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Health Technology Briefing
February 2023

Cabotegravir (long-acting injection) for prevention of HIV-1 infection

Company/Developer	ViiV Healthcare UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 17174	NICE ID: 10294	UKPS ID: 643620

Licensing and Market Availability Plans

Currently in phase II and III clinical development.

Summary

Cabotegravir is in clinical development as an alternative method of protecting an individual from contracting the human immunodeficiency virus type 1 (HIV-1). HIV is a chronic life altering condition that requires, daily antiretroviral therapy (ART) as a regular treatment routine. If left unmanaged it can lead to serious complications, such as acquired immunodeficiency syndrome (AIDS). Interventions that help prevent HIV acquisition are therefore imperative for those who are at greater risk. For example, men who have unprotected sex with men and heterosexual men and women who have unprotected sex with people that are HIV positive. Pre-exposure prophylaxis (PrEP) are ARTs which when taken regularly significantly reduce the risk of the transmission of HIV during unprotected sex. Currently, the only preventative treatment available is tenofovir disoproxil fumarate/emtricitabine tablets taken daily. Whilst these are highly effective at preventing HIV when taken as prescribed, they can cause adherence issues and therefore a long-acting form of PrEP medication is desirable.

Cabotegravir is a type of ART designed to block the action of a specific viral enzyme that integrates the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, blocking it can halt the spread of the virus. If licensed, cabotegravir would be administered as a long-acting intramuscular injection for maintenance every 2 months and would present an alternative method of HIV prevention, which would provide a treatment option for patients who would have sub-optimal efficacy, tolerability or adherence with oral treatments.

Proposed Indication

Long-acting injection for the prevention of human immunodeficiency virus type 1 (HIV-1) infection.[1-4]

Technology

Description

Cabotegravir (CAB) is a novel HIV-1 integrase strand-transfer inhibitor with potent antiviral activity.[5] It blocks the viral integrase from incorporating the viral genome into the human host cell.[6,7] Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.[8,9] It is formulated as both an oral tablet for oral lead-in and bridging only and as a long acting injectable formulation for maintenance (CAB LA).[10]

Cabotegravir pre-exposure prophylaxis (PrEP) has been trialled in two pivotal Phase IIb/III studies (NCT02720094, NCT03164564). During these trials, patients in the cabotegravir arm took cabotegravir orally (30mg once a day for 5 weeks) plus placebo for tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), then received intramuscular injections (600mg (3mL) two injections four weeks apart and every eight weeks thereafter) plus placebo for TDF/FTC, until the required number of incident HIV infections was reached.[1,2] CAB LA for PrEP is also under investigation in adolescents (those <18 years old and sexually active) in two Phase II studies NCT04692077, NCT04824131).[11,12]

Key Innovation

Oral pre-exposure prophylaxis (PrEP) medication, such as tenofovir disoproxil fumarate-based regimens, have been shown to be highly effective for HIV prevention in diverse populations with varied routes of exposure, but they require rigorous adherence to prescribed dosing.[13] Daily oral treatments are not always appropriate for patients at risk of HIV due to reasons such as an inability to swallow tablets, contraindications to current PrEP options, pill fatigue, stigma causing fear of disclosure of the need for PrEP and adherence issues with daily tablets. By introducing other product types and modes of delivery for PrEP the probability that at least one product will fit an individual's needs increase.[10] Utilising an injectable may alleviate pill fatigue and adherence challenges for individuals for whom daily administration is difficult to impossible.[13]

Cabotegravir is a white to light pink, prolonged-release suspension for injection.[8] Cabotegravir long acting injections would offer another option for HIV prevention, which are not required daily and could increase adherence. Additionally, having another option for HIV prevention could increase the probability of people partaking in such a prevention.[14]

Regulatory & Development Status

Cabotegravir, in combination with rilpivirine, is currently licensed in the UK for the treatment of HIV-1 in adults who are virologically suppressed on stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI (non-nucleoside reverse transcriptase inhibitor) and INI (integrase inhibitor) class.[8,9]

