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HEALTH TECHNOLOGY BRIEFING
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Cabotegravir in combination with rilpivirine long acting injection for the treatment of HIV-1 infection

NIHRIO ID	17175	**NICE ID**	10226
Developer/Company	ViiV Healthcare UK	**UKPS ID**	645729

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Cabotegravir and rilpivirine long acting injections are in development for the treatment of HIV-1 patients that are considered clinically suitable for injectable therapy. HIV (Human Immunodeficiency Virus) is a type of viral infection caused by a virus referred as retrovirus. HIV-1 is the most common and highly communicable type of HIV. HIV is a lifelong, chronic disease that nowadays can be managed with antiretroviral therapies. Usually patients take between one and 4 or 6 tablets a day. Failing to do so will result in a weaken immune system and increased vulnerability to infections. Cabotegravir is a type of drug known as integrase inhibitor, is designed to block the action of a viral enzyme that inserts the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus. Rilpivirine is a non-nucleoside reverse transcriptase inhibitor, it binds to and blocks HIV reverse transcriptase (an HIV enzyme). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating. The injectable formulation of cabotegravir and rilpivirine administered once every two months has the potential to give people living with HIV two months between doses with similar safety and efficacy as today's standard of care.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of Human Immunodeficiency Virus- type 1 (HIV-1) infection – adults where a long-acting injectable is considered clinically appropriate.[a]

TECHNOLOGY

DESCRIPTION

Cabotegravir is a HIV-1 integrase strand transfer inhibitor (INSTI). Cabotegravir, an analog of dolutegravir, prevents viral DNA integration into the host genome and inhibits HIV replication.[1]

Rilpivirine (Edurant) is a diarylpyrimidine non-nucleoside reverse-transcriptase inhibitor (NNRTI) of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.[2]

Cabotegravir and rilpivirine are being evaluated as a long-acting (LA) formulation for intramuscular injection administered as two separate injections. The proposed dosage regimen consists of initial oral lead-in therapy with cabotegravir and rilpivirine, followed by cabotegravir 600mg + rilpivirine 900mg, as separate injections, once every two months.[a,b]

INNOVATION AND/OR ADVANTAGES

HIV treatment adherence to antiretroviral therapy (ART) remains unsatisfactory and varies between 27 and 80% across different population in various studies, compared with the required level of 95%.[3] The large number of pills that some patients have to take on daily basis is probably the most common complaint of HIV-patients. A meta-analysis performed on studies between 2005 and 2014 shows a significantly higher adherence in patients with a once-daily fixed-dose ("single tablet regimen") compared to any other treatment regimen.[4] The LA injectable regimen of cabotegravir and rilpivirine has the potential to give people living with HIV two months between doses with similar safety and efficacy as today's standard of care – an oral three-drug regimen that has to be taken every day.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

LA cabotegravir in combination with rilpivirine injections do not currently have Marketing Authorisation in the EU/UK for any indication.

Rilpivirine tablets in combination with other antiretroviral medicinal products, are indicated for the treatment of HIV-1 infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/ml.[6] The most frequent side effects with rilpivirine (seen in more than 1 patient in 10) are headache, insomnia, dizziness, nausea (feeling sick), and increased levels of total cholesterol, low-density-lipoprotein (LDL) cholesterol, pancreatic amylase (an enzyme produced in the pancreas that breaks down starch into sugars) and transaminases (liver enzymes).[7]

[a] Information provided by ViiV Healthcare UK Ltd in UK PharmaScan
[b] Information provided by ViiV Healthcare UK Ltd

Cabotegravir is also being studied as a once-daily oral tablet for use as lead-in to establish the tolerability of cabotegravir prior to long-acting injection.[5]

PATIENT GROUP

DISEASE BACKGROUND

HIV is a pathogen that works by attacking the human immune system. It belongs to a class of viruses called retroviruses and more specifically, a subgroup called lentiviruses, or viruses that cause disease slowly. HIV cannot replicate on its own, so in order to make new copies of itself, it must infect cells of the human immune system, called CD4 cells. CD4 cells are white blood cells that play a central role in responding to infections in the body. Over time, CD4 cells are killed by HIV and the body's ability to recognise and fight some types of infection begins to decline. If HIV is not controlled by treatment, the loss of CD4 cells leads to the development of serious illnesses, or 'opportunistic infections'. In people with normal CD4 cell levels, these infections would be recognised and cleared by the immune system. Experiencing a collection of these infections is the most advanced stage of HIV, which is when a person is also said to have AIDS (Acquired Immune Deficiency Syndrome). Effective testing and treatment of HIV means that the large majority of people living with HIV do not reach this stage.[8]

Although HIV can be controlled by ART, it cannot be eliminated from the body. This is because HIV evades the normal immune system mechanisms for getting rid of cells infected by viruses. HIV integrates itself into the DNA of human immune system cells and only replicates when the cell is stimulated to respond to an infection. These cells are called latently-infected cells. These cells are not recognised as infected by the immune system and killed off, allowing them to persist for as long as the cell lives. Some of the cells infected by HIV are very long-lasting memory T-cells. Reservoirs of latently- infected cells become established in the lymph nodes, the spleen and the gut. HIV also infects cells in the brain, but it is unclear if HIV can pass from the brain to other parts of the body. HIV may also persist for many years in macrophages – immune cells found largely in tissues – and in dendritic cells, which recognise infectious agents and alert other immune cells to remove them. Latently-infected cells can proliferate without being activated and HIV may also pass from cell to cell within tissues in the gut and other reservoirs. This means they evade the immune system and are not suppressed by antiretroviral drugs before infecting other cells. It's unclear how quickly a reservoir of HIV-infected cells becomes established in the body. Observations in small numbers of people who have started antiretroviral treatment within a few days or weeks of infection show that they have fewer HIV-infected cells and if they stop antiretroviral treatment, some can control HIV for long periods without resuming treatment.[8]

There are two main types of HIV – HIV-1 (the most common) and HIV-2 (relatively uncommon and less infectious).[9] The strains of HIV-1 can be classified into four groups. Of these, M is the 'major' group and is responsible for the majority of the global HIV epidemic.[9]

Most people diagnosed with HIV in the UK acquire the virus through unprotected vaginal or anal sex. Also HIV infection can be transmitted through unprotected oral sex and sharing sex toys with someone infected with HIV.[10] Other risk factors for getting HIV include sharing needles, syringes and other injecting equipment; transmission of the virus from mother to baby before or during birth or by breastfeeding; receiving unsafe injections, blood transfusions (now very rare in the UK); experiencing accidental needle stick injuries, including among health workers.[10,11]

People who are infected with HIV often experience a short flu like illness that occurs 2 to 6 weeks after infection. This is known as primary HIV infection. The most common symptoms

are fever (raised temperature), sore throat and body rash. Other symptoms can include tiredness, joint pain, muscle pain, swollen glands. After the initial symptoms disappear, HIV may often not cause any further symptoms for many years. During this time, HIV continues to be active and causes progressive damage to the immune system. Once the immune system becomes severely damaged, symptoms can include weight loss, chronic diarrhoea, night sweats, skin problems, recurrent infections, serious life-threatening illnesses.[12]

CLINICAL NEED AND BURDEN OF DISEASE

HIV-1 accounts for around 95% of all HIV infections worldwide.[9] In 2017, 92% (Credible interval (CrI) 88 to 94%) of the estimated 101,600 (CrI 99,300 to 106,400) people living with HIV infection in the UK were diagnosed, 98% of people diagnosed were receiving treatment and 97% of people receiving treatment were virally suppressed. Overall, 87% of people living with HIV in the UK were estimated to have an undetectable viral load and therefore unable to pass on the infection.[13]

The estimated annual number of new infections acquired by gay, bisexual and other men who have sex with men in the UK has more than halved from a peak of around 2,700 (95% CrI 2,200 to 3,200) in 2012 to 1,200 (CrI 600 to 2,100) in 2017. New HIV diagnoses in both black African and black Caribbean heterosexuals have been decreasing steadily over the past 10 years (black African: 78%, from 2,424 in 2008 to 542 in 2017; black Caribbean: 77%, from 231 to 52). Declines have been observed for the first time among non-black African and non-black Caribbean heterosexual men, particularly among white heterosexual men (31%, from 429 in 2016 to 296 in 2017).[13]

