV-infected people but rather by the ART therapies administered lifelong, which are efficaciously decreasing viral loads to undetectable levels and extending the average life expectancy of HIV-positive patients. That said, virologically-suppressed patients represent a strategic market.

Fig. 8: Segmentation of HIV-positive patients in the US



HIV virologically suppressed patients represent 30% of the total HIV-infected people living in the US vs. 37% for patients treated with an ART.

Source: (CDC.gov, 2014)

Global HIV market size

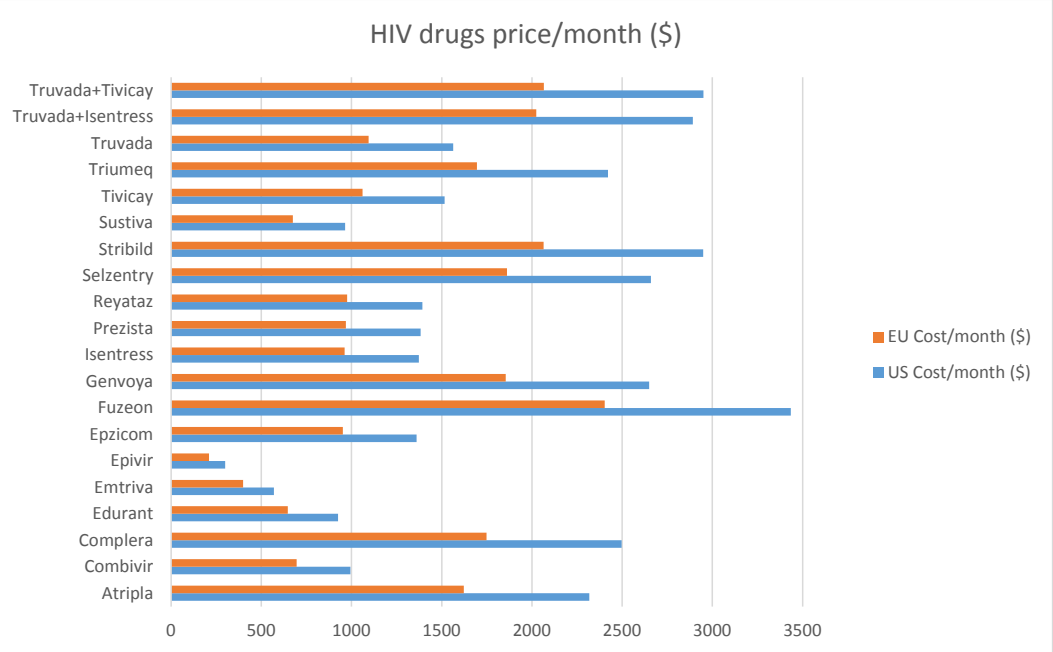
Limited market growth rate by 2023

The HIV market in 2015 reached USD20.5bn and is expected to grow with a CAGR of about 2% over the period of 2015-2023, thus reaching USD23bn in 2023 (GlobalData 2015, BG 2016).

By contrast, the global HIV Diagnostics market's CAGR is estimated at 9.5% over the 2015-2022 period and to reach USD4.48bn by 2022. This growth is mainly driven by the expanding demand for efficient and technologically-advanced methods to ease/systematise earlier diagnosis. Thus, competition has been intensifying with home testing HIV kits available over the counter (OTC) (Grand View Research, 2015).

Major HIV drug prices and sales

Fig. 9: Major HIV drug prices per month in the US and Europe (USD)



US prices were collected from different sources and EU prices were assumed to be 30% les than in the US. We are conscious of price variabilities due to several factors (listed/retail price, discounts, rebates, coupons).

Source: (Denver University) (Holland & Cherney, 2015) (Clayden, 2014) (Drugs.com) (GoodPx)

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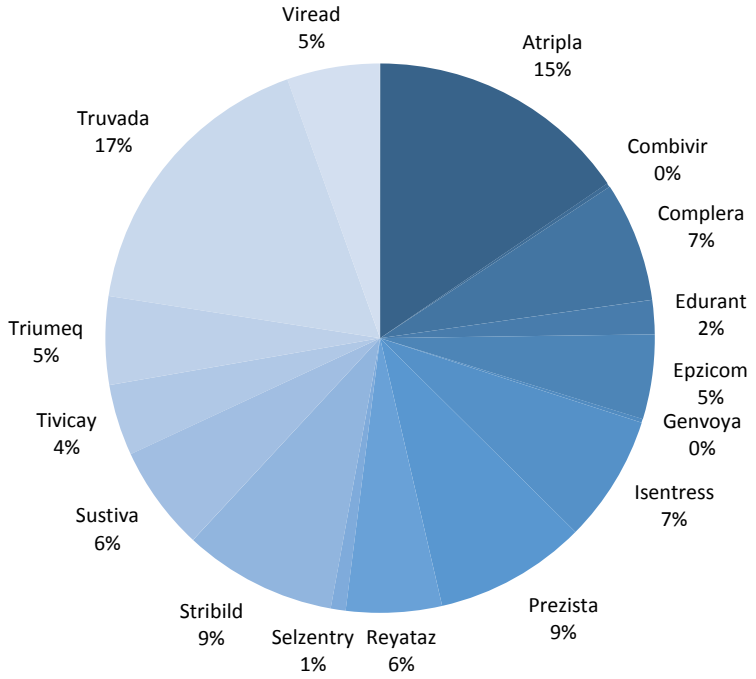
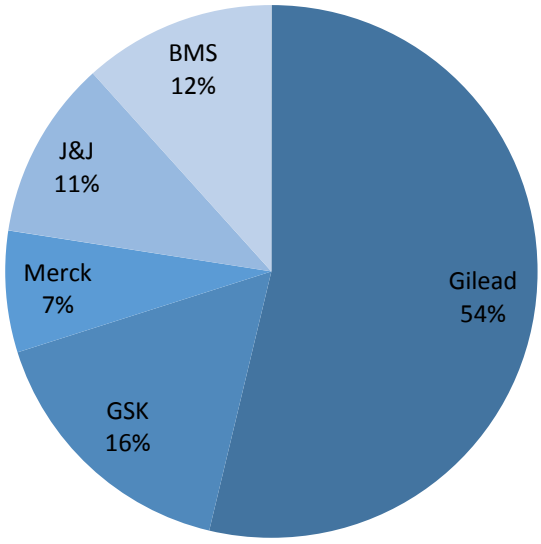
Fig. 10: Market share of major antiviral drugs in 2015



Source: Company Data; Bryan, Garnier & Co ests.

Fig. 11: Market shares of major companies in HIV



In 2015, Gilead Science's annual sales of major HIV products amounted to USD10,998m and GSK's reached USD3,343m. The sum of the major HIV drug sales was of USD20,463m.

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 12: Top prescribed HIV regimens dominated by Gilead's

U.S.

Rank	Naïve	All Patients
1	Stribild	Atripla
2	Other STR	Stribild
3	Complera	Complera
4	Atripla	Other STR
5	Genvoya	Truvada + other 3rd Agent

US Naïve Source: Ipsos Healthcare HIV U.S. Scope Q4 2015.
US All Patient Source: Ipsos Healthcare HIV U.S. Monitor Q4 2015.

Europe Big-5

Rank	Naïve	All Patients
1	Stribild	Atripla
2	Other STR	Eviplera
3	Eviplera	Stribild
4	Truvada + other 3rd Agent	Truvada + other 3rd Agent
5	Atripla	Other STR

EU Naïve Source: Ipsos Healthcare HIV EU Scope Q4 2015.
EU All Patient Source: Ipsos Healthcare HIV EU Monitor Q3 2015.

Gilead STR

Source: Gilead Q1 2016 results presentation.

HIV market trends

A duopoly

The HIV drug market is highly concentrated in a dual competition between Gilead Sciences (54%) and GSK (16%). This dual dominance is completed with other key players including Bristol-Myers Squibb (BMS), Johnson & Johnson (J&J) and Merck. The Americas, APAC, EMEA are the major regions for the HIV market. The global HIV market benefits from an increasing public awareness, in addition to the WHO's "treat all" recommendation. As the goal of ending the HIV epidemic is planned for 2030, the HIV market may reach maturity and is not likely to grow substantially thereafter. The global HIV market size is not likely to change (GlobalData report), but the treatment landscape is shifting to Integrase Inhibitor drugs, fixed-dose combination (FDC) single tablet regimens (STR) and dual-drug therapies.

Market growth is limited by patent expiration and so by development of affordable generics, in particular in Europe where financial austerity measures are more pronounced than in the US (Clayden, 2014) (WHO/UNAIDS, 2015). In 2015, generics were already available for zidovudine (ZDV), lamivudine (3TC), nevirapine (NPV), efavirenz (EFV), rilpivirine (RTV). In 2016, abacavir (ABC), and boosted-liponavir (LPV/r) patents will expire. In 2017, tenofovir DF (TDF), boosted-atazavanir (ATZ/r), boosted-darunavir (DRV/r) will also see their patents expire. Then the major ART drugs and combination patent expiry dates will be: Epzicom (ABC/3TC, 2019); etravidine (ETR, 2021); Truvada (TDF/FTC, 2024); raltegravir (2025); Atripla (TDF/3TC/EFV, 2026) and Complera (TDF/FTC/RPV, 2026); Triumeq (ABC/3TC/DTG, 2029).

Replacing 1L TDF and zidovudine with TAF

TAF is currently replacing TDF in fixed-dose combinations and both are predominant in 1st-line NRTI backbones, moving zidovudine (NRTI also) from 1st-line to 2nd-line.

- Replacing 1L nNRTI with INSTI

Efavirenz is superior to neviparine in the long-term but both are replaced with dolutegravir. The 1st-line ART guideline is shifting from the nNRTI-based regimen to the INSTI-based regimen. Dolutegravir (INSTI) has become the gold-standard for 1st-line HIV treatments, and even further. Atripla (FTC/TDF/EFV) was downgraded in the DHHS guidelines in April 2015.

- Replacing 2L Lopinavir

The Protease Inhibitor lopinavir is being replaced with zidovudine due to its lower cost and once-daily dosing. PI is used in combination with either NRTI (Guidelines) or with INSTI (dolutegravir).