Cabotegravir, for PrEP, was granted a priority review and breakthrough therapy designation by the U.S Food and Drug Association.[15]

Cabotegravir is currently not in clinical development for any other indication.[16]

Patient Group

Disease Area and Clinical Need

HIV is a virus that attacks the cells of the immune system. Damage to the immune system caused by HIV can lead to acquired immunodeficiency syndrome (AIDS), which is a chronic and potentially life-threatening condition.[17] Upon initial infection, symptoms of HIV include fever, rash, sore throat, swollen glands, headache, upset stomach or diarrhoea, joint aches and pains, and muscle pain. After primary infection symptoms have dissipated, an asymptomatic phase occurs and further symptoms may not present for many years (e.g. 10-15 years). In the later stage of HIV the symptoms include weight loss, chronic diarrhoea, night sweats, fever, persistent cough, mouth and skin problems, regular infections, and serious illness or disease.[18,19] There are two main types of HIV. The most common is HIV-1, while HIV-2 is relative uncommon and less infectious. The strains of HIV-1 can be classified into four groups. M is the 'major' group and is responsible for the majority of the global HIV epidemic.[20] HIV can be acquired in multiple ways, with the most common method attributed to sexual transmission (unprotected vaginal or anal sex). Additionally, HIV infections can occur from unprotected oral sex and sharing sex toys with someone infected with HIV.[21] Other risk factors for contracting HIV include sharing needles, syringes and other injecting equipment, when contact is made with infected blood or mother to child during pregnancy, childbirth or breast-feeding.[17,22]

In 2022, the UK Health Security Agency published statistics that showed a decrease in 2021 of newly diagnosed HIV in the UK (including people previously diagnosed abroad) to 2,955 people. Of these, 90% (2,692) were diagnosed in England. New HIV diagnoses have declined among men who have sex with men (MSM) born in the UK and in White MSM, much slower declines have been observed among Black African MSM, individuals born abroad and heterosexual individuals, and these populations currently comprise a substantial proportion of new HIV diagnoses in England.[23] Additionally, in 2021 7.4% (87,828) of people who were HIV negative were defined as having a PrEP need. Among those at high risk of contracting HIV 79.1% (69,507) had their need identified through clinical consultation, and 69.6% (61,092) initiated or continued PrEP.[24] According to the hospital episodes statistics for England in 2021-22 there were 2,838 finished consultant episodes (FCE), 1,463 admissions, and 18,662 FCE bed days (ICD-10: B20-B24).[25]

Recommended Treatment Options

PrEP drugs as per the British HIV Association (BHIVA) recommendations:[26,27]

- Tenofovir disoproxil plus emtricitabine (TDF-FTC) for at-risk men who have sex with men (MSM), transgender women (TGW), transgender men and heterosexual men and women.
- Tenofovir alone is not recommended in men who have sex with men, due to a lack of evidence. It can, however, be offered to heterosexual men and women, where FTC is contraindicated.

Other methods for prevention of HIV contraction:[28]

- Condoms. Both male and female condoms are available. A condom is the most effective form of protection against HIV and other STIs. It can be used during vaginal, anal and oral sex (performed on men).
- Lubricant. It adds moisture to either the vagina or anus during sex. This makes sex safer by reducing the risk of tears caused by dryness or friction, and can also prevent condoms from tearing. Only water-based lubricants should be used.

- Avoid sharing needles and injecting equipment. Injecting drugs can expose people to HIV and other viruses. It is therefore important that people do not share needles, syringes, injecting equipment such as spoons or swabs, or the actual drugs and the liquids used to dilute them.
- Screening for HIV in pregnancy. All pregnant women are offered a blood test to assess if they have HIV as part of the routine antenatal screening.