In the UK, the population of people living with diagnosed HIV infection (93,385) is growing older and diversifying. In 2017, 98% of people receiving care were on ART, and 97% on treatment had an undetectable viral load.[13] According to the Hospital Episodes Statistics for England between 2017 and 2018 there were a total of 2,663 admissions to hospital due to HIV disease resulting in infections or cancer (ICD-10 codes B20 to B24) as primary diagnosis.[14]

In 2017, 428 people with HIV infection died from any cause and over half of deaths (62%) were among people aged 50 years and over. In 2017, the crude overall mortality rate among those aged 15 to 59 years who had their HIV infection diagnosed promptly (CD4 cell count $\geqslant$350 cells/mm3) was 1.22 per 1,000.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

While there is no cure for HIV, there are very effective treatments that enable most people with the virus to live a long and healthy life.[15] Current British HIV guidelines recommend that people living with HIV should be given the opportunity to be involved in making decisions about their treatment.[16]

For people that have been exposed to the virus, post-exposure prophylaxis (PEP) must be started within 72 hours for it to be effective. For people that already have HIV, regular blood tests to monitor the progress of the HIV infection are recommended before starting treatment. The blood tests will measure the HIV viral load (the amount of HIV virus in the blood) and CD4 lymphocyte cell count (how the HIV has affected the person's immune

system). ART drugs can be started at any point after diagnosis. These drugs aim to stop the virus replicating in the body. Since HIV virus can quickly adapt and become resistant, a combination of drugs is normally used.[15] ART nearly always includes at least three active drugs.[17] Usually, people who have just been diagnosed with HIV take between 1 and 4 pills a day.[15]

CURRENT TREATMENT OPTIONS

There are six main types of drugs that work at different parts of the HIV life cycle, these include: nucleoside/tide reverse transcriptase inhibitors or nucleoside/tide analogues (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase (strand transfer) inhibitors (INIs or INSTIs), CCR5 inhibitors (a type of entry inhibitor), monoclonal antibodies (mAbs) – which also block entry to the CD4 cell and fusion inhibitors (another type of entry inhibitor).[18]

Treatment of HIV-1 infection is initiated with 2 nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, or an integrase inhibitor; the regimens of choice contain tenofovir disoproxil and emtricitabine with either efavirenz or ritonavir-boosted atazanavir, or ritonavir-boosted darunavir, or raltegravir. Alternative regimens contain abacavir and lamivudine with either lopinavir with ritonavir, or ritonavir-boosted fosamprenavir, or nevirapine, or rilpivirine.[19] A new formulation of tenofovir disoproxil, known as tenofovir alafenamide is indicated in combination with one or more HIV drugs for the treatment of HIV-1 infection is adults and/or adolescents (please refer to the eMC for the specific drug combination and populations).[20]

Zidovudine, a NRTI was the first anti-HIV drug to be introduced. Other NRTIs include abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir disoproxil.[19]

The PIs include atazanavir, darunavir, fosamprenavir (a pro-drug of amprenavir), lopinavir (available as lopinavir with ritonavir), ritonavir, saquinavir, and tipranavir. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, lopinavir (available as lopinavir with ritonavir), saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. The PIs are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. PIs are associated with lipodystrophy and metabolic effects.[19]

The NNRTIs efavirenz, etravirine, nevirapine, and rilpivirine are used in the treatment of HIV-1 infection. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other NNRTIs and PIs.[19] Doravirine is indicated in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class.[21]

Enfuvirtide, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide, as well as other antiretroviral drugs, should be combined with other potentially active antiretroviral drugs.[19]

Maraviroc is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV.[19]

Dolutegravir, elvitegravir and raltegravir are inhibitors of HIV integrase. They are licensed for the treatment of HIV infection in combination with other antiretroviral drugs.[19]

Cobicistat is a pharmacokinetic enhancer that boosts the concentrations of other antiretrovirals, but it has no antiretroviral activity itself.[19]

PLACE OF TECHNOLOGY

If licenced for this indication, long-acting cabotegravir in combination with rilpivirine intramuscular injections administered every 2 months may potentially become a well-tolerated and effective therapy substitute to the daily oral standard three-drug regimen that can improve patient adherence whilst achieving equal viral suppression than in the oral regimen.

CLINICAL TRIAL INFORMATION

Trial	**LATTE, NCT01641809; adults 18 years and over; once daily cabotegravir and rilpivirine oral induction and investigator-selected background NRTIs; phase II**	**LATTE 2, NCT02120352, EudraCT- 2013-000783-29; adults 18 years and over; intramuscular LA injection of cabotegravir and rilpivirine after oral induction with cabotegravir and fixed dose combination (FDC) abacavir/lamivudine vs oral regimen of cabotegravir plus FDC of abacavir/lamivudine, phase IIb extension**
Sponsor	ViiV Healthcare	ViiV Healthcare
Status	Completed and published	Ongoing and published
Source of Information	Trial registry,[22] Publication[23]	Trial registry,[24] Publication[25]
Location	USA and Canada	EU (not incl UK), USA and Canada
Design	Randomised, active-controlled	Randomised, active-controlled, open label
Participants	n=244; aged 18 and over; screening plasma HIV-1 RNA >=1000 c/mL, CD4+ cell count >=200 cells/millimetre (mm)^3, ART-naive defined as having =<10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection.	n=309; aged 18 and over; HIV-1 infection as documented by Screening plasma HIV-1 RNA>=1000 c/mL; CD4+ cell count >=200 cells/mm^3 (or higher as local guidelines dictate); ART-naive defined as having no more than 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection. Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor will be exclusionary.
Schedule	Randomised to: • Experimental: Arm 1 cabotegravir 10 mg In the Induction Phase subjects will receive oral tablets of cabotegravir 10 mg + matching placebo +	Randomised to: • Experimental: Cabotegravir LA 600 mg + rilpivirine LA 900 mg every 8 weeks for 96 weeks

	investigator-selected background NRTIs (either abacavir/lamivudine or tenofovir/emtricitabine) once daily from Day 1 to Week 24. Subjects continuing in the Maintenance Phase will receive oral tablets of cabotegravir 10 mg + matching placebo + Rilpivirine 25 mg once daily from Week 24 to Week 96. • Experimental: Arm 2 cabotegravir 30 mg In the Induction Phase subjects will receive oral tablets of cabotegravir 30 mg + matching placebo + investigator-selected background NRTIs (either abacavir/lamivudine or tenofovir/emtricitabine) once daily from Day 1 to Week 24. Subjects continuing in the Maintenance Phase will receive oral tablets of cabotegravir 30 mg + matching placebo + Rilpivirine 25 mg once daily from Week 24 to Week 96. • Experimental: Arm 3 cabotegravir 60 mg In the Induction Phase subjects will receive oral tablets of cabotegravir 60 mg + investigator-selected background NRTIs (either abacavir/lamivudine or tenofovir/emtricitabine) once daily from Day 1 to Week 24. Subjects continuing in the Maintenance Phase will receive oral tablets of cabotegravir 60 mg + Rilpivirine 25 mg once daily from Week 24 to Week 96. • Active Comparator: Arm 4 efavirenz 600 mg In the Induction Phase and Maintenance Phase subjects will receive oral tablets of efavirenz 600 mg + investigator-selected background NRTIs (either abacavir/lamivudine or tenofovir/emtricitabine).	• Experimental: Cabotegravir LA 400 mg + rilpivirine LA 600 mg every 4 weeks for 96 weeks • Active Comparator: oral regimen of Cabotegravir 30 mg once daily plus Abacavir/Lamivudine 600/300 mg once daily for 96 weeks or 104 if going on to the extension period. For all arms in the Induction Period of 20 weeks, subjects will receive an oral regimen of Cabotegravir 30 mg once daily plus FDC Abacavir/Lamivudine 600/300 mg once daily. In the last 4 weeks of the Induction Period subjects will also receive rilpivirine 25 mg tablet once daily.
Follow-up	Active treatment for 96 weeks	Active treatment for 96 weeks
Primary Outcomes	• Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 [Time Frame: 48 weeks]	• The proportion of subjects with HIV-1 Ribonucleic acid (RNA) <50 copies/millilitre (c/mL) at Maintenance Week 32 [Time Frame: Week 32]