- Replacing 3L Raltegravir with Dolutegravir

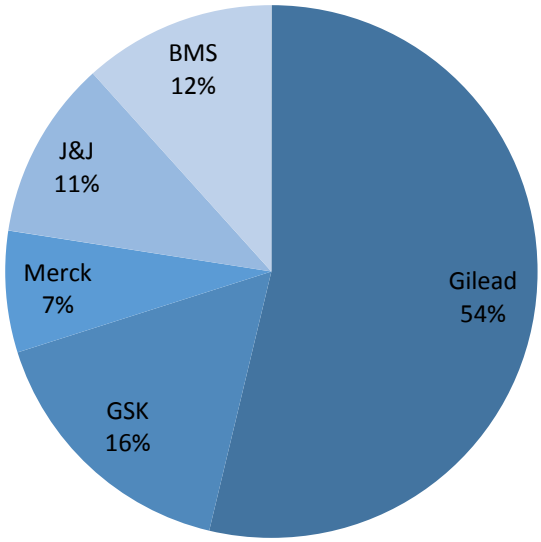
3rd-line ART is mainly occupied with raltegravir. However, dolutegravir will be used in patients who did not take raltegravir in 1st-line.

4. Place of GSK in the market

4.1. Challenger number 1 to Gilead

In trying to find official figures for the HIV market size, we found very diverging data, many of which underestimated the actual numbers if only because they were below the sum of the well-known and individually identified products in annual reports. So, we made our own calculation which is based on the Top 5 companies that have products in the field. This creates a market of USD20.5bn which therefore is a base because some other minor players including generic companies also work in this market segment.

Fig. 13: Market shares of major companies in HIV



In 2015, Gilead Science's annual sales of major HIV products amounted to USD10,998m and GSK's reached USD3,343m. The sum of the major HIV drug sales was of USD20,463m.

Source: Company Data; Bryan, Garnier & Co ests.

What we can say for sure is that ViiV Healthcare – which we sometimes report as GSK – is clearly back in the game in this HIV market with a seat of number 2, however still far from the leader Gilead.

4.2. Dolutegravir: GSK's lead asset

4.2.1. A powerful Integrase Inhibitor

■ Indication

Dolutegravir (DTG) was approved by the FDA in 2013 and is indicated in combination with other ART drugs for the treatment of HIV-1 infected adults and adolescents from 12 years old and weighing at least 40 kg.

Efficacy in HIV1-treatment naive patients

Dolutegravir demonstrated best-in-class status

This recommendation was based on two non-inferiority phase III, randomised, multicentre, double-blind, controlled clinical trials assessing dolutegravir's efficacy: SPRING-2 (ING113086, N=822), and SINGLE (ING114467, N=833).

While SPRING-2 compared dolutegravir with raltegravir (first-generation INSTI), in combination with 2NRTI, the SINGLE study compared dolutegravir with efavirenz (nNRTI), also in combination with 2NRTI (ABC/3TC or TDF/FTC).

In SPRING-2, dolutegravir demonstrated a similar efficacy, a similar discontinuation rate and a similar adverse events profile as raltegravir. By contrast, in the SINGLE trial, dolutegravir demonstrated higher antiviral efficacy (88% vs 81%) and a lower discontinuation rate due to fewer adverse events (7% vs 13%) compared to efavirenz.

Efficacy in HIV1-treatment-experienced patients

In addition to being indicated for initial therapy, dolutegravir has also been indicated in HIV-1-treatment-experienced patients. This recommendation was based on several trials, including SAILING (NCT01231516), and VIKING-3 (NCT01328041).

SAILING, a non-inferiority phase III, randomised international, multicentre, double-blind, controlled trial (N=719) compared 50mg one dose-daily dolutegravir with 400mg twice dose-daily raltegravir, both in combination with up to two ART agents, in HIV-treatment experienced subjects. Dolutegravir demonstrated a better antiviral efficacy compared to raltegravir (79% vs 70%), driven by better virological outcomes and not caused by a difference in patient withdrawal. The CD4 cell count was similar.

In VIKING-3, a multicentre, open-label, single arm trial (N=183), HIV-treatment experienced adults with virological failure or current or historical evidence of raltegravir and/or elvitegravir resistance were recruited. They were given 50mg dolutegravir twice dose-daily with their current failing background regimen for one week, before receiving dolutegravir with optimised background therapy from day 8 to week 24. Dolutegravir brought a clear therapeutic improvement as 63% of the subjects reached the primary endpoint that is a viral load of under 50 copies per ml.

Adverse events

Dolutegravir is known to be very well tolerated, with fewer adverse events compared to efavirenz. The most common adverse events were headaches and insomnia (Grades 2-4).

Why dolutegravir is of great interest

In summary, dolutegravir, reduces the viral load and increases the CD4 cell count as efficiently as raltegravir and better than efavirenz in HIV-1 treatment-naïve patients. In HIV-1 treatment-experienced subjects, dolutegravir has a stronger antiviral efficacy than raltegravir. As, dolutegravir has a better tolerability leading to fewer adverse events, thus reducing withdrawals compared to efavirenz, this latter is replaced with dolutegravir.

Please see the section headed "Important information" on the back page of this report.

Furthermore, dolutegravir presents additional advantages that support its new status of "preferred" ART regimen for initial therapy. 1/ Dolutegravir benefits from a higher drug resistance barrier; 2/ dolutegravir consists in one daily-dose compared to the twice daily-dose of raltegravir, thus easing the patient's adherence. Indeed dolutegravir (DTG) has favourable pharmacokinetic properties that allows once daily-dosing, thus avoiding additional booster agents, unlike elvitegravir that needs a booster; 3/it has excellent absorption and can be taken with or without food regardless of fat content; 4/it showed less intersubject variability compared to raltegravir, which should prevent plasma variations resulting in less toxicity and fewer therapeutic failures; and 5/less than 1% of DTG undergoes renal elimination, so there is no dose adjustment required in patients with mild to severe renal impairment.

4.2.2. Dolutegravir today

■ Tivicay

Tivicay (dolutegravir, DTG) was launched in 2013 and its patent will expire in 2027. Tivicay represents a strategic asset for GSK as HIV guidelines recommend it as a preferred 1st-line treatment. Tivicay proved to be more interesting for patients compared to first-generation INSTI (twice dose-daily raltegravir; boosted-elvitegravir) and nNRTI (efavirenz).

As the main strength of dolutegravir versus raltegravir is its single daily-dose, it was good news to learn Merck's once-daily dosing raltegravir (800mg) was not approved after the QDMRK trial which failed to show non-inferiority vs. the approved twice dose-daily raltegravir (400mg) (Eron, Rockstroh, & Reynes *et al.*, 2011). However, Merck is currently investigating a reformulated raltegravir (MK-0518) 1200 mg once-daily, and the results are expected in early 2017.

⇨ Tivicay competes directly with other INSTIs such as Isentress (raltegravir, Merck), Vitekta (elvitegravir, Gilead) and indirectly with ART agents from other therapeutic classes.

■ Triumeq

Triumeq (abacavir/lamivudine/dolutegravir) was approved in 2014, is indicated for the treatment of HIV-1 infection, and is one of the preferred first-line recommended treatment by the DHSS. Efficacy was assessed based on the SINGLE and SAILING trials (as described previously). In the SINGLE trial, Tivicay (DTG) + Epzicom (ABC/3TC) demonstrated higher efficacy compared to Atripla (EFV/TDF/FTC) at 96 weeks.

⇨ Triumeq competes with fixed dose combinations including Atripla (EFV/TDF/FTC), Genvoya (FTC/TAF/EVG-boosted), Stribild (FTC/TDF/EVG-boosted), Complera (FTC/TDF/RPV) and Odefsey (FTC/TAF/RPV). Only Triumeq, Stribild, Genvoya are among first-line preferred treatment options.

4.2.3. Towards a dual dolutegravir-based regimen

Dolutegravir: GSK wants to do more with it

GSK addresses future challenges in HIV treatment options. GSK assumed that since dolutegravir is powerful, a dual dolutegravir-based therapy could be as effective as a tri-therapy. If results support this hypothesis, then it would allow HIV-infected patients to decrease the number of drugs taken daily, thus reducing adverse events to drugs, drug interactions and lower costs (Girouard, 2016) (Baril, *et al.*, 2016).

Both combinations that GSK is developing aim to improve patient tolerability and adherence but they do not target the same population segment. While the DTG/RPV combination positioning is to maintain effectively the viral load under 50 RNA copies per ml in HIV virologically-suppressed patients, DTG/3TC is being tested as an initial therapy in HIV treatment-naïve individuals. If these clinical results demonstrate that dual-regimens can be considered as appropriate alternatives to standard regimens for initial treatment or maintenance, the DHHS guidelines might have to be changed.

■ Dolutegravir (Tivicay)/Rilpivirine (Edurant)

This dual combination consists of 1INSTI + 1nNRTI and would be indicated for HIV maintenance, after the viral load reaches 50 RNA copies/ml, referred to as undetectable viral load. The dolutegravir (DTG)/rilpivirine (RPV) launch is planned for H1 2018.

Two replicates of a 148-week phase III, randomised, open-label, multicentre, clinical trial (SWORD-1: NCT02429791; SWORD-2: NCT02422797) are assessing the efficacy, safety, and tolerability of switching to DTG/RPV from an ART tri-therapy in HIV-1-infected virologically-suppressed adults. Clinical completion is expected by 2021.

Currently, no dual-therapy on the market has a similar positioning. However, ritonavir-boosted atazanavir (100mg/300mg, Mylan), and cobicistat-boosted atazanavir (Evotaz) can be taken for therapy in experienced patients. As these are boosted-PI and not combinations of two distinct antiviral agents, we believe that GSK's dual regimen would lead to more sales compared with ritonavir/atazanavir.

⇨ DTG/RPV targets the HIV maintenance market and competes directly with: standard ART regimens, and the future HIV pipeline targeting also the HIV virologically-suppressed patients segment

- Therapeutic positioning of Rilpivirine

Rilpivirine (Edurant) is the most recent nNRTI FDA-approved drug (2011) and is indicated in combination with other ART drugs in HIV-1 treatment-naïve adult patients with a pre-treatment viral load of under 100,000 copies per ml and a CD4 cell count of over 200 cells per ml.

⇨ That is why the DTG/RPV targets virologically-suppressed patients, as they meet these pre-treatment requirements

This indication was based on two randomised, double-blind, active controlled, phase III trials: ECHO (TMC278-209) and THRIVE (TMC278-215). Both trials had the same design except for the background regimen and so the data were pooled for analysis. Both studies assessed the efficacy, safety and tolerability of 25mg once-daily dose rilpivirine (N=686) versus 600mg efavirenz (N=682) in treatment-naïve patients, stratified upon their viral load. At week 48, rilpivirine showed a similar efficacy to efavirenz overall. Virologic failure and resistance were higher in rilpivirine-treated patients having a pre-treatment viral load of over 100,000 copies per ml. Moreover, virologic failure was more frequently encountered in rilpivirine-treated patients with a pre-treatment CD4 cell count of under 200 cells per ml. Higher pre-treatment viral loads and lower pre-treatment CD4 cell counts were associated with higher virologic failure and higher resistance in the rilpivirine arm.