Clinical Trial Information

Trial	NCT04692077; Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV Among Adolescent Males - A Sub-study of HPTN 083 **Phase II –** Active, not recruiting **Locations:** USA **Estimated primary completion date:** August 2023
Trial Design	Single group assignment, open label
Population	N = 50 (estimated); born female; aged 18-45 years, HIV-uninfected; sexually active
Intervention(s)	Step 1: Participants will receive daily oral cabotegravir (30 mg) and oral tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) placebo (300 mg/200 mg fixed dose combination tablet) for 5 weeks. Step 2: Participants will receive 600 mg (3mL) cabotegravir administered as one intramuscular injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter (Weeks 5, 9, 17, 25 & 33). A safety visit will follow each injection to ascertain safety data, including injection site reactions. Step 3: Participants will receive daily oral tenofovir disoproxil fumarate/emtricitabine (300/200mg dose combination) for up to 48 weeks, starting no later than 8 weeks after the last injection.
Comparator(s)	None
Outcome(s)	• Safety endpoint: proportion of participants experiencing any grade 2 or higher clinical adverse events and laboratory abnormalities among participants who receive at least one injection of CAB LA. • Tolerability endpoint: proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections or burden of study procedures. • Acceptability endpoint: proportion of participants who complete all scheduled injections and proportion of participants who receive at least one injection who would consider using CAB LA for HIV prevention in the future. See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

Trial	NCT04824131; Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV Among Adolescent Females - A Sub-study of HPTN 084 **Phase III –** Active, not recruiting **Locations:** Countries in Africa **Estimated primary completion date:** May 2023
Trial Design	Single group assignment, open label
Population	N = 50 (actual); assigned female at birth; aged <18 years, HIV-uninfected; sexually active
Intervention(s)	Step 1: Participants will receive daily oral cabotegravir (30 mg) and oral tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) placebo (300 mg/200 mg fixed dose combination tablet) for 5 weeks. Step 2: Participants will receive 600 mg (3mL) cabotegravir administered as one intramuscular injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter (Weeks 5, 9, 17, 25 & 33). A safety visit will follow each injection to ascertain safety data, including injection site reactions. Step 3: Participants will receive daily oral tenofovir disoproxil fumarate/emtricitabine (300/200mg dose combination) for up to 48 weeks, starting no later than 8 weeks after the last injection.
Comparator(s)	None
Outcome(s)	• Safety endpoint: proportion of participants experiencing any grade 2 or higher clinical adverse events and laboratory abnormalities among participants who receive at least one injection of CAB LA. • Tolerability endpoint: proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections or burden of study procedures. • Acceptability endpoint: proportion of participants who complete all scheduled injections and proportion of participants who receive at least one injection who would consider using CAB LA for HIV prevention in the future. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03164564; A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women **Phase III –** Active, not recruiting **Locations:** Countries in Africa **Estimated primary completion date:** May 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 3200 (estimated); born female; aged 18-45 years, HIV-uninfected; sexually active
Intervention(s)	Step 1: Participants will receive daily oral cabotegravir (30 mg) plus placebo oral. for 5 weeks. Step 2: At Week 5, Participants will receive 600 mg cabotegravir administered as one 3 mL (600 mg) intramuscular injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter plus placebo tablet. Step 3: Participants will receive open label daily tenofovir disoproxil fumarate/emtricitabine or CAB LA injections.
Comparator(s)	Step 1: Participants will receive daily oral tenofovir disoproxil fumarate/emtricitabine (300mg/200mg fixed dose combination tablet) and oral cabotegravir placebo (tablets) for 5 weeks. Step 2: Participants will receive daily tenofovir disoproxil fumarate/emtricitabine and placebo cabotegravir long-acting injections (3mL intramuscular injection in the gluteal muscle) at two time points 4 weeks apart and every 8 weeks thereafter beginning at week 5. Step 3: Participants will receive open label daily tenofovir disoproxil fumarate/emtricitabine or CAB LA injections.
Outcome(s)	• Number of documented incident HIV infections in steps 1 and 2 (time frame: measured through week 81). • Number of grade 2 or higher clinical and laboratory adverse events (time frame: measured through participants last study visit, up to 4.6 years after study entry, depending on when they enrol in the study). See trial record for full list of other outcomes.
Results (efficacy)	The trial was stopped early for efficacy on review of the results of the first preplanned interim end-point analysis by the Data Safety Monitoring Board (DSMB). CAB LA was superior to daily oral TDF/FTC at preventing new HIV infections in cis-gender women (p=0.000027). There were 40 incidences of infection observed over 3898 person years (HIV 1.% (95% CI: 0.73 to 1.4); four in the cabotegravir group (HIV incidence 0.2 cases per 100 person-years [95% CI: 0.06 to 0.31]) and 36 in the TDF-FTC group (1.85 cases per 100 person-years [95% CI: 1.3 to 2.57]); hazard ratio 0.11 (0.01 to 0.31), risk difference -1.6% (-1 to 2.3%). In a random subset of 405 TDF-FTC participants, 812 (42.1%) of 1929