		• The proportion of subjects with protocol defined virologic failures over time [Time Frame: Up to Week 96/Withdrawal] • Incidence and severity of adverse events (AEs) over time [Time Frame: Up to Week 96/Withdrawal] • Incidence and severity of laboratory abnormalities over time [Time Frame: Up to Week 96/Withdrawal]
Secondary Outcomes	• Proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL over time by visit [Time Frame: Through Week 96] • Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 16 and Week 24 in Induction Phase [Time Frame: 16 weeks, 24 weeks] • The proportion of subjects with HIV-1 RNA <50 copies/mL from Week 24 through Week 96 by visit in Maintenance Phase [Time Frame: 24 weeks through Week 96] • Absolute values and change from Baseline in plasma HIV-1 RNA by visit [Time Frame: Baseline (Study Day 1), and up to Week 96] • Incidence of disease progression [Time Frame: Up to Week 96] • Absolute values and changes from baseline in CD4+ cell counts by visit [Time Frame: Baseline (Study Day 1), and up to Week 96] • Incidence of treatment emergent genotypic and phenotypic resistance to cabotegravir, RPV and other on-study ART for protocol-defined	• Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Up to Week 96/Withdrawal] • Absolute values and change from Baseline in plasma HIV-1 RNA, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Baseline to Week 96] • Absolute values and changes from Baseline in CD4+ cell counts, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Baseline to Week 96] • Incidence of disease progression for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Up to Week 96/Withdrawal] • Incidence and severity of AEs over time, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Up to Week 96/Withdrawal]

	virologic failures [Time Frame: Up to Week 96] • Incidence and severity of Adverse Events (AEs) and laboratory abnormalities over time [Time Frame: Up to Week 96] • Absolute values and changes in laboratory parameters by visit [Time Frame: Up to Week 96] • Proportion of subjects who discontinue treatment due to AEs [Time Frame: Up to Week 96] • Incidence of any clinically significant changes in QRS duration, QTc interval, HR, PR interval based on electrocardiograph (ECG) readings by visit [Time Frame: Baseline (Study Day 1), and up to Week 96] • Plasma cabotegravir pharmacokinetic (PK) parameters [area under the concentration time curve over the dosing interval (AUC[0-tau]), maximum observed concentration (Cmax), and concentration at the end of a dosing interval (Ctau)] [Time Frame: 2 weeks, 12 weeks, 26 weeks, and 36 weeks (Pre-dose and 2 to 4 hours (h) post dose)] • Plasma rilpivirine PK parameters [AUC(0-tau), Cmax, Ctau] [Time Frame: 2 weeks, 12 weeks, 26 weeks, and 36 weeks (Pre-dose and 2 to 4 hours (h) post dose)] • Adherence to IP [Time Frame: Up to Week 96]	• The incidence and severity of laboratory abnormalities over time, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Up to Week 96/Withdrawal] • Absolute values and changes in laboratory parameters over time, for oral dose of Cabotegravir 30 mg plus Abacavir/Lamivudine [Time Frame: Up to Week 96/Withdrawal] • Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Proportion of subjects with protocol defined virologic failures over time, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • The absolute values and change from Baseline in plasma HIV-1 RNA, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus

		Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Absolute values and changes from Baseline in CD4+ cell counts, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • The incidence of disease progression for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Incidence of disease progression through Week 96 of the Maintenance Period. [Time Frame: Up to Week 96/Withdrawal] • Incidence and severity of AEs, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Incidence and severity of laboratory abnormalities, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg

		every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Absolute values and changes in laboratory parameters, for Cabotegravir LA 400 mg IM plus rilpivirine LA 600 mg IM every 4 weeks and Cabotegravir LA 600 mg IM plus rilpivirine LA 900 mg every 8 weeks, relative to Cabotegravir 30 mg plus Abacavir/Lamivudine orally once daily [Time Frame: Up to Week 96/Withdrawal] • Plasma pharmacokinetic (PK) parameters for Cabotegravir LA and rilpivirine LA during the Maintenance Period [Time Frame: Up to Week 96/Withdrawal] • Plasma Cabotegravir and rilpivirine trough concentrations [Time Frame: Up to Week 96/Withdrawal] • PK-pharmacodynamic (PD) assessment for Cabotegravir LA and rilpivirine LA [Time Frame: Up to Week 48] • Incidence of treatment emergent genotypic and phenotypic resistance to Cabotegravir, rilpivirine, and other on-study Antiretroviral Therapy (ART). [Time Frame: Up to Week 96/Withdrawal] • The proportion of subjects with plasma HIV-1 RNA <50 c/mL over time. [Time Frame: Up to Week 96/Withdrawal]

		• To evaluate the treatment satisfaction for subjects on the long-acting injectable regimens with those on the oral regimen using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)), through Week 96 of the Maintenance Period. [Time Frame: Up to Week 96/Withdrawal] • To evaluate the change in treatment satisfaction for subjects using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ[c]) through Week 32 of the Maintenance Period. [Time Frame: Up to Week 32] • To evaluate medication adherence over time using the HIV Medication Questionnaire (HIVMQ). [Time Frame: Up to Week 96/Withdrawal]
Key Results	Of 243 patients randomly allocated and treated, 156 (86%) of 181 patients in the cabotegravir groups (52 [87%] of 60, 51 [85%] of 60, and 53 [87%] of 61 patients in the 10 mg, 30 mg, and 60 mg groups, respectively) and 46 (74%) of 62 in the efavirenz group had fewer than 50 copies per mL of HIV-1 RNA after induction therapy. After patients in the cabotegravir groups were changed over from dual NRTIs to rilpivirine at week 24, 149 (82%; 95% CI 77-88) patients in the cabotegravir groups (48 [80%; 70-90], 48 [80%; 70-90], and 53 [87%; 78-95] patients in the 10 mg, 30 mg, and 60 mg groups, respectively) versus 44 (71%; 60-82) in the efavirenz group were virologically suppressed at week 48, and 137 (76%; 69-82) receiving cabotegravir (41 [68%; 57-80], 45 [75%; 64-86], and 51 [84%; 74-93] patients in the 10 mg, 30 mg, and 60 mg groups, respectively) versus 39 (63%; 51-75)	This study is currently ongoing. At 32 weeks following randomisation, both long-acting regimens met primary criteria for comparability in viral suppression relative to the oral comparator group. Viral suppression was maintained at 32 weeks in 51 (91%) of 56 patients in the oral treatment group, 108 (94%) of 115 patients in the 4-week group (difference 2·8% [95% CI -5·8 to 11·5] vs oral treatment), and 109 (95%) of 115 patients in the 8-week group (difference 3·7% [-4·8 to 12·2] vs oral treatment). At week 96, viral suppression was maintained in 47 (84%) of 56 patients receiving oral treatment, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group.

	in the efavirenz group were virologically suppressed at week 96.	
Adverse effects (AEs)	Treatment-related adverse events were reported by 93 (51%) cabotegravir-treated patients (28 [47%], 32 [53%], and 33 [54%] patients in the 10 mg, 30 mg, and 60 mg groups, respectively) and 42 (68%) efavirenz-treated patients. Six (3%) patients in the cabotegravir groups (one [2%], one [2%], and four [7%] patients in the 10 mg, 30 mg, and 60 mg groups, respectively) withdrew because of treatment-emergent adverse events compared with nine (15%) in the efavirenz group.	Three patients (1%) experienced protocol-defined virological failure (two in the 8-week group; one in the oral treatment group). Injection-site reactions were mild (3648 [84%] of 4360 injections) or moderate (673 [15%] of 4360 injections) in intensity and rarely resulted in discontinuation (two [<1%] of 230 patients); injection-site pain was reported most frequently. Serious adverse events during maintenance were reported in 22 (10%) of 230 patients in the intramuscular groups (4-week and 8-week groups) and seven (13%) of 56 patients in the oral treatment group; none were drug related.
Expected reporting date	Previously reported as Oct 2013	Previously reported as Aug 2015. Study completion date December 2020.