The only advantage of using rilpivirine is the lower adverse events (Grades 1-4) frequency compared to efavirenz. Rilpivirine-treated patients experienced less nausea, abdominal pain, vomiting, fatigue dizziness, abnormal dreams and skin rashes compared to efavirenz. However, they encountered neuropsychiatric disorders including depressive disorders and insomnia at the same frequency as efavirenz-treated patients.

Rilpivirine is not recommended as a "preferred" ART regimen but instead as an "alternative" option. Indeed, given the availability of other effective treatments that do not require immunologic and virologic pre-treatment restrictions, rilpivirine is only used when the recommended combination of 2NRTI (tenofovir DF+ emtricitabine) and 1 nNRTI (efavirenz) is not adapted to the patient.

One clinical trial (NCT01286740) demonstrated that the switch from an efavirenz-based regimen to a rilpivirine-based regimen in virologically-suppressed patients, maintained the viral load to below 50 copies per ml at 12 and 48 weeks.

Note that rilpivirine's high frequency drug resistance prevents the use of other nNRTI, while efavirenz-treated patients developing a nNRTI resistance still have the opportunity to take other nNRTIs (etravidine or rilpivirine) as further options. When in combination with dolutegravir, the DTG/RPV overcomes this drawback.

■ Dolutegravir (Tivicay)/Lamivudine (Epivir)

This dual combination consists of an INSTI plus NRTI and is developed for initial therapy. The dolutegravir (DTG)/lamivudine (3TC) launch is planned for H1 2019. A phase IV pilot open-label, single-arm exploratory trial (PADDLE: NCT02211482, N=20, completion: Apr. 2016) assessed the antiviral efficacy, safety and tolerability of the DTG/3TC combination in HIV treatment-naive patients. A similar phase II clinical trial (NCT02582684, N=120, completion: Nov. 2016) is also studying the DTG/3TC combination.

⇨ The DTG/3TC targets HIV treatment-naïve patients and competes directly with standard ART therapies such as: Triumeq (ABC/3TC/DTG), Genvoya (FTC/TAF/EVG-boosted), Stribild (FTC/TDF/EVG-boosted), amongst others.

- Therapeutic positioning of Lamivudine

Lamivudine (Epivir) has been approved by the FDA since 1995 and is indicated in combination with other ART drugs in HIV-1-infected adults and children. Lamivudine has a low genetic resistance barrier and the most common adverse events in adults were headache, nausea, fatigue, diarrhoea and cough, and in the paediatric population the most recurrent adverse events were fever and cough. Lamivudine (3TC) and emtricitabine (FTC) are clinically equivalent and both widely used in all currently recommended HIV guidelines (Ford, 2013) but their concomitant use is not recommended. While dolutegravir has a higher genetic drug resistance barrier than lamivudine, both antiviral agents are very effective, safe and well tolerated.

4.3. Cabotegravir, a Long-Acting INSTI

A second integrase inhibitor is approaching the market

Cabotegravir (GSK1265744), an Integrase Inhibitor and dolutegravir-analogue, is currently being investigated for both the prevention and treatment of HIV-1 infection. It benefits from a high barrier to drug resistance and does not need any booster. Two forms of cabotegravir are being studied: an oral tablet and a long-acting injection. It has a half-life that lasts more than 40 hours under the oral tablet formulation allowing for once-daily dosing, and a half-life of more than 40 days when used as a long-acting parenteral injection, allowing monthly or quarterly injections.

4.3.1. HIV maintenance

To overcome bioavailability, water solubility, stability weaknesses of oral ART, GSK took advantage of nano-formulation technologies to offer a long-lasting effect for its combination cabotegravir LA/rilpivirine LA. The Long-Acting (LA) rilpivirine has been developed in collaboration with Janssen. The launch is expected in 2019/2020.

A phase IIb, randomised, multicentre, open-label clinical trial (LATTE-2: NCT02120352) assessed the efficacy, safety, tolerability of intramuscular (IM) injections of cabotegravir LA + rilpivirne LA in HIV-1 virologically-suppressed patients compared with orally cabotegravir (30 mg) + abacavir (600 mg)/lamivudine (300 mg) regimen. The first part (Induction) consists in treating all patients with orally cabotegravir (30 mg) + abacavir (600 mg)/lamivudine (300 mg) regimen once-daily for 20 weeks. The second part (Maintenance) consists of treating eligible subjects (viral load < 50 copies/ml) with either cabotegravir LA (400 mg)/rilpivirine LA (600 mg) every 4 weeks (Q4W); cabotegravir LA (600mg)/rilpivirine LA (900mg) every 8 weeks (Q8W); or continue the oral induction regimen of cabotegravir (30 mg) + abacavir (600 mg)/lamivudine (300 mg) for 96 weeks.

Both dual-drug IM injections demonstrated higher viral efficacy compared to the three-drug oral regimen (94.5% vs 91%). Adverse events leading to withdrawal were higher in the lower dosing dual-drug IM injection (5% for the Q4W; 2% for the Q8W) vs the three-drug oral regimen (2%). The most common adverse event was pain at the injection site. Hopefully, these injection-site reactions (pain, swelling, nodules) were mild to moderate and usually resolved within 3-7 days and became less common over time.

- ⇨ CAB LA/RPV LA targets the HIV maintenance market and competes with: DTG/RPV (GSK), DRV/COBI/FTC/TAF (Gilead), FTC/TAF (Gilead).

4.3.2. HIV prevention

Three pre-exposure prophylaxis regimens are currently approved: FTC/TDF (Truvada), TDF (Viread) and FTC (Emtriva).

■ Cabotegravir LA monotherapy

A phase IIa, randomised, multicentre, two-arm, double-blind clinical trial (ECLAIR: NCT02076178) is investigating the safety, tolerability and acceptability of the intramuscular injection of cabotegravir LA (800mg, Q12W) in HIV-uninfected adult males at high risk compared with placebo. The same trial will start at end-2016 with women at high HIV infection risk. GSK is expecting the launch in 2020+.

- ⇨ Given cabotegravir's long lasting effect, it is not impossible to believe that it could graze PrEP market shares (Truvada, Emtriva, Viread, and VRC01).

■ Cabotegravir LA/Antibodies

The use of antibodies for HIV prevention is still disappointing since the virus undergoes mutations.

VRC01 is a broadly neutralising antibody (BnAb) which targets the HIV's CD4 binding site. GSK has planned investigations combining cabotegravir LA/broad neutralising antibodies that would compete with other ART drugs on the PrEP market segment.

- ⇨ To conclude, long-acting injectable cabotegravir-based therapies are of interest for maintenance regimens in HIV virologically-suppressed patients but also for HIV-1 prevention in populations at substantial risk of infection.
- ⇨ Broad neutralising antibodies, in combination with other antiviral agents could enhance ART treatments' efficacy as they combine agents with different mechanisms of actions but also improve prevention outcomes.
- ⇨ There is no such long-acting antiviral agent/broad neutralising antibody combination, so if GSK makes it, it would be the first on the market.

4.4. HIV pipeline 2016

The anti-retroviral pipeline in 2016 is quite encouraging as it provides innovations including Gilead's TAF research programmes and Janssen's long-acting rilpivirine. Also, for people with resistance to current ART agents, BMS's attachment inhibitor (BMS-663068), maturation inhibitor (BMS-955176), and Merck's new nNRTIcompound (MK-1439) bring hope.

Fig. 14: Most advanced HIV pipeline overview

Compound	Class	Company	Status	Completion
Tenofovir Alafenamide Fumarate (TAF)	NRTI	Gilead	Phase 3	2018
GS-9883	INSTI	Gilead	Phase 3	2018
Doravirine (MK-1439)	nNRTI	Merck	Phase 3	2017
Fostemsavir (BMS-663068) *Sold to GSK*	Attachment inhibitor	BMS	Phase 3	2018
BMS-955176 *Sold to GSK*	Maturation inhibitor	BMS	Phase 3	2017
Pro 140	CCR5-humanized monoclonal Ab	CytoDyn	Phase 3	2018
Ibalizumab (TMB-355; TNX-355)	CD4-humanised monoclonal Ab	TaiMed Biologics	Phase 3	2017

Source: (Pipeline Report)

4.5. Major threats for GSK

4.5.1. Gilead Science: more than a strong a competitor

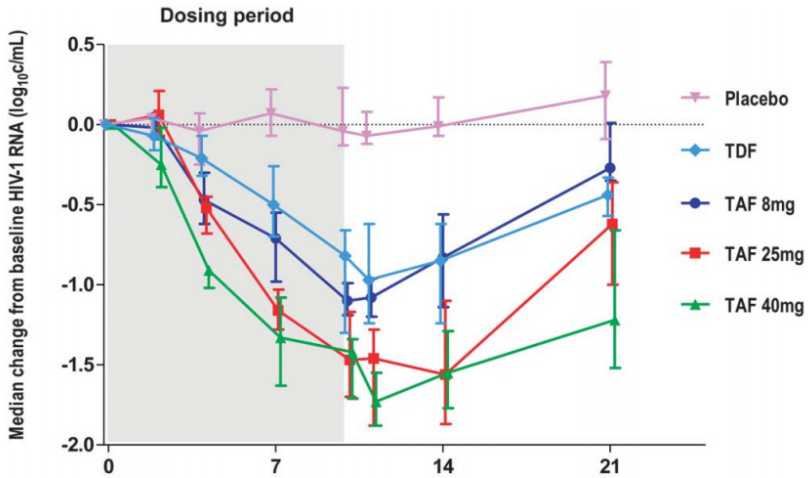
■ Tenofovir Alafenamide Fumarate (TAF): Gilead's lead asset

Tenofovir Disoproxil Fumarate (TDF), a NRTI agent, was approved by the FDA in 2001 and is widely used in NRTI backbones. Lately, Tenofovir Alafenamide Fumarate (TAF) has been investigated and used in fixed-dose combination pills, replacing TDF (Genvoya, Odefsey, Descovy).