	plasma samples had tenofovir concentrations consistent with daily use. Injection coverage was 93% of the total number of person-years.[29] Post hoc, centralised testing of stored samples resulted in re-adjudication of one of the 4 incident infections in the CAB LA arm as a baseline infection.[30]
Results (safety)	Adverse event rates were similar across both groups, apart from injection site reactions, which were more frequent in the cabotegravir group than in the TDF-FTC group (577 or 1519 vs 162 of 1516) but did not result in injection discontinuation.[29]

Trial	NCT02720094; A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine For Pre-Exposure Prophylaxis in HIV-Uninfected Men and Transgender Women Who Have Sex With Men **Phase IIb/III –** Active, not recruiting **Locations:** USA and other countries **Estimated study completion date:** July 2024
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 4750 (actual); men having sex with men and transgender women; aged 18 and above; HIV-uninfected; at high-risk for sexually acquiring HIV infection.
Intervention(s)	Step 1: Participants receive daily oral cabotegravir (30 mg tablets) and daily oral 300 mg/200 mg fixed-dose combination placebo (tenofovir disoproxil fumarate/emtricitabine) tablets for 5 weeks. Step 2: Participants receive 600 mg cabotegravir administered as one 3 mL (600 mg) intramuscular injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter (to week 153). Step 3: Participants receive open label daily oral tenofovir disoproxil fumarate/emtricitabine tablets or CAB LA.
Comparator(s)	Step 1: Participants receive daily oral tenofovir disoproxil fumarate/emtricitabine (300mg/200mg fixed-dose combination tablets) and daily oral cabotegravir placebo (tablets) for 5 weeks. Step 2: Participants receive daily oral tenofovir disoproxil fumarate/emtricitabine (300mg/200mg fixed-dose combination tablets) and placebo for cabotegravir long-acting injection (3mL injection into the gluteal muscle) at two time points 4 weeks apart and every 8 weeks thereafter to week 153. Step 3: participants receive open label daily oral tenofovir disoproxil fumarate/emtricitabine (300mg/200mg fixed-dose combination tablets) or CAB LA.

Outcome(s)	• Number of documented incident HIV infections in steps 1 and 2 (time frame: measured through participant's last visit, up to 4 years after study entry). • Number of grade 2 or higher clinical and laboratory adverse events (time frame: measured through participant's last study visit, up to 4 years after study entry). See trial record for full list of other outcomes.
Results (efficacy)	The trial was stopped early for efficacy on review of the results of the first pre-planned interim end-point analysis by the DSMB. CAB LA was superior to daily oral TDF/FTC at preventing new HIV infections in MSM and TGW ($p<0.001$). Incident HIV infection occurred in 52 participants: 13 in the cabotegravir group (incidence 0.41 per 100 person-years) and 39 in the TDF-FTC group (incidence 1.22 per 100 person-years), hazard ratio 0.34 (95% CI: 0.18 to 0.62).[31] Post hoc, centralised testing of stored samples resulted in re-adjudication of one of the 13 incident infections in the CAB LA arm as a BL infection.[32]
Results (safety)	Injection site reactions were reported in 81.4% of participants in the cabotegravir group and 31.3% of those in the TDF-FTC group. No safety concerns were identified.[31]