Trial	**POLAR, NCT03639311; adults 18 years and over; intramuscular LA injections of cabotegravir (CAB) and rilpivirine (RPV) vs oral fixed dose combination (FDC) of dolutegravir plus rilpivirine; phase IIb**
Sponsor	ViiV Healthcare
Status	Ongoing
Source of Information	Trial registry[26]
Location	USA and Canada
Design	Non-Randomised, open-label
Participants	N=98; aged 18 and over; Must have been on oral cabotegravir 30 mg plus rilpivirine 25 mg regimen through at minimum Week 300 of the LATTE study as per LATTE protocol dosing requirements and until Day 1 of the POLAR study; Plasma HIV-1 RNA <50 c/mL at Week 300
Schedule	Participants allocated (non-randomised) to: • Experimental: subjects from LATTE trial, who were administered oral cabotegravir 30 mg plus rilpivirine 25 mg, who successfully complete week 300 (experimental arm 2) receive Injection cabotegravir 600 mg LA + rilpivirine 900 mg LA injections within 2 hours of the final oral dose of LATTE given on the same day. The second loading injections will be administered 1 month after initial loading dose (CAB LA 600 mg plus RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring Q2M thereafter. Subjects will continue to receive the treatment until the study intervention is locally approved and commercially available. HAART therapy will be initiated within 8 weeks after the last Q2M injection.

	• Experimental: subjects from LATTE, who were administered oral Cabotegravir 30 mg plus rilpivirine 25 mg, who successfully complete week 300 (experimental arm 2) receiving Oral dolutegravir plus rilpivirine on Day 1 until Month 12. Subjects will continue to receive the treatment until the study intervention is locally approved and commercially available.
Follow-up	Active treatment for 12 months
Primary Outcomes	• Number of subjects with HIV-RNA >=50 c per mL as per Food and Drug Administration (FDA) Snapshot algorithm at Month 12 [Time Frame: Month 12]
Secondary Outcomes	• Number of subjects with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 12 using the FDA Snapshot algorithm [Time Frame: At Month 12] • Number of subjects with protocol defined confirmed virologic failure (CVF) over time [Time Frame: Up to 40 months] • Number of subjects with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm over time [Time Frame: Up to 40 months] • Absolute values of HIV- viral load over time [Time Frame: Up to 40 months] • Absolute values of cluster of differentiation 4 (CD4+) cell counts over time [Time Frame: Up to 40 months] • Change from Baseline in HIV viral load over time [Time Frame: Baseline and Up to 40 months] • Change from Baseline in CD4+ cell count over time [Time Frame: Baseline and Up to 40 months] • Number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Up to 40 months] • Number of subjects who discontinue treatment due to AEs over time. [Time Frame: Up to 40 months] • Number of subjects with abnormal haematology findings [Time Frame: Up to 40 months] • Number of subjects with abnormal clinical chemistry findings [Time Frame: Up to 40 months] • Number of subjects with abnormal lipid findings [Time Frame: Up to 40 months] • Change from Baseline in haematology parameters of platelets, WBC count, basophils, eosinophils, lymphocytes, monocytes and neutrophils [Time Frame: Baseline and Up to 40 months]

	• Change from Baseline in haematology parameters of RBC count [Time Frame: Baseline and Up to 40 months] • Change from Baseline in haematology parameters- Haemoglobin [Time Frame: Baseline and Up to 40 months] • Change from Baseline in haematology parameter of haematocrit [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of sodium, potassium, carbon-dioxide (total), chloride, and glucose [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of creatinine and total bilirubin [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of ALT, ALP and AST [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of Creatine phosphokinase [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of Creatinine clearance [Time Frame: Baseline and Up to 40 months] • Change from Baseline in clinical laboratory parameters of lipase [Time Frame: Baseline and Up to 40 months] • Change from Baseline in urinalysis parameters, urine albumin to creatinine ratio [Time Frame: Baseline and Up to 40 months] • Change from Baseline in urinalysis parameters, urine protein to creatinine ratio [Time Frame: Baseline and Up to 40 months] • Change from Baseline in urinalysis parameters, urine phosphate [Time Frame: Baseline and Up to 40 months] • Change from Baseline in fasting lipid parameters: Total cholesterol, HDL cholesterol, LDL cholesterol, and Triglycerides [Time Frame: Baseline and Up to 40 months] • Number of subjects with treatment emergent genotypic resistance for cabotegravir, rilpivirine, and DTG plus rilpivirine [Time Frame: Up to 40 months] • Trough concentrations (Ctrough) for cabotegravir LA [Time Frame: Pre-dose: Day 1 and Month 12] • Number of subjects with treatment emergent phenotypic resistance for cabotegravir, rilpivirine, and DTG plus rilpivirine [Time Frame: Up to 40 months]

	• Ctrough for rilpivirine LA [Time Frame: Pre-dose: Day 1 and Month 12] • Change from Baseline (Day 1) in HIV Dependent Quality of Life (HIVDQoL) [Time Frame: Baseline and Up to Month 12] • Change from baseline (Day 1) in HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) [Time Frame: Baseline and Up to Month 12] • Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire (HIVTSQc) [Time Frame: Baseline and Up to Month 12]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as January 2020

Trial	**ATLAS**, NCT02951052, EudraCT-2016-001647-39; **adults 18 years and over; cabotegravir LA and rilpivirine LA administered every 4 weeks vs continued standard antiretroviral treatment; phase III**	**ATLAS 2-M**, NCT03299049, EudraCT-2017-002946-62; **adults 18 years and over, cabotegravir (CAB) LA and rilpivirine (RPV) LA administered every 8 weeks (Q8W) compared to cabotegravir LA and rilpivirine LA administered every 4 weeks (Q4W); phase III extension**
Sponsor	ViiV Healthcare	ViiV Healthcare
Status	Ongoing and published	Ongoing
Source of Information	Trial registry,[27] Manufacturer;[28] Conference Presentation[29]	Trial registry,[30] Manufacturer[31]
Location	US, Canada, Europe (not inc UK), and other countries	US, Canada, Europe (not inc UK), and other countries
Design	Randomised, active-controlled	Randomised, active-controlled, open-label study
Participants	N= 618, adults aged 18 and over, virologically suppressed on current treatment with plasma HIV-1 RNA <50 c/mL at screening	N=1049, adults aged 18 and over; subjects receiving oral SOC treatment for HIV-1 (not participating in ATLAS Trial) Documented evidence of at least two plasma HIV-1 RNA measurements <50 copies/mL in the 12 months prior to Screening: one within the 6 to 12-month window, and one within 6 months prior to Screening; Participants transitioning from 201585

		(ATLAS): plasma HIV-1 RNA <50 copies/mL at Screening.
Schedule	Randomised to: • Experimental: cabotegravir LA + rilpivirine LA every 4 weeks Eligible subjects receive Oral cabotegravir 30 mg + rilpivirine 25 mg once daily for four weeks, IM cabotegravir LA 600 mg and rilpivirine LA 900 mg for the first injection, and Week 4 onwards subjects will receive cabotegravir LA (400 mg) + rilpivirine LA (600 mg) injections every 4 weeks until withdrawal. • Active Comparator: Current antiretroviral regimen Eligible subjects will continue their current anti-retroviral regimen (2 NRTIs plus an INI, NNRTI, or a PI) for 52 weeks. After 52 weeks subjects have the option to continue study participation by switching to cabotegravir LA + rilpivirine LA in the Extension Phase where they will follow the procedure of cabotegravir LA + rilpivirine LA arm.	Randomised to: • Experimental: Subjects in group 1 receiving study treatment once in 4 weeks Group 1 will consist of subjects randomized from current ART SOC therapy. Subjects in group 1 will be randomized to receive CAB LA plus RPV LA Q4W via intramuscular (IM) route. All subjects will receive oral therapy with CAB 30 mg + RPV 25 mg once daily prior to randomization. • Experimental: Subjects in group 1 receiving study treatment once in 8 weeks Group 1 will consist of subjects randomized from current ART SOC therapy. Subjects in group 1 will be randomized to receive CAB LA plus RPV LA Q8W via IM route. All subjects will receive oral therapy with CAB 30 mg + RPV 25 mg once daily prior to randomization. • Experimental: Subjects in group 2 receiving study treatment once in 4 weeks Group 2 will consist of subjects currently receiving CAB LA + RPV LA Q4W in ATLAS study. Subjects in Group 2 will be randomized to continue CAB LA plus RPV LA Q4W administration via IM route. • Experimental: Subjects in group 2 receiving study treatment once in 8 weeks Group 2 will consist of subjects currently receiving CAB LA + RPV LA Q4W in ATLAS study. Subjects in Group 2 will be randomized to receive CAB LA plus RPV LA Q8W via IM route.
Follow-up		
Primary Outcomes	• Number of Participants With Virologic Failure (HIV-1 Ribonucleic Acid [RNA] >=50 Copies Per Millilitre [mL]) Using Snapshot Algorithm at Week 48 [Time Frame: Week 48]	• Percentage of subjects with plasma HIV ribonucleic acid (RNA) >=50 copies per millilitre (copies/mL) at Week 48 [Time Frame: Week 48]