Both TDF and TAF are pro-drugs that require phosphorylation to be converted into tenofovir diphosphate (TFV-DP), the active metabolite. A pro-drug is an inactive drug, until the body converts it into an activated form. While TDF is converted to tenofovir DP in the blood, TAF enters into lymphocytes and other cells (even HIV-infected cells) to undergo alterations that convert it tino the active metabolite.

A randomised, partially-blinded, active and placebo-controlled phase Ib investigated the differences in antiviral activity, safety, pharmakocinetics of a short-term monotherapy with three doses of TAF (8;25;40 mg) versus TDF (300mg) and placebo in 38 HIV-positive treatment-naïve and experienced adults. TAF demonstrated more potent antiviral activity, higher peripheral blood mononuclear cell intracellular tenofovir diphosphate (active metabolite) levels with a lower TFV-DP plasma exposure (1/10 of the dose) (Ruane, DeJesus, & Berger *et al.*, 2013). Low TAF dosing (10 or 25mg) along with reduced tenofovir exposure has the potential of reducing kidney and bone toxicities compared with TDF dosing (300mg).

Fig. 15: TAF has a higher median change potency from baseline in HIV-1 RNA



HIV-infected treatment naive and experienced adults were given a dose of TAF ranging from 8 to 40mg per day. After 10 days of this monotherapy, the median change from baseline in HIV-1 RNA was measured and TAF seems to have higher antiviral potency compared to TDF.

Source: (Ruane, DeJesus, & Berger et al.*, 2013)*

Recent clinical studies suggest that TAF has a similar antiviral activity at a lower dose, a similar tolerability profile, and improves surrogate laboratory markers of renal and bone safety compared with TDF. Two randomised, double-blind, active-controlled trials 104 and 111 compared Genvoya (N=866) (COBI/EVG/FTC/TAF 10mg) to Stribild (N=867) (COBI/EVG/FTC/TDF 300mg) in

treatment-naïve adults. The primary endpoint (viral load<50 copies/ml) was reached with similar effectiveness in the Genvoya-treated arm compared to the Stribild-treated arm (92% vs 90%). Virological failure was also similar in both groups (4%). Patients' withdrawal due to adverse events or death was similar (1% vs 2%). The most common adverse events were diarrhoea, nausea and headache. However, bone mineral density and kidney function were significantly improved in the Genvoya-treated arm.

Commercialised TAF-based combinations

- **Genvoya: the first TAF-based regimen to be approved**

Genvoya (emtricitabine/cobicistat/elvitegravir/TAF) was approved by both the EMA and FDA in November 2015 and is indicated in HIV-infected adults and adolescents from 12 years old weighing at least 35kg, whereas, its main competitor, Stribild (Gilead) is only indicated in adults from 18 years old. Genvoya has been added to the "Recommended" category in the DHHS guidelines and preferred ART regimens in the EU. Genvoya has demonstrated similar efficacy, safety and tolerability compared to Stribild (emtricitabine/cobicistat/elvitegravir/TDF), but offers improvement in short-term renal and bone safety markers (48w). These improvements are of much interest since HIV-infected people can now live longer, thus decreasing further risks for complications. The long-term effect, an accurate measure of a potential decrease in risks of bone fractures/nephrotoxicity remains to be demonstrated.

Genvoya is prescribed as a second-line option for several reasons: 1/ the Integrase Inhibitor used in the composition, elvitegravir, has a lower genetic drug resistance barrier vs. dolutegravir or raltegravir; 2/ Elvitegravir requires a booster to prolong its half-life and thus allowing the once-daily dose; 3/ Cobicistat is known to create drug interactions; and 4/ existing alternatives (DTG-based regimen) have a better tolerability and less drug interactions.

⇨ Genvoya will cannibalise both Stribild (50% of patients currently on Genvoya shifted from Stribild) and Atripla (EFV/FTC/TDF) as efavirenz is not well tolerated.

- **Odefsey**

Odefsey (rilpivirine/emtricitabine/TAF) was approved by the FDA in March 2016, and is in EU regulatory submission. The combination consists of Gilead's lead NRTI backbone (emtricitabine/TAF) and a nNRTI (rilpivirine). Odefsey is indicated in HIV treatment-naïve patients from 12 years old and with a pre-treatment viral load less than or equal to 100 000 RNA copies per ml.

In addition, this fixed dose combination is being investigated in HIV virologically-suppressed patients (phase III, NCT02345252, N=632, completion: June 2018). However, odefsey is not recommended in patients with a creatinine clearance lower than 30ml/min.

⇨ Odefsey (RPV/FTC/TAF) will cannibalised Complera (RPV/FTC/TDF) and might compete also with the future HIV pipeline targeting the HIV maintenance segment.

- **Descovy: NRTI backbone leader**

Descovy (FTC/TAF) was approved by the FDA in April 2016, and the CHMP has recommended the granting of a marketing authorisation in Europe. Descovy is indicated in combination with other ART agents for the treatment of HIV-1 infection in adults and adolescents from 12 years old. It is not recommended as a PrEP therapy (yet). The most frequent adverse events are nausea, bone mineral density decline, diarrhoea, headache, fatigue. Descovy competes directly with NRTI backbones.

⇨ Descovy (FTC/TAF) will cannibalise Truvada (FTC/TDF).

■ TAF-based quad therapy

In Gilead's pipeline, another TAF-fixed dose combination is currently under investigation in both HIV treatment-naïve and experienced patients.

A randomised, active-controlled, open-label phase III clinical trial (NCT02269917, N=1146, completion: March 2018) aims to assess the efficacy, safety and tolerability of switching to a once-daily single-tablet darunavir/cobicistat/emtricitabine/Tenofovir AF regimen from an oral boosted-protease inhibitor (PI) combined with tenofovir DF/emtricitabine regimen in HIV virologically-suppressed subjects.

Also a randomised, active-controlled, double-blind phase III trial (N CT02431247, N= 670, Completion: Apr. 2020) is evaluating the efficacy and safety of Darunavir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide once-daily fixed-dose combination (FDC) vs a regimen consisting of Darunavir/Cobicistat FDC co-administered with Emtricitabine/Tenofovir Disoproxil Fumarate FDC in HIV treatment-naïve subjects.

⇨ DRV/COBI/FTC/TAF targets both HIV treatment-naïve and experienced patients, and competes directly with the TDF/TAF-based FDC own by Gilead, DTG-based regimens and all standard ART regimens.

■ TAF-based dual therapy

In the French HAS, the commission has indicated that all TDF-based regimens should be replaced with TAF as soon as possible. Also, Gilead tends to exploit its new strategic asset in new HIV treatment options. As, for example, in an open-label, multi-cohort phase II/III clinical trial (NCT02285114, N=100, completion: May 2018), Gilead aims to assess the pharmakocinetics, safety and efficacy of switching to FTC/TAF from an FTC/TDF regimen in HIV-infected virologically-suppressed adults and adolescents.

A TAF-based fixed dose combination (FDC) of potential interest would be DTG/FTC/TAF, which doesn't exist yet as a FDA-approved FDC. Indeed, DTG proved to be effective as well as benefiting from a high drug resistance barrier and excellent safety and tolerability profiles, and does not require any booster, thus reducing drug interactions. In addition, TAF's active compound seems to bring more long-term healthy advantages compared to TDF. So, a combination associating both of them, could end-up with additional benefits for HIV-infected patients. Also, a switch to DTG/TAF after a three-drug regimen could be considered if GSK and Gilead agree to a collaboration.

- ⇨ TAF as a NRTI containing backbones does not represent a big threat for GSK. The total replacement scenario of GSK's NRTI drugs (lamivudine, abacavir, and zidovudine) with TAF is unlikely for two reasons: 1/ some patients might not tolerate TAF and need further NRTI backbone options; and 2/ dolutegravir is barely prescribed with FTC/TDF (Truvada), since the combination of branded drugs increases significantly the price of the therapy. However, it is known that an abacavir-containing backbone leads to cardiotoxicity. In addition, as the FTC/TDF is already predominant among NRTI backbones, the expansion of TAF might not affect GSK's position too much in the NRTI market. Note, the expansion of TAF-based combinations is more a strategy for Gilead to keep its market share despite the loss of the TDF patent than a threat for GSK.
- ⇨ By contrast, the TAF-based FDC for either HIV treatment or HIV maintenance represents greater dangers, as GSK's strategy is to go towards the HIV maintenance market with its future dolutegravir-, cabotegravir-based pipeline.

■ A new next-generation INSTI: GS-9883

Over the next couple of years, Gilead may come out with a direct competitor to dolutegravir

Gilead is directly attacking GSK's strongest asset dolutegravir by developing a next-generation INSTI that does not require a booster, unlike Vitekta, (elvitegravir, Gilead). There are five phase III clinical trials comparing GS-9883 with various recommended first-line/second-line treatments in HIV treatment-naive or virologically-suppressed patients. Among these studied comparisons, one randomised, double-blind, phase III trial (NCT02607956, N=300, completion: 2018) is investigating the safety and efficacy of the head-to-head GS-9883/FTC/TAF vs. DTG + FTC/TAF in HIV treatment-naive adults.

Another phase III trial (NCT02603107, N=520, completion: 2018) is assessing the safety and efficacy of switching from regimens consisting of boosted-atazanavir or darunavir + either FTC/TDF or ABC/3TC to GS-9883/FTC/TAF in virologically suppressed HIV-1 infected adults.

- ⇨ The GS-9883/FTC/TAF combination is likely to be Gilead's lead ART regimen, which targets both HIV treatment-naïve and experienced patients.
- ⇨ GS-9883 is probably the biggest threat for GSK, as it is directly competing with the DTG market. Depending upon the results of the clinical trials, three scenarios exist:
  - o Unlikely scenario: if there is superiority over DTG, in terms of efficacy or safety, then GS-9883 could replace DTG in the DHHS guidelines and in the fixed dose combinations. New patients would directly take the GS-9883 but maybe not all patients already under a DTG-based regimen.
  - o Very likely scenario (both molecules are very similar): if there is non-inferiority, GSK might slightly lose market share since GS-9883 would have a similar positioning as DTG. But, DTG would benefit from being the first, better known in the eyes of doctors and patients, as it has became a reference. The DHHS guidelines for initial therapy are unlikely to change for a drug with a similar therapeutic profile. Moreover, if GS-9883 is not cheaper than DTG, there is no point of paying more for a novel drug without any competitive/differentiation advantage versus the well-established reference (usually, novel drugs are more expensive than first generation).
  - o Unlikely scenario: if there is inferiority, GSK keeps its DTG market share intact.
- ⇨ If we were paranoid, we would worry about a possible combination that could be used as a switch from a three-drug ART regimen to a TAF-based dual therapy in HIV virologically-suppressed patients (e.g.: GS-9883/TAF). Indeed, TAF might have stronger assets than

RPV, which could lead to a clinical superiority compared with the DTG/RPV combination that GSK is developing.