Trial	NTC02178800; A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women **Phase IIa** - Completed **Locations:** USA and three other countries **Study completion date:** July 2018
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 199 (actual); men and women; aged 18-65 years, HIV-uninfected
Intervention(s)	Cohorts 1 and 2: receive on GSK1265744 tablet orally (30mg) every day from study entry through week 4. Cohort 1: after the initial period above, receive an injection of GSK1265744 (800mg injection administered as two 400mg intramuscular gluteal injections) at weeks 5, 17 and 29. Cohort 2: after the initial period above, receive an injection of GSK1265744 (600mg injection administered as one intramuscular gluteal injection) at weeks 5, 9, 17, 25, and 33.
Comparator(s)	Cohorts 1 and 2: receive one placebo table orally every day from study entry through week 4. Cohort 1: after the initial period above, receive an injection of placebo (sodium chloride for injection USP, 0.9%, administered as two 400mg intramuscular gluteal injections) at weeks 5, 17, and 29.

	Cohort 2: after the initial period above, receive an injection of placebo (sodium chloride for injection USP, 0.9%, administered as one 600mg intramuscular gluteal injection) at weeks 5, 9, 17, 25, and 33.
Outcome(s)	• Number of participants experiencing any grade 2 or higher clinical adverse events and laboratory abnormalities that occur from the initial injection to week 41 among participants who receive at least one injection (injectable phase only) • Number of participants who discontinue injectable study product for reasons of toxicity, tolerability, or acceptability that occur from the initial injection to week 41 among participants who receive at least one injection (injectable phase only) • Plasma drug levels of cabotegravir at designated time points after each injection of long-acting injectable formulation (time frame: measured through week 41) See trial record for full list of other outcomes
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Trial	**ÉCLAIR; NCT02076178;** A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ECLAIR) **Phase IIa –** completed **Location:** USA **Study completion date:** Feb 2016
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 127 (actual), men, aged 18-45 years, HIV-uninfected
Intervention(s)	Oral phase: Participants received daily oral cabotegravir (30mg) tablets for 4-weeks, followed by a 1-week washout period, to assess for safety and tolerability prior to receiving cabotegravir injections. Injection phase: Participants received injections of cabotegravir (800mg intramuscular injections) at 3 time points at 12-week intervals (week 5, 17, and 29).
Comparator(s)	Oral phase: Participants received matching placebo tablets for 4-weeks, followed by a 1-week washout period, to assess for safety and tolerability prior to receiving matching placebo injections. Injection phase: Participants received placebo injections (800mg) at 3 time points at 12-week intervals (week 5, 17, and 29).
Outcome(s)	• Number of participants with any grade 2 or higher event in the injection phase (time frame: up to week 41) • Number of participants who received injection site reaction related concomitant medication in the injection phase (time frame: up to week 41)

	• Number of participants who experienced grade 2 or higher laboratory results in the injection phase (time frame: up to week 41) • Number of participants who had abnormal electrocardiogram findings in the injection phase (time frame: up to week 41) • Change from baseline in vital sign assessment for systolic blood pressure and diastolic blood pressure in the injection phase (time frame: baseline (week 5) to week 41) • Change from baseline in vital sign assessment for heart rate in the injection phase (time frame: baseline (week 5) to week 41) • Number of participants with ISR for the injection phase defined by maximum grades (time frame: up to week 41) See trial record for full list of other outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Estimated Cost

Cabotegravir is already marketed as Vocabria and licensed in the UK for the treatment of HIV-1:[33]

- A 600mg/3ml vial costs £1,197.02 per vial
- A 30mg oral tablet costs £638.57 per 30 tablets

These prices are for Vocabria which has its own license specifically for the treatment of HIV-1 in combination with Rekambys (Rilpivirine), therefore, they're not indicative of the price for Cabotegravir long-acting for PrEP which is still under discussion.[a]

Relevant Guidance

NICE Guidance

- NICE guideline. Reducing sexually transmitted infections (NG221). June 2022.
- NICE guideline. HIV testing: increasing uptake among people who may have undiagnosed HIV (NG60). December 2016.
- NICE quality standard. Sexual health (QS178). February 2019.
- NICE quality standard. HIV testing: encouraging uptake (QS157). September 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Proposition: Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults. F03X06. 2016.
- 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.