Secondary Outcomes	• Number of Participants With HIV-1 RNA <50 Copies/mL Using Snapshot Algorithm at Week 48 [Time Frame: Week 48] • Number of Participants With HIV-1 RNA <200 Copies/mL Using Snapshot Algorithm at Week 48 [Time Frame: Week 48] • Number of Participants With Confirmed Virologic Failure (CVF) [Time Frame: Week 48[c]] • Absolute Values for Plasma HIV-1 RNA at Week 48 [Time Frame: Week 48] • Change From Baseline Values for Plasma HIV-1 RNA [Time Frame: Baseline and Week 48] • Absolute Values for CD4+ Lymphocyte Count at Week 48 [Time Frame: Week 48] • Change From Baseline Values for CD4+ Lymphocyte Count at Week 48 [Time Frame: Baseline (Day 1) and Week 48] • Number of Participants With Disease Progression [Time Frame: Up to Week 48] • Number of Participants With Non-serious Adverse Events (Non-SAEs) and Serious Adverse Events (SAEs) [Time Frame: Up to Week 48] • Severity of Adverse Events [Time Frame: Up to Week 48][d] • Absolute Values for Haematology Parameters Over Time Including Week 48: Basophil, Eosinophils, Leukocytes, Lymphocytes,	• Percentage of subjects with plasma HIV-1 RNA <50 copies/mL [Time Frame: Up to Week 96] • Percentage of subjects with protocol-defined confirmed virologic failure (CVF) [Time Frame: Up to Week 96] • Percentage of subjects with HIV-RNA >=50 copies/mL [Time Frame: Up to Week 96] • Change from Baseline in viral load [Time Frame: Baseline and Up to Week 96] • Change from Baseline in cluster of differentiation (CD)4+ cell counts [Time Frame: Baseline and Up to Week 96] • Number of subjects with Adverse events (AEs) and serious AEs [Time Frame: Up to Week 96] • Number of subjects with abnormal clinical chemistry values [Time Frame: Up to Week 96] • Number of subjects with abnormal clinical hematology values [Time Frame: Up to Week 96] • Percentage of subjects who discontinue treatment due to AEs [Time Frame: Up to Week 96] • Change from Baseline in albumin [Time Frame: Baseline and up to Week 96] • Change from Baseline in Alkaline phosphatase, ALT, AST, creatine phosphokinase,

[c] Information provided by ViiV Healthcare UK Ltd
[d] Information provided by ViiV Healthcare UK Ltd

	Neutrophils, Monocytes, and Platelets [Time Frame: up to week 48]**Error! Bookmark not defined.** • Absolute Values for Haematology Parameters: Erythrocyte Mean Corpuscular Volume [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Haematology Parameters: Erythrocytes [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Haematology Parameters: Haemoglobin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Haematology Parameters: Haematocrit [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline for Haematology Parameters: Basophil, Eosinophils, Leukocytes, Lymphocytes, Neutrophils, Monocytes, and Platelets [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline for Haematology Parameters: Erythrocyte Mean Corpuscular Volume [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline for Haematology Parameters:	lipase [Time Frame: Baseline and up to Week 96] • Change from Baseline in total bilirubin and creatinine [Time Frame: Baseline and up to Week 96] • Change from Baseline in glucose, sodium, potassium, total CO2, BUN, chloride, phosphate [Time Frame: Baseline and up to Week 96] • Change from Baseline in total cholesterol, High density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides [Time Frame: Baseline and Up to Week 96] • Change from Baseline in creatinine clearance [Time Frame: Baseline and Up to Week 96] • Change from Baseline in basophils, eosinophils, monocytes, lymphocytes, neutrophils and platelet count [Time Frame: Baseline and Up to Week 96] • Change from Baseline in haematocrit levels [Time Frame: Baseline and Up to Week 96] • Change from Baseline in haemoglobin levels [Time Frame: Baseline and Up to Week 96] • Change from Baseline in RBC count [Time Frame: Baseline and Up to Week 96] • Change from Baseline in WBC count [Time Frame: Baseline and Up to Week 96]

	Erythrocytes [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline for Haematology Parameters: Haematocrit [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline for Haematology Parameters: Haemoglobin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Over Time Including Week 48: Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST) and Creatinine Kinase (CK) [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameter Over Time Including Week 48: Albumin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Over Time Including Week 48: Bilirubin, Direct Bilirubin and Creatinine [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters: Total Carbon-dioxide (CO2), Chloride, Glucose, Phosphate, Potassium, Sodium and Urea Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at	• Change from Baseline in MCV levels [Time Frame: Baseline and Up to Week 96] • Number of incidences of treatment emergent genotypic resistance [Time Frame: Up to Week 96] • Number of incidences of treatment emergent phenotypic resistance [Time Frame: Up to Week 96] • Trough plasma concentration (Ctrough) of CAB LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • Ctrough of RPV LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • Ctrough of CAB LA: Q8W dosing [Time Frame: Pre-dose at Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • Ctrough of RPV LA: Q8W dosing [Time Frame: Pre-dose at Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • Maximum plasma concentration (Cmax) of CAB LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • Cmax of RPV LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • Cmax of CAB LA: Q8W dosing [Time Frame: Pre-dose at Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • Cmax of RPV LA: Q8W dosing [Time Frame: Pre-dose at

	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameter Over Time Including Week 48: Lipase [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameter Over Time Including Week 48: Creatinine Clearance [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Number of Participants With Abnormal Urinalysis Parameters Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48.] • Number of Participants With Urine Potential of Hydrogen (pH) Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Change From Baseline in Clinical Chemistry Parameters Over Time Including Week 48: ALT, ALP, AST and CK [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameter Over Time Including Week 48: Albumin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Over Time Including Week 48: Bilirubin, Direct Bilirubin and Creatinine [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48]	Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • Area under the curve (AUC) of CAB LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • AUC of RPV LA: Q4W dosing [Time Frame: Pre-dose at Week 4B, 8, 16, 24, 32, 40, 48 and 96] • AUC of CAB LA: Q8W dosing [Time Frame: Pre-dose at Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • AUC of RPV LA: Q8W dosing [Time Frame: Pre-dose at Week 8, 9, 16, 24, 32, 40, 41, 48 and 96] • Number of subjects with different demographic parameters: For inter-participant variability [Time Frame: Up to Week 96] • Number of subjects with different demographic parameters: For intra participant variability [Time Frame: Up to Week 96] • Change from Baseline in health related quality of life (HRQoL) of subjects using the HIV/Acquired immunodeficiency syndrome (AIDS) Targeted Quality of Life (HAT-QoL) questionnaire [Time Frame: Baseline and up to Week 48] • Change from Baseline in total "treatment satisfaction" score of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) [Time Frame: Baseline and up to Week 48]