4.5.2. Merck: a next-generation nNRTI Doravirine

Merck's new nNRTI drug is of particular interest since doravirine (MK-1439A) has demonstrated similar antiviral activity as efavirenz with a better tolerability profile, when none of the approved nNRTI drugs are recommended for first-line ART. Indeed, efavirenz (Sustiva) causes neuropsychiatric disorders (abnormal dreams, depressions, insomnia, and dizziness), rilpivirine (Edurant) has a lower antiviral efficacy in patients with higher pre-treatment viral load, and neviparine (Viramune) is susceptible to drug resistance.

A clinical trial phase IIb (NCT01632345, N=342, completion: March 2016) consisting in two parts compared doravirine to efavirenz. In part 1, a dose of doravirine (25, 50, 100 and 200mg) in combination with FTC/TDF was given in 208 treatment-naïve patients. The 100mg dose was selected for part 2. All original participants continued with the 100mg doravirine dose, and an additional 132 people were randomly given doravirine (100mg) or efavirenz (600mg) combined with the FTC/TDF NRTI background. Efficacy and safety results were similar in doravirine and efavirenz groups (73.1% vs 72.2%) at week 24 and week 48. However, subjects with higher pre-treatment viral loads were less likely to push their viral load below 40 copies/ml (60.5% with doravirine vs 65.5% with efavirenz) compared with those whose viral loads were lower (83.3% with doravrine and 85.7% with efavirenz). Interestingly, subjects treated with doravirine were less than half as likely as the efavirenz-treated group to withdraw from the trial (4.6% vs 11.9%), mainly driven by the higher level of adverse events in the efavirenz group. Serious adverse events were fewer in the doravirine arm. Doravirine-treated subjects reported less dizziness versus the efavirenz group (9.3% vs 27.8%) and less abnormal dreams (6.5% vs 17.6%). Nonetheless, the doravirine group experienced a higher level of nausea (7.8% vs 2.4%) and fatigue (7.2% vs 4.8%).

Another multicentre, double-blind, randomised, active comparator-controlled phase III clinical trial (NCT02275780, MK-1439-018, N=680, completion: 2017) evaluates the safety and efficacy of doravirine compared with a protease inhibitor (darunavir). HIV-infected treatment-naïve participants are given either 100mg dose-daily doravirine or ritonavir boosted-darunavir (100mg/800mg), each in combination with FTC/TDF (truvada) or ABC/3TC (epzicom) for 48 weeks.

Finally, a multicentre, open-label, randomised phase III study (NCT02397096, N=660, completion: March 2017) evaluates a switch to MK-1439A in HIV virologically-suppressed subjects on a regimen of a ritonavir-boosted Protease Inhibitor and 2 NRTI.

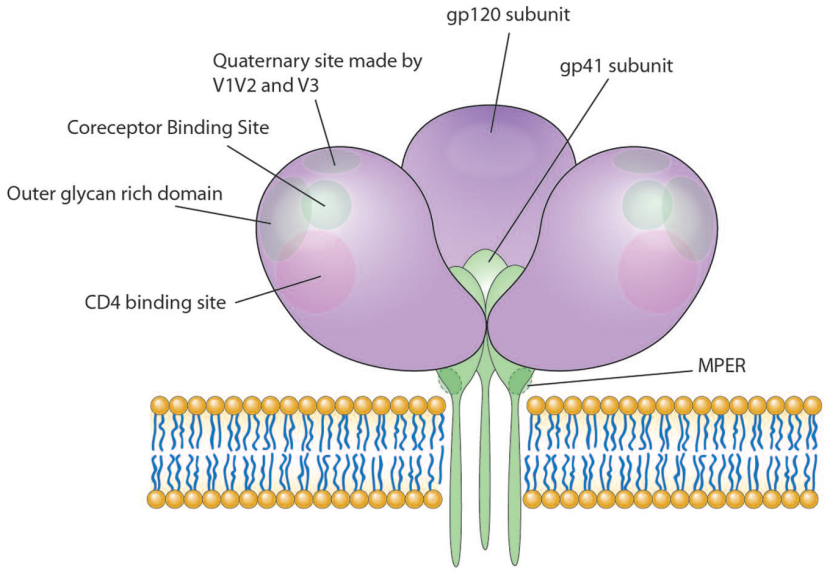
- ⇨ Doravirine could be used with NRTI generics in fixed-dose combinations, offering an alternative to less tolerated first-generation nNRTI, in both HIV treatment-naïve (MK-1439A/3TC/TDF) and experienced patients (MK-1439A/ABC/3TC).
- ⇨ A comparison between MK-1439A versus DTG would be interesting to see if DTG has superiority over a nNRTI, as it has superiority over efavirenz (nNRTI).

4.5.3. Antibody-based therapy

Vaccines to cure HIV are still a long way in the future. On the contrary, antibody-based therapy, with the development of Broad Neutralising Antibodies (brNAb) have brought some optimism for both the prevention and treatment of HIV as they can neutralise most circulating HIV-1 strains, demonstrate potent antiviral activity, without safety concerns, and could be used in combination with

other ART classes. The target of HIV-neutralising antibodies is the trimeric Env spike on the viral membrane: it is a trimeric heterodimer composed of gp120 Env (recognises the CD4 receptor) and the gp41 transmembrane glycoprotein (responsible for the fusion of the viral membrane with the host cell). Broad Neutralising Antibodies fall into 4 classes depending upon the location of the viral spike of the conserved epitopes that they recognise (Kwong, Mascola, & Nabel, 2013) (Corti & Lanzavecchia, 2013).

Fig. 16: Potential sites of antibody response on Env spike



The Envelope (Env) consists of three glycoprotein 120 (gp120), and three transmembrane gp41 subunits. The Env is shown in an open conformation (after CD4 binding) and thus revealing the co-receptor binding site (for either CCR5 and/or CXC4).

Source: (Ringe & Bhattacharya, 2013)

■ CytoDyn: Pro 140

PRO 140 is a humanised IgG4 monoclonal antibody (mAb) anti-CCR5 only, preventing HIV entry. Thus PRO 140 does not prevent HIV entry if the virus is a CXC4-tropic virus. PRO 140 has demonstrated antiviral activity in HIV-infected patients resistant to maraviroc (Olson & Jacobson, 2009).

A randomised, double-blind, placebo-controlled phase IIa (NCT00642707, N=44, completion: 2008) demonstrated potent antiviral activity, a good tolerability and safety profiles for PRO 140 administered subcutaneously. A multi-centre, randomised, double-blind, placebo-controlled phase III trial (NCT02483078, N=300, completion: 2018) is assessing the efficacy, safety, and tolerability of PRO 140 in conjunction with existing ART (failing regimen) for one week and an optimised background regimen for 24 weeks in HIV treatment-experienced patients with CCR5-tropic virus facing limited treatment options.

⇨ Pro 140 competes with maraviroc (CCR5-antagonist).

■ TaiMed Biologics: Ibalizumab

Ibalizumab (TMB-355) is a humanised IgG4 monoclonal anti-CD4 that prevents HIV entry.

A randomised, double-blind, multicentre, dose-response phase IIb trial (NCT00784147, N=113, completion: 2011) assessed the safety and efficacy of Ibalizumab combined with an optimised background therapy in HIV treatment-experienced patients for 24 weeks. This study proved that Ibalizumab had a potent antiviral activity without any safety concerns, with most common adverse effects being rash, diarrhoea, headache, and nausea.

Several phase III clinical trials are ongoing, including the trial NCT02707861 (N= 50, completion: March 2017), which is investigating the safety and tolerability of intravenously-administered (IV) ibalizumab combined with an optimised background regimen for treating multi-drug resistant HIV-1 infection (a similar trial has just completed in 2016: NCT02475629, N= 30).

■ VRC01

VRC01 is being developed by the US National Institutes of Health (NIH) Vaccine Research Center. VRC01 is referred to as broadly neutralising antibody, and targets the gp120-CD4 binding site. However, the viral Env employs several mechanisms to evade the host's humoral immune response including trimeric exclusion, occluded co-receptor binding sites by conformational masking, shielding of conserved epitopes by variable flexible loops, limiting the induction of BrNAb. VRC01 is mainly studied to prevent HIV-1 infection in populations at high HIV infection risk. For example, the phase IIb clinical trial (NCT02716675, N=2700, completion: 2020) is investigating the safety and efficacy of VRC01 in reducing the acquisition of HIV-1 infection among men and transgender individuals having sex with men. VRC01 did not show much effect in HIV treatment-experienced patients, who had their viral load already controlled by their ART therapy, but demonstrated a potent antiviral activity in HIV-positive untreated patients (Brachmann, 2016).

4.6. Opportunities: acquisition of BMS's HIV pipeline

Two innovative compounds acquired from BMS

In December 2015, GSK acquired BMS's late-stage HIV R&D assets, including an attachment inhibitor BMS-663068, a maturation inhibitor BMS-955176 and a back-up maturation inhibitor BMS-986173. Also, GSK acquired BMS's preclinical and discovery stage HIV research assets such as BMS-986197, which has a triple mechanism of action, a further maturation inhibitor, an allosteric integrase inhibitor and a capsid inhibitor. By acquiring these assets, GSK intends to diversify its HIV pipeline, in order to manage risks and to be a major player in the HIV market.

In our view, these novel HIV assets are more innovative compared to the rest of the HIV pipeline, as they offer alternatives for HIV treatment-experienced patients with drug resistance or intolerance. Consequently, exploiting these innovative antiviral assets in new combinations would multiply market opportunities.