Other Guidance

[a] Information provided by ViiV Healthcare UK Ltd

- BHIVA/BASHH. Guidelines on the use of HIV pre-exposure prophylaxis (PrEP). 2018.[27]
- European AIDS Clinical Society (EACS). Pre-exposure Prophylaxis (PrEP).[34]

Additional Information

References

1 Clinicaltrials.gov. *Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women. Trial ID: NCT03164564*. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03164564#contacts [Accessed 4th January 2023].

2 Clinicaltrials.gov. *Injectable Cabotegravir Compared to TDF/FTC For PrEP in HIV-Uninfected Men and Transgender Women Who Have Sex With Men. Trial ID: NCT02720094*. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT02720094 [Accessed 4th January 2023].

3 Clinicaltrials.gov. *Evaluating the Safety, Tolerability, and Pharmacokinetics of an Investigational, Injectable HIV Medicine (GSK1265744) in HIV-Uninfected Adults. Trial ID: NCT02178800*. 2021. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02178800 [Accessed 4th January 2023].

4 Clinicaltrials.gov. *Study to Evaluate the Safety Tolerability and Acceptability of Long Acting Injections of the Human Immunodeficiency Virus (HIV) Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ECLAIR). Trial ID: NCT02076178*. 2017. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02076178 [Accessed 4th January 2023].

5 Cattaneo D, Gervasoni C. Pharmacokinetics and Pharmacodynamics of Cabotegravir, a Long-Acting HIV Integrase Strand Transfer Inhibitor. *European Journal of Drug Metabolism and Pharmacokinetics*. 2019;44(3):319-27. Available from: https://doi.org/10.1007/s13318-018-0526-2.

6 Park TE, Mohamed A, Kalabalik J, Sharma R. Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection. *Expert Review of Anti-infective Therapy*. 2015;13(10):1195-212. Available from: https://doi.org/10.1586/14787210.2015.1075393.

7 Podany AT, Scarsi KK, Fletcher CV. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors. *Clinical Pharmacokinetics*. 2017;56(1):25-40. Available from: https://doi.org/10.1007/s40262-016-0424-1.

8 Electronic Medicines Compendium. *Vocabria 600 mg prolonged-release suspension for injection*. 2022. Available from: https://www.medicines.org.uk/emc/product/12957/smpc [Accessed 4th January 2023].

9 Electronic Medicines Compendium. *Vocabria 30 mg film-coated tablets*. 2022. Available from: https://www.medicines.org.uk/emc/product/12958/smpc [Accessed 4th January 2023].

10 Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. *PLOS Medicine*. 2018;15(11):e1002690. Available from: https://doi.org/10.1371/journal.pmed.1002690.

11 Clinicaltrials.gov. *Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV Among Adolescent Males - A Sub-study of HPTN 083*. 2022.

Available from: https://clinicaltrials.gov/ct2/show/NCT04692077 [Accessed 24th Febraury 2023].

12 Clinicaltrials.gov. *Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV Among Adolescent Females - A Sub-study of HPTN 084*. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT04824131?term=NCT04824131&draw=2&rank=1 [Accessed 24th Febraury 2023].

13 Landovitz RJ, Li S, Eron JJ, Grinsztejn B, Dawood H, Liu AY, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. *The Lancet HIV*. 2020;7(7):e472-e81. Available from: https://doi.org/10.1016/S2352-3018(20)30106-5.