	• Change From Baseline Values for Clinical Chemistry Parameters Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameter Over Time Including Week 48: Lipase [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameter Over Time Including Week 48: Creatinine Clearance. [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Fasting Lipid Panel Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Week 48] • Change From Baseline Values in Urine Albumin/Creatinine Ratio and Urine Protein/Creatinine Ratio Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Change From Baseline Values in Urine Creatinine Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Change From Baseline Values in Urine Phosphate Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Change From Baseline Values in Urine Retinol Binding Protein Over Time Including Week 48 [	• Change from Baseline in individual item score of HIVTSQs [Time Frame: Baseline and Up to Week 48] • Change in treatment satisfaction using the HIV Treatment Satisfaction Change Questionnaire (HIVTSQc) [Time Frame: Week 48] • Change from Week 8 in Dimension scores using the Perception of injection questionnaire (PIN) [Time Frame: Week 8 and up to Week 48] • Change from Week 8 in individual item score using PIN [Time Frame: Week 8 and Up to Week 48] • Change from Baseline in treatment acceptance using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire [Time Frame: Baseline and up to Week 48] • CD4+ cell counts [Time Frame: Baseline and up to Week 96] • Number of subjects preferring CAB LA+ RPV LA injectable treatment, using preference questionnaire [Time Frame: Week 48] • Number of subjects preferring CAB LA + RPV LA Q8W, using preference questionnaire [Time Frame: Week 48]

	Time Frame: Baseline (Day 1) and at Week 48] • Change From Baseline Values in Urine Specific Gravity Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Change From Baseline Values in Urine pH Over Time Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 24 and 48] • Number of Participants Who Discontinued or Withdrawn Due to AEs Over Time Including Week 48 [Time Frame: Up to Week 48] • Percentage Change From Baseline in Fasting Lipids Overtime Including Week 48 [Time Frame: Baseline (Day 1) and at Week 48] • Number of Participants With Phenotypic Resistance Through Week 48 [Time Frame: At the time of CVF] • Number of Participants With Genotypic Resistance Through Week 48 [Time Frame: At the time of CVF] • Number of Participants With AEs as per Baseline Third Agent Treatment Class [Time Frame: Up to Week 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: ALT, ALP, AST and CK [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment	

	Class Overtime Including Week 48: Albumin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Bilirubin, Direct Bilirubin and Creatinine [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Creatinine Clearance [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Lipase [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Absolute Values for Fasting Lipid Panel Using Baseline Third Agent Treatment Class Overtime Including Week 48 [Time Frame: Baseline (Day 1) and at Week 48] • Number of Participants Discontinued or Withdrawn Due to AEs When Baseline Third Agent Treatment Class Was Used Over Time Including Week	

	48 [Time Frame: Up to Week 48] • Plasma Trough Concentration (Ctrough) for cabotegravir LA [Time Frame: Pre-dose at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Ctrough for rilpivirine LA [Time Frame: Pre-dose at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Area Under the Curve (AUC) for cabotegravir LA and rilpivirine LA [Time Frame: Pre-dose at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 96; 1 Week post-dose at Weeks 5 and 41] • Maximum Concentration (Cmax) in Plasma for cabotegravir LA [Time Frame: Week 41- 1 Week post dose] • Cmax in Plasma for rilpivirine LA [Time Frame: Week 41- 1 Week post dose] • Percentage of Participants With a Virologic Failure Using Snapshot Algorithm by Baseline Third Agent [Time Frame: Week 48] • Percentage of Participants With Plasma HIV-1 RNA <50copies/mL Using Snapshot Algorithm by Baseline Third Agent [Time Frame: Week 48] • Number of Participants With Severity of Adverse Events by Baseline Third Agents [Time Frame: Up to Week 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: ALT, ALP, AST and CK [Time	

	Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Albumin [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Bilirubin, Direct Bilirubin and Creatinine [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Creatinine Clearance [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48: Lipase [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48] • Change From Baseline Values for Clinical Chemistry Parameters Using Baseline Third Agent Treatment Class Overtime Including Week 48 [Time Frame: Baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48]	

	• Change From Baseline Values for Fasting Lipid Panel Using Baseline Third Agent Treatment Class Overtime Including Week 48 [Time Frame: Baseline (Day 1) and at Week 48] • Number of Participants With Genotypic Resistance Using Baseline Third Agent Through Week 48 [Time Frame: At the time of CVF] • Number of Participants With Phenotypic Resistance Using Baseline Third Agent Through Week 48 [Time Frame: At the time of CVF] • Change From Week 5 in Dimension Scores Using Perception of Injection Questionnaire (PIN)-Last Observation Carried Forward (LOCF) in Q4W Arm [Time Frame: Week 5 and at Weeks 41 and 48] • Percentage of Participants With Extremely or Very Acceptable Pain and Local Reaction: Acceptability Score on PIN Questionnaire in Q4W Arm [Time Frame: Weeks 5, 41 and 48] • Change From Baseline in Life Satisfaction (LISAT) Using HIV/AIDs-targeted Quality of Life (HATQoL) Questionnaire [Time Frame: Baseline (Day 1) and at Weeks 24 and 48] • Change From Baseline in HIV Medication, MEDWO Using HATQoL [Time Frame: Baseline and at Weeks 24 and 48] • Change From Baseline in DISWO Using HATQoL [Time	

	Frame: Baseline and at Weeks 24 and 48] • Change From Baseline in Health Status Using 12-item Short Form Survey (SF-12) [Time Frame: Baseline and at Weeks 24 and 48] • Change From Baseline in Total Treatment Satisfaction Using HIV Treatment Satisfaction Questionnaire (HIVTSQs) at Weeks 4b, 24 and 44 [Time Frame: Baseline and at Weeks 4b, 24 and 44] • Change in Treatment Satisfaction Over Time Using HIVTSQ Change (HIVTSQc) at Week 48 in Q4W Arm [Time Frame: Week 48] • Change From Baseline in Treatment Acceptance at Weeks 8, 24 and 48 Using "General Acceptance" Dimension of the Chronic Treatment Acceptance (ACCEPT) Questionnaire [Time Frame: Baseline and at Weeks 8, 24 and 48] • Change From 4b in Tolerability of Injection at Week 5, 40 and 41 Using Numeric Rating Scale (NRS) Within CAB LA+RPV LA Arm [Time Frame: Weeks 4b, 5, 40 and 41] • Change From Baseline in Individual Item Scores of HIVTSQc at Weeks 4b, 24 and 44 [Time Frame: Baseline and Weeks 4b, 24 and 44] • Number of Participants With Different Demographic Parameters for Inter-subject Variability [Time Frame: Up to Week 48]	
Key Results	The study showed long-acting cabotegravir and rilpivirine, injected	The study met its primary endpoint, showing that the long-

	once a month, had similar efficacy to a standard of care, daily, oral three-drug regimen at Week 48. The injectable treatment regimen met the primary endpoint for non-inferiority (the proportion of participants with plasma HIV-1 RNA ≥50 copies per millilitre [c/mL] using the FDA Snapshot algorithm at Week 48). Overall safety, virologic response and drug resistance results for the injectable regimen were consistent with results from the phase II LATTE and LATTE-2 studies.	acting regimen of cabotegravir and rilpivirine, injected every two months, was non-inferior to cabotegravir and rilpivirine administered every month at Week 48. Non-inferiority was assessed by comparison of the proportions of participants with plasma HIV-RNA ⩾ 50 copies per millilitre (c/mL) using the FDA Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITTE] population). Overall safety, virologic response and drug resistance results for the every-two-months injectable regimen were consistent with results from the phase III ATLAS study.
Adverse effects (AEs)	• Injection site reactions were mostly grade 1 or 2 and short-lived with few associated discontinuations • Grade 3/4 and serious AEs were infrequent in both treatment arms	-
Expected reporting date	Primary completion date previously reported as May 2018. Study completion date February 2022.	Primary completion date previously reported as June 2019. Study completion date March 2022.

Trial	**FLAIR**, NCT02938520, EudraCT-2016-001646-25; **LA cabotegravir and rilpivirine maintenance after integrase inhibitor switch; HIV-1 participants; 18 years and over; phase III**
Sponsor	ViiV Healthcare
Status	Ongoing and published
Source of Information	Trial registry;[32] Conference Presentation[33]
Location	US, Canada, Europe (inc UK) and other countries
Design	Randomised, active-controlled, open-label study
Participants	N= 631, adults 18 years or greater, HIV-1 infected, ART-naïve, plasma HIV-1 RNA >=1000 c/mL
Schedule	Randomised to: • Experimental: cabotegravir LA + rilpivirine LA every 4 weeks After Induction Phase with abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) (or DTG + two NRTIs), eligible participants will receive oral cabotegravir 30 mg + rilpivirine 25 mg once daily for approximately four weeks. At visit Week 4b subjects will receive an initial loading dose of cabotegravir LA (600 mg) and rilpivirine LA (900 mg) at Week 4b.