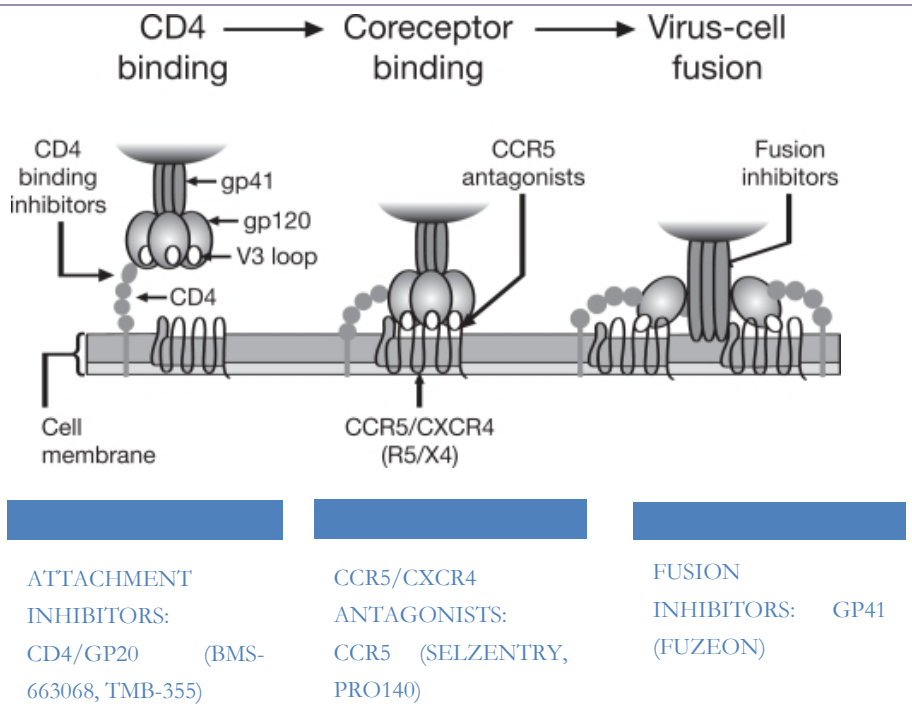
Most of the new drugs come from the same classes as those actually in use (NRTI, nNRTI, INSTI), offering modest improvements in terms of daily-dosing convenience (FDC), tolerability (TAF, doravirine), potency (DTG/3TC), long-lasting pharmacokinetics characteristics (CABLA/RPV LA). But few companies have bet on uncommon ART classes such as attachment inhibitors, or a totally new class, maturation inhibitors. Consequently, GSK is exploring antiviral drugs in therapeutic classes

that are not overcrowded by competitors yet. Should it be a success, GSK would provide first-in-class attachment and maturation inhibitor drugs.

■ A new attachment inhibitor: BMS-663068 (Fostemsavir)

Fostemsavir is the pro-drug of the attachment inhibitor BMS-626529 (temsavir). Attachment inhibitors bind directly to gp120, a viral protein on the HIV outer surface, causing conformational changes, thus blocking the interaction with the target cells and preventing the HIV from entering into the cells.

Fig. 17: HIV-1 entry mechanism with current antiviral therapeutic classes



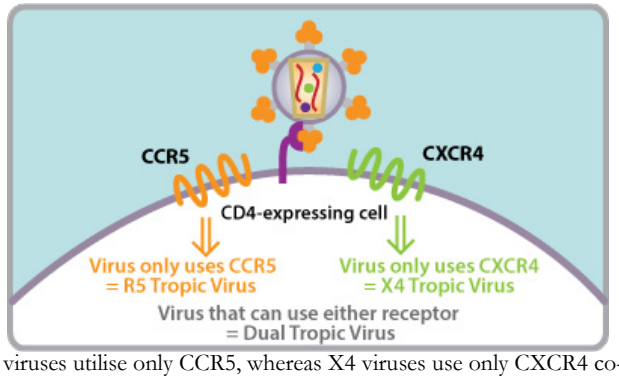
Source: (Moore & Doms, 2003)

BMS-663068 is active regardless of whether the HIV strain uses CCR5 or CXCR4 co-receptors as entry points. The co-receptor utilisation patterns differ in various HIV strains and define their cell tropism, thus determining if a cell can be infected. The advantage of BMS-663068 compared to CCR5 antagonists and fusion inhibitors is that it blocks upstream the HIV entry mechanism.

The only FDA-approved entry inhibitors are the CCR5 antagonist (Selzentry: maraviroc, GSK) and the fusion inhibitor (fuzeon: enfuvirtide, or T-20, Roche). Maraviroc is not recommended as initial therapy as it requires testing for CCR5 tropism before initiation of therapy, does not offer a virologic benefit when compared with other recommended regimens, requires twice-daily dosing and can cause serious adverse events. Given its unique mechanism of action, most HIV-1 strains are susceptible to enfuvirtide. However, acquired drug resistance is always possible. Fuzeon is administered by subcutaneous injection twice daily. Injection site reactions are the main drawback of this drug. Fuzeon combined with other ART agents is an effective treatment option for HIV-1 infected people. Given the twice dose-daily injection and the local injection reactions, Fuzeon is considered as a salvage option for treatment-experienced patients.

Antibodies and small molecules, including PRO 140 (anti-CCR5), ibalizumab (anti-CD4), are being developed to block HIV entry. However, the danger with inhibiting cellular receptors (CCR5, CXCR4) is that it may lead to dangerous unforeseen adverse events. Conversely, these safety concerns are absent with attachment (gp120)/fusion (gp41) inhibitors that target viral proteins. Another challenge to overcome with peptide inhibitors is their administration which is through an injectable formulation and not by oral tablets.

Fig. 18: HIV-1 cell tropism



HIV strains termed R5 viruses utilise only CCR5, whereas X4 viruses use only CXCR4 co-receptors. Dual tropic viruses (X4R5) are able to enter target cells through either chemokine receptors CCR5 or CXCR4.

Source: (Monogram BIOSCIENCES)

A phase IIb clinical trial (NCT01384734, N=250, completion: September 2016), assessed the efficacy, safety and dose-response characteristics of the BMS-663068+raltegravir+TDF combination in HIV-treatment experienced people. The trial was designed with five groups: fostemsavir doses of 400mg or 800mg twice daily; or 600mg or 1200mg once daily; or ritonavir-boosted atazanavir as a control. At week 48, efficacy was similar across all groups in terms of virologic and immunologic outcomes. Fostemsavir was globally safe and well tolerated. There were less adverse events and no trends in laboratory abnormalities in the fostemsavir-arm compared with the boosted-protease inhibitor atazanavir (associated with hyperbilirubinemia or jaundice). The most recurrent adverse events were headaches, nausea and abdominal pain with most of them occurring in the atazanavir group. The only inconvenience of the fostemsavir treatment is the higher number of pills taken per day compared to the active control arm.

A multi-arm, randomised, double-blind, placebo-controlled, phase III clinical trial (NCT02362503, N=410, completion: May 2018), is investigating the efficacy of fostemsavir in HIV heavily treatment-experienced patients with multi-drug resistances.

- ⇨ BMS-663068/RAL/TDF targets HIV-treatment experienced patients, and competes with other combinations targeting this segment, including Fuzeon, Selzentry, DTG (replacing raltegravir in 3rd-line), BMS-955176 and antibodies.

■ A brand new therapeutic class: the maturation inhibitor BMS-955176

The final step of the HIV replication cycle is when complex polyproteins (Gag) are cut by protease enzymes and assembled to form the capsid around the viral RNA strand, resulting in new mature virions. Mature inhibitors block this final step leading to immature viruses that cannot infect other cells.

Bevirimat was the first generation maturation inhibitor, but it was withdrawn in 2010 for its antiviral potential that was limited for common Gag polymorphisms (Gag variations), and due to formulation problems.

BMS-955176, a small molecule, is of particular interest, since it demonstrated potential antiviral activity even in bevirimat-insensitive patients, and in patients with NRTI, nNRTI, PI drug resistance. BMS-955176 as a monotherapy showed a strong antiviral activity and no significant safety issue was reported from a phase IIa trial (NCT01803074, N=107). A randomised, active-controlled, open-label phase IIb clinical trial (NCT02386098, N=200, completion date: 2020) is assessing the safety, efficacy of BMS-955176 combined with dolutegravir and atazanavir (with/without booster) in HIV treatment-experienced adult participants. In parallel, the safety, efficacy and dose-response of BMS-955176 combined with tenofovir DF/emtricitabine are evaluated in HIV treatment-naïve subjects in a randomised, active-controlled (efavirenz), double-blind phase II trial (NCT02415595, N=200, completion: October 2017).

- ⇨ BMS-955176 targets both HIV treatment-naive and treatment-experienced patients, and is in combination with TDF/FTC (Tri-therapy) or DTG/ATV+/-ritonavir (Quad-therapy).
- ⇨ Synergies with other classes of antivirals could be interesting to investigate in order to optimise drug combinations.
- ⇨ If this new active compound demonstrates further efficacy, safety and tolerability in larger studies, then it would be the first maturation inhibitor to be approved (in combination with other ART drugs).

5. Conclusion

The figure below summarises what we understand from the HIV pipeline of the industry as of mid-2016, when classified by settings, i.e. treatment in first line and subsequent lines, maintenance therapy and prophylaxis. Obviously, Gilead and GSK/ViiV have the lion's share of it.

Fig. 19: Overview of the HIV pipeline positioning

TREATMENT			**TREATMENT**			**MAINTENANCE**			**PREVENTION**		
Treatment-naive			*Treatment-experienced*			*HIV-positive virologically suppressed*			*HIV-negative at risk*		
Major drugs on the market			Major drugs on the market			Major drugs on the market			Major drugs on the market		
Drug name	Company	2015 sales (mUSD)	Drug name	Company	2015 sales (mUSD)	Drug name	Company	2015 sales (mUSD)	Drug name	Company	2015 sales (mUSD)
Combivir (3TC/ZDV)	GSK	49	Selzentry (MVC)	GSK	178	Standard ART	GSK/Gilead		Truvada (FTC/TDF)	Gilead	3459
Descovy (FTC/TAF)	Gilead	N/A	Fuzeon (T-20)	Roche	?	Pipeline			Viread (TDF)	Gilead	1108
Epzicom (ABC/3TC)	GSK	1005	Tivicay (DTG)	GSK	846	DCI/code	Company	Launch date	Emtriva (FTC)	Gilead	?
Trizivir (ABC/3TC/ZDV)	GSK	37	Standard ART	GSK/Gilead		CAB LA/RPV LA	GSK	2019/2020	Pipeline		
Truvada (FTC/TDF)	Gilead	3459	Pipeline			DTG/RPV	GSK	H1 2018	DCI/code	Company	Launch date
Viread (TDF)	Gilead	1108	DCI/code	Company	Launch date	DRV/COB/F/TAF	Gilead	Q2 2019/2020	CAB monotherapy	GSK	2020+
Triumeq (ABC/DTG/3TC)	GSK	1051	Ibalizumab/TM-355	TaiMed Biologics	2020+	F/TAF	Gilead	2021/2022	CAB/VRC01	GSK	?
Atripla (EFV/FTC/TDF)	Gilead	3134	Pro 140	CytoDyn	2020+	GS-9883/F/TAF	Gilead	2019/2020			
Complera (FTC/RPV/TDF)	Gilead	1427	Fostemsavir/ BMS-663068	GSK	Q2 2019/2020	FTC/RPV/TAF (Odefsey)	Gilead	Q3 2019/2020			
Genvoya (EVG/COBI/FTC/TAF)	Gilead	45	BMS-955176	GSK	2023/2024						
Odefsey (FTC/TAF/RPV)	Gilead	N/A	Doravirine/MK-1439	Merck	Q1 2018/2019						
Stribild (EVG/COBI/FTC/TDF)	Gilead	1825									
Tivicay (DTG)	GSK	846									
Isentress (RAL)	Merck	1511									
Pipeline											
DCI/code	Company	Launch date									
Doravirine/MK-1439	Merck	2019/2020									
BMS-955176	GSK	2020/2021									
DTG/3TC	GSK	H1 2019									
GS-9883/F/TAF	Gilead	H1 2018									
DRV/COB/F/TAF	Gilead	Q2 2021/2022									