14 Kerrigan D, Mantsios A, Grant R, Markowitz M, Defechereux P, La Mar M, et al. Expanding the Menu of HIV Prevention Options: A Qualitative Study of Experiences with Long-Acting Injectable Cabotegravir as PrEP in the Context of a Phase II Trial in the United States. *AIDS and Behavior*. 2018;22(11):3540-9. Available from: https://doi.org/10.1007/s10461-017-2017-x.

15 U.S. Food and Drug Association. *FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention*. 2021. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention [Accessed 25 January 2023].

16 Clinicaltrials.gov. *Cabotegravir*. 2023. Available from: https://www.clinicaltrials.gov/ct2/results?cond=&term=cabotegravir&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=f&phase=1&phase=2 [Accessed 4th January 2023].

17 Mayo Clinic. *HIV/AIDS: Overview*. 2022. Available from: https://www.mayoclinic.org/diseases-conditions/hiv-aids/symptoms-causes/syc-20373524 [Accessed 4th January 2023].

18 beintheknow.org. *HIV symptoms*. 2022. Available from: https://www.beintheknow.org/hiv-and-stis/understanding-hiv-and-aids/hiv-symptoms [Accessed 4th January 2023].

19 NHS. *HIV and AIDS: Symptoms*. 2021. Available from: https://www.nhs.uk/conditions/hiv-and-aids/symptoms/ [Accessed 4th January 2023].

20 Ellis R, Reviewer: Khatri, M. *Types and Strains of HIV*. 2022. Available from: https://www.webmd.com/hiv-aids/types-strains-hiv [Accessed 25th January 2023].

21 NHS. *HIV and AIDS: Causes*. 2021. Available from: https://www.nhs.uk/conditions/hiv-and-aids/causes/ [Accessed 4th January 2023].

22 World Health Organization (WHO). *HIV*. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids [Accessed 4th January 2023].

23 UK Health Security Agency. *HIV: annual data tables*. 2022. Available from: https://www.gov.uk/government/statistics/hiv-annual-data-tables [Accessed 10th February 2023].

24 UK Health Security Agency. *HIV testing, PrEP, new HIV diagnoses, and care outcomes for people accessing HIV services: 2022 report*. 2022. Available from: https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2022-report#pre-exposure-prophylaxis-prep [Accessed 4th January 2023].

25 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 4th January 2023].

26 Terrence Higgins Trust. *PrEP (pre-exposure prophylaxis)*. 2020. Available from: https://www.tht.org.uk/hiv-and-sexual-health/prep-pre-exposure-prophylaxis [Accessed 4th January 2023].

27 British HIV Association. *BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018*. 2018. Available from: https://www.bhiva.org/PrEP-guidelines [Accessed 4th January 2023].

28 NHS. *HIV and AIDS: Prevention*. 2021. Available from: https://www.nhs.uk/conditions/hiv-and-aids/prevention/ [Accessed 4th January 2023].

29 Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *The Lancet*. 2022;399(10337):1779-89. Available from: https://doi.org/10.1016/S0140-6736(22)00538-4.

30 Marzinke MA, Delany-Moretlwe S, Agyei Y, Piwowar-Manning E, Anderson P, Hendrix C, et al. Long-acting injectable PrEP in women: laboratory analysis of HIV infections in HPTN 084. *IAS*. 2021.

31 Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *New England Journal of Medicine*. 2021;385(7):595-608. Available from: https://doi.org/10.1056/NEJMoa2101016.

32 Marzinke M, Grinsztejn B, Fogel J, Piwowar-Manning E, Hanscom B, Coelho L, et al. Laboratory analysis of HIV infections in HPTN 083: Inhectable CAB for PrEP. *Conference on Retroviruses and Opportunistic Infections*. Virtual: 2021.

33 National Institute for Health and Care Excellence. *Cabotegravir: Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/cabotegravir/medicinal-forms/ [Accessed 4th January 2023].

34 European AIDS Clinical Society. *Pre-exposure Prophylaxis (PrEP)*. Available from: https://eacs.sanfordguide.com/art/pre-exposure-prophylaxis#autotoc-item-autotoc-0 [Accessed 10th February 2023].

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