	From Week 8 onwards, subjects will receive cabotegravir LA (400 mg) + rilpivirine LA (600 mg) injections every 4 weeks. • Active Comparator: ABC / DTG / 3TC (600 mg/50mg/300mg) once daily After the Induction Phase with ABC/DTG/3TC (or DTG + two NRTIs), eligible participants will continue to receive oral ABC/DTG/3TC (or DTG + two NRTIs) initiated during the Induction Phase for 100 weeks. At the end of the Maintenance Phase, eligible participants receiving ABC/DTG/3TC (or DTG + two NRTIs) have the option to continue in the study by switching to cabotegravir LA + rilpivirine LA in the Extension Phase. These participants will transition to LA dosing at either Week 100 (direct to inject) or Week 104b (if using optional oral lead-in with cabotegravir 30 mg + rilpivirine25 mg once daily).
Follow-up	Active treatment for 100 weeks
Primary Outcomes	• Proportion of participants with a 'virologic failure' endpoint as per Food and Drug Administration (FDA) Snapshot algorithm at Week 48 (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population). [Time Frame: Week 48]
Secondary Outcomes	• Proportion of participants with Plasma HIV-1 RNA <50 c/mL at Week 48 [Time Frame: Week 48] • Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 96 [Time Frame: Week 96] • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 [Time Frame: Week 48] • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 96 [Time Frame: Week 96] • Proportion of participants with plasma HIV-1 RNA >=50 c/mL at Week 96 [Time Frame: Week 96] • Proportion of participants with confirmed virologic failure at Week 48 [Time Frame: Week 48] • Proportion of participants with confirmed virologic failure at Week 96 [Time Frame: Week 96] • Change from Baseline in plasma HIV-1 RNA [Time Frame: Baseline (Day 1) and up to Week 96] • Change from Baseline in CD4+ cell counts [Time Frame: Baseline (Day 1) and up to Week 96] • Number of participants with disease progression [Time Frame: Baseline (Day 1) and up to Week 96] • Number of participants with adverse events (AEs), serious AEs (SAEs) and AEs by severity [Time Frame: Up to Week 96] • Number of participants with laboratory abnormalities [Time Frame: Up to Week 96]

	• Number of participants with abnormal change from Baseline in laboratory parameters. [Time Frame: Baseline (Day 1) and up to Week 96] • Number of participants who discontinue treatment due to AEs [Time Frame: Up to Week 96] • Number of participants with treatment emergent resistance [Time Frame: Up to Week 96] • Change from Baseline in fasting lipids [Time Frame: Baseline (Day 1) and up to Week 96] • Plasma trough concentration (Ctrough) for CAB LA arm [Time Frame: Pre-dose at Weeks 4b, 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, 96, 100, 101, 104a, 104b, 108.] • Plasma trough concentration (Ctrough) for RPV LA arm [Time Frame: Pre-dose at Weeks 4b, 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, 96, 100, 101, 104a, 104b, 108.] • Maximum concentration (Cmax) in plasma for CAB LA arm [Time Frame: At any time post-dose at Weeks 5, 41 and 101] • Maximum concentration (Cmax) in plasma for RPV LA arm [Time Frame: At any time post-dose at Weeks 5, 41 and 101] • Plasma area under the concentration-time curve (AUC) for CAB LA arm [Time Frame: Pre-dose at Weeks 4b, 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, 96, 100, 101, 104a, 104b, 108; At any time post-dose at Weeks 5, 41 and 101] • Plasma area under the concentration-time curve (AUC) for RPV LA arm [Time Frame: Pre-dose at Weeks 4b, 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, 96, 100, 101, 104a, 104b, 108; At any time post-dose at Weeks 5, 41 and 101] • Change from Week 5 in Dimension Scores [Time Frame: Week 5 and up to Week 96] • Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable [Time Frame: Week 5 to Week 96] • Change from Baseline in health related quality of life (HR QoL) [Time Frame: Baseline (Day 1) and up to Week 96] • Change from Baseline in treatment satisfaction [Time Frame: Day 1 up to Week 96] • Change in treatment satisfaction at Week 48 [Time Frame: Baseline (Day 1) and up to Week 48]

	• Change from Baseline in health status [Time Frame: Baseline (Day 1) and up to Week 96] • Change from Baseline in treatment acceptance [Time Frame: Baseline (Day 1) and up to Week 96] • Change in tolerability of injection (for CAB LA + RPV LA) [Time Frame: Week 4b and up to Week 96] • Number of participants with potential predictors of inter- and intra-subject variability for pharmacokinetic parameters [Time Frame: Up to Week 96] • Proportion of participants with HIV-1 RNA >= 50 c/mL at Week 124 in extension phase [Time Frame: Up to Week 124] • Proportion of participants with plasma HIV-1 RNA <50 c/mL over time in extension phase [Time Frame: Up to Week 124] • Proportion of participants with plasma HIV-1 RNA <200 c/mL over time in extension phase [Time Frame: Up to Week 124] • Proportion of participants with confirmed virologic failure over time in extension phase [Time Frame: Up to Week 124] • Number of participants with treatment emergent genotypic and phenotypic resistance to CAB and RPV over time in extension phase [Time Frame: Up to Week 124] • Change from Baseline in CD4+ cell counts in extension phase [Time Frame: Up to Week 124] • Number of participants with AEs, SAEs and AEs by severity in extension phase [Time Frame: Up to Week 124] • Number of participants with laboratory abnormalities in extension phase [Time Frame: Up to Week 124] • Number of participants with abnormal change from Baseline in laboratory parameters in extension phase [Time Frame: Up to Week 124] • Number of participants who discontinue treatment due to AEs in extension phase [Time Frame: Up to Week 124] • Plasma CAB and RPV concentrations in the Extension Phase (direct to inject without oral lead-in) [Time Frame: Weeks 100, 101 and 104a] • Plasma CAB and RPV concentrations in the Extension Phase (oral lead-in participants) [Time Frame: Week 104b]
Key Results	Six participants in the LA arm (2.1%) and 7 in the CAR arm (2.5%) had HIV-1 RNA ≥50 c/mL at W48, meeting non-inferiority criteria for the

	primary endpoint and for the key secondary endpoint of HIV-1 RNA <50 c/mL (LA 93.6% vs CAR 93.3%). Four LA recipients (1.4%) had CVF; 3 had mutations in the NNRTI + INSTI domains (K101K/E/Q + G140R, E138K + Q148R, and E138E/A/K/T + Q148R, respectively) and 1 was not tested (PO only). The CAR arm had 3 CVFs with no INSTI resistance. Of 263 LA participants completing HIVTSQc at W48, 99% were more satisfied with CAB+RPV compared with their prior daily oral CAR.
Adverse effects (AEs)	AEs leading to withdrawal and serious AEs were infrequent in both arms. The most common drug-related AE was injection site reactions (ISRs; 82% of participants in the LA arm); frequency decreased over time. 99% of ISRs were Grade 1 or 2; the median duration was 3 days.
Expected reporting date	Primary completion date previously reported as August 2018. Study completion date July 2022

ESTIMATED COST

The cost of cabotegravir LA injection or rilpivirine LA injection is not yet known.

The NHS indicative price for a pack of 30 x 25 mg rilpivirine tablets is £200.27.[34]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. HIV testing: increasing uptake among people who may have undiagnosed HIV. 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infections (all ages). B06/P/a. 2019.
- NHS England. Clinical Commissioning Policy: Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents. 170028P. 2018.
- NHS England. Clinical Commissioning Policy: Use of cobicistat as a booster in treatment of HIV infection (all ages). F03/P/b. 2015 updated 2018.
- NHS England. Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents. 16043/P. 2016.
- NHS England. Clinical Commissioning Policy: Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults. F03/P/a. 2015.
- NHS England. Clinical Commissioning Policy: Treatment as prevention (TasP) in HIV infected adults. F03/P/c. 2015
- NHS England. 2013/2014 NHS Standard Contract for Specialised Human Immunodeficiency Virus services (Adults). B06/S/a.
- NHS England. 2013/2014 NHS Standard Contract for Specialised Human Immunodeficiency Virus services (Children). B06/S/b.