In « HIV treatment-experienced » patients, 3 subgroups overlap : 1/patients treated with their 2nd or further ART therapy, 2/patients on failing ART therapy due to multi-drug resistance, 3/patients treated with a successful ART therapy and with a stabilised viral load (<50 RNA copies/ml), also called "HIV-positive virologically-suppressed"

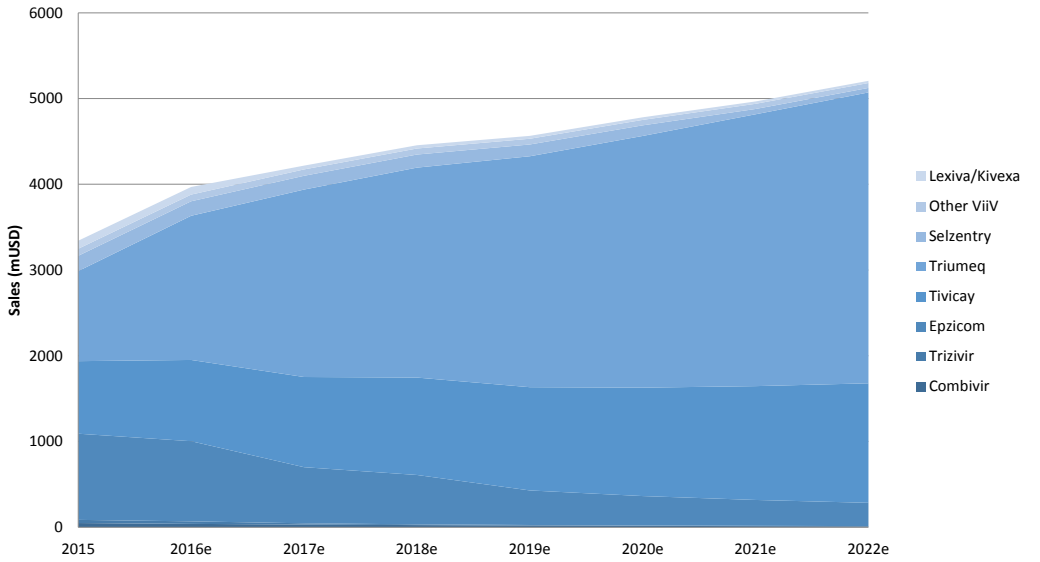
Source: Company Data; Bryan, Garnier & Co ests.

Fig. 20: Estimated sales of GSK's HIV products on the market (USDm)

Name	Molecule	Uniqueness	Launch date	Patent exp.	CAGR	2015	2016e	2017e	2018e	2019e	2020e	2021e	2022e
Combivir	3TC/ZDV	Genericised	1997-1998	2012	-20,00%	49	39	31	25	20	16	13	10
			1st-line Zidovudine replaced with other NRTI backbones (TDF, TAF); ZDV used in 2nd-line; Generics risks; progressive disappearance				-20%	-20%	-20%	-20%	-20%	-20%	-20%
Trizivir	3TC/ABC/ZDV	Me too; genericised	2000-2002	2016	-29,56%	37	30	15	9	6	5	4	3
			Will be totally cannibalized by Triumeq				-20%	-50%	-40%	-30%	-20%	-20%	-20%
Epzicom	ABC/3TC	Me too	2004	2016-2019	-17,06%	1,005	935	654	576	403	343	301	271
			Most often prescribed in combination with DTG; Major impact expected from generics				-7%	-30%	-12%	-30%	-15%	-12%	-10%
Tivicay	DTG	Unique	2013	2027	8,42%	846	948	1,052	1,146	1,238	1,339	1,419	1,490
			1st-line AND 2nd-line DHHS guidelines; DTG replaces raltegravir and efavirenz; best INSTI; but future DTG-based dual therapies will impact Tivicay sales (2018/2019/2020); GS-9883 is likely to compete with DTG from 2018				12%	11%	9%	8%	7%	6%	5%
Triumeq	ABC/3TC/DTG	Unique	2014	2029	18,22%	1,051	1,682	2,186	2,448	2,693	2,936	3,170	3,392
			1st-line AND 2nd-line gold-standard combination; recent launch; DTG/3TC positioning similar to Triumeq, might affect Triumeq; GS-9883/FTC/TAF will compete with DTG-based combinations from 2018				60%	30%	12%	10%	9%	8%	7%
Selzentry	Maraviroc, anti-CCR5	Me too	2007-2010	2021-2022	-16,00%	178	169	161	153	137	124	62	53
			No similar drug to compare with; Many drawbacks (costs, AE, restricted eligible patients); BMS-663068/RAL/TDF, BMS-955176/DTG/ATZ might be launched by 2019/2020 and offer alternatives; Generics will cut prices; might decrease sharply				-5%	-5%	-5%	-10%	-10%	-50%	-15%
Other ViiV	/	Genericised	/	/	-5,00%	82	78	74	70	67	63	60	57
			Generics impact:				-5%	-5%	-5%	-5%	-5%	-5%	-5%
Lexiva/Kivexa	Fosamprenavir FPV	Unique	2003	2017	-17,03%	94	89	44	38	34	30	28	25
			PI are used in 1st-line, or in treatment-experienced patients with drug resistance; but other alternatives maybe less toxic are in development; generics will cut price				-5%	-50%	-15%	-11%	-10%	-9%	-8%
TOTAL Drugs						**3,342**	**3,968**	**4,217**	**4,465**	**4,598**	**4,855**	**5,058**	**5,303**

Source: Company Data; Bryan, Garnier & Co ests

Fig. 21: Estimated sales of GSK's HIV products on the market (USDm)



Source: Company Data; Bryan, Garnier & Co ests.

As illustrated in the chart above, growth will remain strong in 2016 and 2017 despite Epzicom's patent expiry, as Tivicay and Triumeq are expected to gain further market shares. Beyond 2017, we expect growth to slow down as competition with Gilead intensifies and to derive exclusively from Triumeq until new drugs from the pipeline are approved.

Fig. 22: Estimated sales of GSK's HIV pipeline in USDm (risk-adjusted)

Molecules	Population	Comparable	Status	Launch US	Launch EU	PoS (%)	2015	2016	2017	2018	2019	2020	2021	2022
DTG/RPV	Maintenance	Not directly in this indication; FTC/TAF (Descovy); DTG/ABC/3TC (Triumeq)	III	2018	2019	55%	0	0	0	33	99	149	178	196
CAB LA/RPV LA	Maintenance	FTC/TAF (Descovy)	IIb	2019/20	2020/21	35%	0	0	0	0	0	18	53	79
CAB mono	Prevention	TDC/FTC (Truvada)	II/III	2025	2026	30%	0	0	0	0	0	0	0	0
BMS-663068 (attachment inhibitor)	Treatment-experienced	Enfuvirtide (Fuzeon); Maraviroc (selzentry)	III	2019	2020	50%	0	0	0	0	48	95	152	213
BMS- 955176 (maturation inhibitor)	Treatment-naive AND experienced	None directly;Enfuvirtide (Fuzeon); dolutegravir (tivicay) for its uniqueness	II	2020	2021	30%	0	0	0	0	0	27	108	216
DTG/3TC	Treatment-naive	DTG/ABC/3TC (Triumeq)	II	2019	2020	30%	0	0	0	0	29	86	145	167
TOTAL Pipeline							**0**	**0**	**0**	**33**	**175**	**374**	**636**	**871**

Source: Company Data; Bryan, Garnier & Co ests.

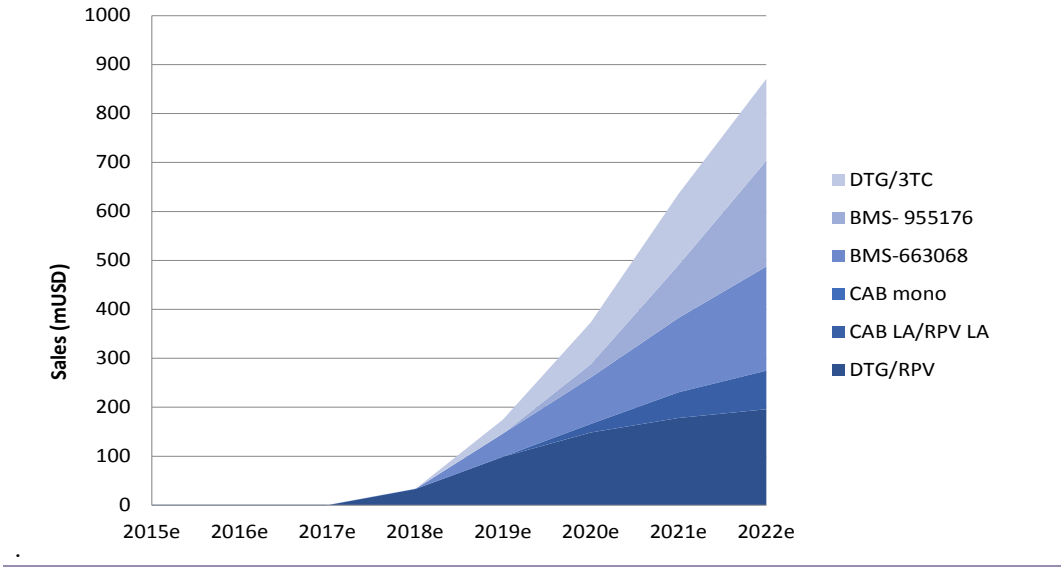
Our FV is increased by GBp40 as we factor in ViiV's pipeline for the first time

GSK/ViiV's pipeline has strengthened considerably over the last couple of years and can be divided into three parts: (i) two dolutegravir-based new combinations with 3TC and RPV to have an even more comprehensive range of FDC; (ii) two projects based on long-acting integrase inhibitor cabotegravir, one in monotherapy and the other in combination with RPV for maintenance therapy; and (iii) two innovative compounds acquired from BMS that could open up the way to new combinations once they have established their respective proof of concept (PoC) in monotherapy.