OTHER GUIDANCE

- European AIDS Clinical Society (EACS). Guidelines. Version 9.1. October 2018.[35]
- British HIV Association. British HIV Association guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015 (2016 interim update). 2016.[16]

ADDITIONAL INFORMATION

REFERENCES

1 AIDS info. *Cabotegravir* 2019. Available from: https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/professional [Accessed 24 September 2019].

2 electronic Medicies Compendium (eMC). *Rilpivirine.* 2019. Available from: https://www.medicines.org.uk/emc/product/4968/smpc [Accessed 24 September 2019].

3 Iacob SA, Iacob DG, Jugulete G. Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations. *Frontiers in pharmacology*. 2017;8:831-. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29218008 10.3389/fphar.2017.00831.

4 Clay PG, Nag S, Graham CM, Narayanan S. Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens. *Medicine (Baltimore)*. 2015 Oct;94(42):e1677. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26496277 10.1097/md.0000000000001677.

5 ViiV Healthcare. *ViiV Healthcare submits New Drug Application to US FDA for the first monthly, injectable, two-drug regimen of cabotegravir and rilpivirine for the treatmen of HIV.* 2019. Available from: https://viivhealthcare.com/en-gb/media/press-releases/2019/april/viiv-healthcare-submits-new-drug-application-to-us-fda-for-the-first-monthly-injectable-two-drug-regimen-of-cabotegravir-and-rilpivirine-for-treatment-of-hiv/ [Accessed 24 September 2019].

6 electronic Medicies Compendium (eMC). *Edurant 25 mg tablets.* 2019. Available from: https://www.medicines.org.uk/emc/product/4968/smpc [Accessed 24 September 2019].

7 European Medicines Agency. *European public assessment report (EPAR): Edurant (rilpivirine).* 2011. Report No.: EMA/752608/2015. Available from: https://www.ema.europa.eu/en/documents/overview/edurant-epar-summary-public_en.pdf.

8 Avert: Global Information and education on HIV and AIDS. *The science of HIV and AIDS - Overview.* 2019. Available from: https://www.avert.org/professionals/hiv-science/overview [Accessed 24 September 2019].

9 Avert: Global Information and education on HIV and AIDS. *HIV strains and types.* 2019. Available from: https://www.avert.org/professionals/hiv-science/types-strains [Accessed 24 September 2019].

10 NHS. *HIV and AIDS: causes.* 2018. Available from: https://www.nhs.uk/conditions/hiv-and-aids/causes/ [Accessed 25 September 2019].

11 World Health Organization (WHO). *HIV/AIDS.* 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids [Accessed 25 September 2019].

12 NHS Inform. *Symptoms of HIV.* 2019. Available from: https://www.nhsinform.scot/illnesses-and-conditions/immune-system/hiv#symptoms-of-hiv [Accessed 24 September 2019].

13 Public Health England. *Progress towards ending the HIV epidemic inthe United Kingdom. 2018 report: summary, key messages and recommendations*. 2018. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/813168/HIV_annual_report_2018_-_Summary_key_messages_and_recommendations.pdf.

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Downloaded 27 November 2018].
15 NHS England. *Treatmen: HIV and AIDS*. 2018. Available from: https://www.nhs.uk/conditions/hiv-and-aids/treatment/ [Accessed 25 September 2019].
16 British HIV Association. *British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)* Last Update Date: 2016. Available from: https://www.bhiva.org/HIV-1-treatment-guidelines [Accessed 25 September 2019].
17 HIV i-Base. *What is ART and what are ARVs?* Available from: http://i-base.info/guides/starting/what-is-art [Accessed 25 September 2019].
18 HIV i-Base. *Main types of HIV drugs*. Available from: http://i-base.info/guides/starting/types-of-hiv-drugs [Accessed 25 September 2019].
19 British Medical Formulary (BNF). *HIV infection*. 2017. Available from: https://doi.org/10.18578/BNF.725824801 [Accessed 25 September 2019].
20 electronic Medicies Compendium (eMC). *Search results for tenofovir alafenamide*. 2019. Available from: https://www.medicines.org.uk/emc/search?q=tenofovir+alafenamide [Accessed 16 Octoberr 2019].
21 electronic Medicies Compendium (eMC). *Pifeltro 100 mg film-coated tablets*. 2019. Available from: https://www.medicines.org.uk/emc/product/9693/smpc [Accessed 15 October 2019].
22 Clinicaltrials.gov. *Dose Ranging Study of GSK1265744 Plus Nucleoside Reverse Transcriptase Inhibitors for Induction of Human Immunodeficiency Virus-1 (HIV-1) Virologic Suppression Followed by Virologic Suppression Maintenance by GSK1265744 Plus Rilpivirine. Trial ID: NCT01641809*. 2012. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01641809 [Accessed 26 September 2019].
23 Margolis DA, Brinson CC, Smith GHR, de Vente J, Hagins DP, Eron JJ, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 Oct;15(10):1145-55. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26201299 10.1016/s1473-3099(15)00152-8.
24 Clinicaltrials.gov. *A Phase IIb Study to Evaluate a Long-Acting Intramuscular Regimen for Maintenance of Virologic Suppression (Following Induction With an Oral Regimen of GSK1265744 and Abacavir/Lamivudine) in Human Immunodeficiency Virus Type 1 (HIV-1) Infected, Antiretroviral Therapy-Naive Adult Subjects. Trial ID: NCT02120352*. 2014. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02120352 [Accessed 25 September 2019].
25 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017 Sep 23;390(10101):1499-510. Available from: 10.1016/s0140-6736(17)31917-7.
26 Clinicaltrials.gov. *Phase 2b, Open-label, Multicenter, Rollover Study to Assess Antiviral Activity and Safety of Long-acting Cabotegravir (CAB LA) Plus Long-acting Rilpivirine (RPV LA), Administered Every 2 Months (Q2M), in Human Immunodeficiency Virus (HIV)- Positive Subjects From the LATTE Study. Trial ID: NCT03639311*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03639311 [Accessed 25 Setempber 2019].
27 Clinicaltrials.gov. *Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine From Current Antiretroviral Regimen in Virologically Suppressed HIV-1-infected Adults. Trial ID: NCT02951052*. 2016. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02951052 [Accessed 26 September 2019].
28 ViiV Healthcare. *ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen*. 2018. Available from: https://viivhealthcare.com/en-us/us-news/us-articles/2016/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen/ [Accessed 4 October 2019].
29 Susan Swindells, Jaime-Federico Andrade-Villanueva, Gary J. Richmond, Giuliano Rizzardini, Axel Baumgarten, Maria Del Mar Masia, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington 2019.
30 Clinicaltrials.gov. *Efficacy, Safety and Tolerability Study of Long-acting Cabotegravir Plus Long-acting Rilpivirine (CAB LA + RPV LA) in Human-immunodeficiency Virus-1 (HIV-1) Infected Adults. Trial ID:*

NCT03299049. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03299049 [Accessed 26 September 2019].
31 ViiV Healthcare. *ViiV Healthcare reports positive phase III study results of investigational, long-acting, injectable HIV-treatment regimen administered every two months.* 2019. Available from: https://viivhealthcare.com/en-gb/media/press-releases/2019/august/viiv-healthcare-reports-positive-phase-iii-study-results-of-inve/ [Accessed 16 October 2019].
32 Clinicaltrials.gov. *Study to Evaluate the Efficacy, Safety, and Tolerability of Long-acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch From an Integrase Inhibitor in HIV-1 Infected Therapy Naive Participants. Trial ID: NCT02938520.* 2016. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02938520 [Accessed 26 September 2019].
33 Chloe Orkin, Keikawus Arastéh, Miguel Górgolas Hernández-Mora, Vadim Pokrovsky, Edgar T. Overton, Pierre-Marie Girard, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR week 48 results. *Conference on Retroviruses and Opportunitc Infections*. Seattle, Washington 2019.
34 electronic Medicies Compendium (eMC). *Rilpivirine.* 2016. Available from: https://doi.org/10.18578/BNF.108558510 [Accessed 27 September 2019].
35 European AIDS Clinical Society (EACS). *Guidelines Version 9.1* Last Update Date: October 2018. Available from: http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf [Accessed 25 September 2019].

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