For the first time, at the end of this report, we are comfortable to add risk-adjusted sales from the ViiV pipeline to GSK's future sales estimates. Once the split in profits (with Shionogi, J&J and BMS) is considered and also when of course minority interests are adjusted, the net impact on our FV is GBp40 per share, hence **our new FV for GSK of GBp1,740**.

We've also tried to value GSK's stake in ViiV Healthcare separately from the rest of the business and although it is not easy to get all we need to do this, we came out with a number somewhere **between GBp20bn and GBp21bn or 430 pence per share** i.e. one quarter of our FV and much more than its weight in group's sales or profits.

Fig. 23: Estimated sales of GSK's HIV pipeline (risk-adjusted)

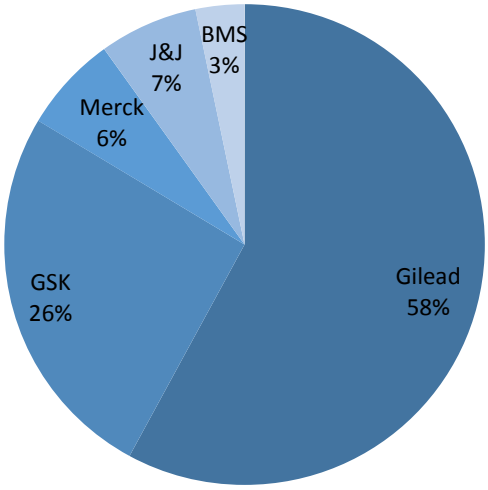


Source: Company Data; Bryan, Garnier & Co ests.

Altogether, when the existing portfolio and the risk-adjusted pipeline are considered, GSK's HIV turnover is expected to reach close to USD6bn in 2022, i.e. close to double the size achieved in 2015 and would account for 26% of the HIV market. Over the 2015-2022 period, CAGR would be 8.8%, when the underlying market is expected to grow by less than 2% per annum.

This is very consistent with a market that is increasingly moving towards fixed-dose combinations and we see mostly if not mainly Gilead and GSK/ViiV as the two companies that are heavily investing in the field to develop new ones. So, we see Merck, J&J (beyond RPV-based combinations) and even more clearly BMS (which divested its HIV portfolio to GSK in exchange for royalties and milestones) with eroding sales in HIV as they prioritise other therapeutic areas. Fig.11 showed that Gilead and GSK represented about 70% of the HIV market in 2015 and Fig.24 suggests that their combined share may reach 84-85% in 2022.

Fig. 24: In 2022, the duopoly in HIV is expected to be even more obvious



In 2022, the HIV market size would amount approx. USD23bn (CAGR < 2%). GSK's estimated sales would be c. USD6bn.

Source: Bryan, Garnier & Co ests.

6. Appendix

Fig. 26: GSK/ViiV sales

GBPm	2014		2015		Q1-16		2016e		2017e		2018e		2019e		2020e		2021e		2022e	
ViiV HealthCare	1 498		2 322	54%	729	57%	3 156		3 255		3 331		3 566		3 778		3 981		4 176	
US	670		1301	77%	426	76%	1799		1867		1910		1970		2064		2153		2233	
Europe	534		716	46%	221	39%	965		974		986		1092		1135		1205		1276	
Intl	294		305	15%	82	31%	392		413		436		505		579		623		667	
Trizivir	36	-61%	26	-28%	5	-43%	22		16		12		10		8		7		6	
US	10	-81%	9	-21%	1	-46%	7	-30%	5	-30%	3	-30%	2	-30%	2	-30%	1	-30%	1	-30%
Europe	22	-28%	14	-29%	3	-35%	13	-15%	11	-15%	9	-15%	8	-15%	7	-15%	6	-15%	5	-15%
Intl	4		3	-43%	1	-73%	3		0		0		0		0		0		0	
Combivir	59	-46%	34	-42%	5	-50%	28		23		19		16		13		11		9	
US	11	-67%	10	-17%	-1		10	-10%	9	-10%	8	-10%	7	-10%	6	-10%	6	-10%	5	-10%
Europe	18	-52%	9	-46%	2	-38%	8	-20%	6	-20%	5	-20%	4	-20%	3	-20%	3	-20%	2	-20%
Intl	30		15	-50%	4	-11%	11	-25%	8	-25%	6	-25%	5	-25%	3	-25%	3	-25%	2	-25%
Epzicom/Kivexa	768	8%	698	-7%	154	-15%	657		449		287		236		193		162		139	
US	274	7%	258	-14%	55	-12%	232	-15%	117	-50%	23	-80%	7	-70%	4	-50%	2	-50%	1	-50%
Europe	335	7%	304	-1%	70	-17%	293	-10%	205	-30%	143	-30%	115	-20%	80	-30%	56	-30%	39	-30%
Intl	159		136	-5%	29	-18%	131	-6%	127	-3%	121	-5%	115	-5%	109	-5%	104	-5%	98	-5%
Selzentry	136	0%	124	-8%	30	-3%	123		117		114		110		102		95		88	
US	53	-4%	60	2%	15	5%	60	-5%	58	-5%	55	-5%	52	-5%	47	-10%	42	-10%	38	-10%
Europe	58	-3%	48	-10%	12	-9%	49	-5%	46	-5%	46	0%	46	0%	44	-5%	42	-5%	40	-5%
Intl	25		16	-26%	3	-13%	14	-15%	13	-5%	13	-5%	12	-5%	11	-5%	11	-5%	10	-5%
Agenerase/Lexiva	87	-17%	65	-25%	14	-13%	51		40		29		22		17		13		10	
US	45	-24%	40	-21%	8	-24%	30	-30%	24	-20%	17	-30%	12	-30%	8	-30%	6	-30%	4	-30%
Europe	20	-25%	12	-32%	2	-39%	9	-30%	6	-30%	4	-30%	4	-15%	3	-10%	3	-10%	3	-10%
Intl	22		13	-27%	4	58%	13	0%	10	-20%	8	-20%	6	-20%	5	-20%	4	-20%	3	-20%
Tivicay + Triumeq	282		1318		516		2 232		2 575		2 819		3 028		3 167		3 237		3 306	
US	200		899		338		1 436	51%	1 636		1 775		1 810		1 845		1 845		1 845	
Europe	56		323		136		588		696		766		870		905		940		974	
Intl	26		96		42		208		244		278		348		418		452		487	
Pipeline ViiV											23		122		260		443		606	
US											13		67		143		244		333	
Europe											9		43		91		155		212	
Intl											1		12		26		44		61	
Others	130	5%	57		5		43		35		28		22		19		15		13	
US	77	55%	25	-27%	10	-1%	25	-5%	20	-20%	16	-20%	13	-20%	10	-20%	8	-20%	7	-20%
Europe	25	-30%	6	-36%	-4		5	-20%	4	-20%	3	-20%	3	-20%	2	-20%	2	-20%	1	-20%
Intl	28		26	0%	-1		13	-50%	11	-20%	8	-20%	7	-20%	6	-10%	5	-10%	5	-10%

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 27: HIV drug name abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonavir
COBI or c	cobicistat
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
EFV/c/TDF/FTC	efavirenz/cobicistat/tenofovir disoproxil fumarate/emtricitabine
ETR	etravirine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat
EVG/c/TAF/FTC	elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine
EVG/c/TDF/FTC	elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine
EVG/r	elvitegravir/ritonavir
FPV	fosamprenavir
FTC	emtricitabine
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MVC	maraviroc
NVP	nevirapine
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
TDF	tenofovir disoproxil fumarate
ZDV	zidovudine

Source: Company Data; Bryan, Garnier & Co ests.

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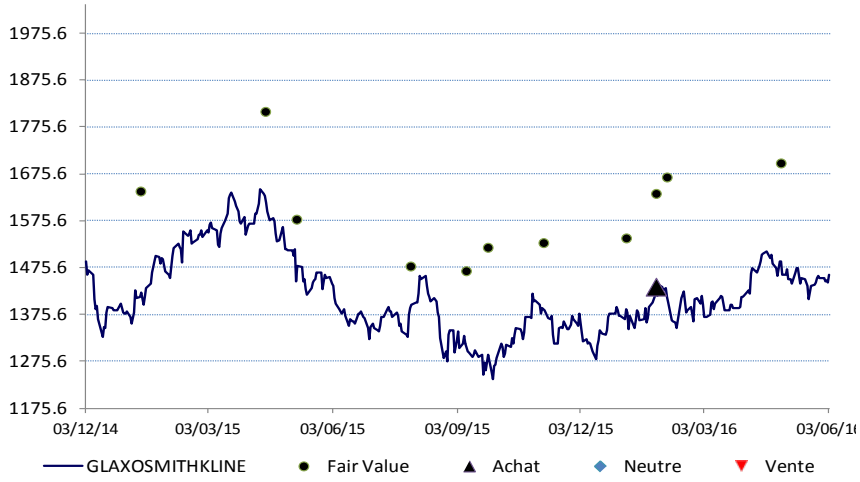
Price Chart and Rating History

GlaxoSmithKline



Ratings

Date	Ratings	Price
27/01/16	BUY	1400p
08/02/12	NEUTRAL	1406p
27/07/11	BUY	1373p
18/07/11	SELL	1330p

Target Price

Date	Target price
28/04/16	1700p
28/04/16	1700p
04/02/16	1670p
27/01/16	1635p
05/01/16	1540p
05/11/15	1530p
25/09/15	1520p
09/09/15	1470p
30/07/15	1480p
07/05/15	1580p
14/04/15	1810p
12/01/15	1640p
23/10/14	1650p
24/07/14	1685p
10/04/14	1755p
13/03/14	1765p
06/02/14	1750p
07/01/14	1850p
24/10/13	1810p
23/09/13	1870p
25/07/13	1900p
14/05/13	1940p

Please see the section headed "Important information" on the back page of this report.

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Stock rating

BUY — Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

NEUTRAL — Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

SELL — Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

Distribution of stock ratings

BUY ratings 56.2% NEUTRAL ratings 34% SELL ratings 9.7%

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