

# Cabotegravir with rilpivirine for treating HIV-1

Technology appraisal guidance

Published: 5 January 2022

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

1 Recommendations .....	4
2 Information about cabotegravir with rilpivirine .....	5
Marketing authorisation indication .....	5
Dosage in the marketing authorisation .....	5
Price.....	5
3 Committee discussion .....	6
The condition.....	6
New treatment option.....	8
Comparators .....	9
Clinical effectiveness .....	11
Cost-effectiveness analysis.....	16
Cost-effectiveness results .....	22
Innovation.....	23
Equalities.....	23
Conclusion .....	25
4 Implementation.....	27
5 Appraisal committee members and NICE project team .....	28
Appraisal committee members .....	28
NICE project team .....	28

# 1 Recommendations

1.1 Cabotegravir with rilpivirine is recommended, within its marketing authorisation, as an option for treating HIV-1 infection in adults:

- with virological suppression (HIV-1 RNA fewer than 50 copies/ml) on a stable antiretroviral regimen and
- without any evidence of viral resistance to, and no previous virological failure with, any non-nucleoside reverse transcriptase inhibitors or integrase inhibitors.

It is recommended only if the company provides it according to the [commercial arrangement](#).

## Why the committee made these recommendations

Current treatment for HIV-1 is antiretroviral regimens taken as tablets (orally) each day. The aim is to keep the number of virus particles in the blood (the viral load) so low that it cannot be detected, so that the virus cannot be transmitted between people. Cabotegravir with rilpivirine is the first long-acting antiretroviral injection available for HIV-1.

Clinical trial results show that cabotegravir with rilpivirine is as effective as oral antiretrovirals at keeping the viral load lower than 50 copies/ml of blood. It is unclear whether there would be a difference in adherence between long-acting injections and daily oral tablets. The most likely cost-effectiveness estimate is likely to be within what NICE normally considers an acceptable use of NHS resources. So, cabotegravir with rilpivirine is recommended.

## 2 Information about cabotegravir with rilpivirine

### Marketing authorisation indication

- 2.1 Cabotegravir (Vocabria, Viiv Healthcare) with rilpivirine (Rekambys, Janssen) is indicated 'for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA fewer than 50 copies/ml) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class'.

### Dosage in the marketing authorisation

- 2.2 The dosage schedules are available in the [summary of product characteristics for cabotegravir](#) and the [summary of product characteristics for rilpivirine](#).

### Price

- 2.3 The list price for cabotegravir is £638.57 for a 30-day pack of oral tablets and £1,197.02 for the bi-monthly (every 2 months) intramuscular injection vial (excluding VAT). The list price for rilpivirine is £200.27 for a 30-day pack of oral tablets and £440.47 for the bi-monthly intramuscular injection vial (excluding VAT). The company has a commercial arrangement (simple discount patient access scheme). This makes cabotegravir with rilpivirine available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

## 3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Viiv Healthcare, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that none of the issues were resolved after technical engagement. It recognised that there were remaining areas of uncertainty associated with the analyses presented (see ERG report, table 1.1, page 12) and took these into account in its decision making. It discussed issues 1 to 10, which were outstanding after the technical engagement stage.

### The condition

#### **HIV is not curable and people living with it currently need to take daily medication for life**

3.1 The committee heard from the clinical and community experts (alternative term for patient expert) that HIV is a retrovirus that attacks the human immune system, specifically macrophages and CD4+ T cells. The HIV-1 subtype accounts for most infections worldwide and can be acquired through sexual contact, breastfeeding, broken skin, or injections using contaminated equipment or substances. People living with HIV-1 that is untreated are at risk of their immune system gradually weakening, which can lead to opportunistic infections and cancers that further deteriorate their health. Despite scientific advances, HIV is still incurable, but the virus can be controlled by modern treatment. The current treatment regimens are oral antiretroviral therapies (ART) taken daily. There are several classes of antiretroviral agents that act on different phases of the HIV-1 virus life cycle either by disrupting its ability to enter the human host cells or to multiply. The ARTs used in the NHS include the following classes of drugs:

- nucleoside reverse transcriptase inhibitors (NRTIs)
- non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- protease inhibitors (PIs)
- fusion inhibitors
- integrase inhibitors (INI or INSTIs)
- CCR5 antagonists.

Therapy involves a combination of different agents, either as single- or multi-tablet regimens that must be taken every day for the rest of a person's life. The clinical experts told the committee that the aim is to suppress the virus to undetectable levels in the blood (defined as HIV-1 RNA fewer than 50 copies/ml) because then it becomes untransmissible. The clinical experts explained that treatment success with current daily oral treatments is mainly determined by adherence, which is influenced by drug side effects and psychosocial issues. They explained that although adherence is important, perfect adherence is not needed to have an undetectable viral load with modern treatments, and current therapy is highly effective. The community experts explained that adherence can be difficult in some cases because of drug-related side effects, toxicity, and other psychosocial issues such as stigma or changes in lifestyle. They also explained that a reduction in adherence might put people living with HIV-1 at risk of developing viral rebound or resistance to antiretrovirals. The committee concluded that HIV-1 is not curable and people living with it currently need to take daily medication for life.

## **Stigma remains an issue for people living with HIV, and can have a negative impact on people's health and relationships**

3.2 One of the community experts said that because people need to take their medication for life, their daily tablets serve as a constant reminder of their HIV status. This reminder can be distressing for some people because it is linked to stigma and having HIV-1. The expert expanded on the stigma around HIV; for some people it triggers the fear of having to disclose their status if people discover their tablets, which can easily happen when living in shared accommodation or taking medication in a public setting. The expert explained that the fear of unwanted disclosure happens constantly throughout people's lives. Stigma can present in various forms, including self-stigma based on negative self-beliefs, anticipated stigma when individuals expect negative treatment based on

their HIV status, and discrimination. The community experts explained that although things have improved over the last decade, stigma is a key barrier to people with HIV living fulfilled and happy lives. The committee understood that people's friendships, trust in others and the quality of their relationships in every sphere of life has more effect than anything else on mental health, physical health and how long we live. For this reason, stigma has a negative impact on personal, social, occupational and healthcare relationships. Furthermore, the community experts explained that stigma can sometimes affect adherence to oral regimens because individuals may miss a dose if they do not feel comfortable taking their medication in front of other people. The committee acknowledged these difficulties and concluded that stigma remains an issue for people living with HIV and can have a negative impact on people's health and relationships.

## New treatment option

### **Cabotegravir with rilpivirine would be beneficial for people who find daily tablets challenging or who would prefer an injectable regimen**

- 3.3 Long-acting cabotegravir and long-acting rilpivirine (referred to as 'cabotegravir with rilpivirine' from here onwards) is administered as 2 separate intramuscular injections. The dosing regimen starts with a 28-day oral lead-in, followed by monthly injections for 2 months. Thereafter, injections are given every 2 months. Cabotegravir is an INSTI and rilpivirine is an NNRTI. The company explained that it is intended to be a new alternative treatment option instead of daily oral ARTs. The clinical experts explained that, even though cabotegravir with rilpivirine has a lower frequency of dosing, people would need to visit an HIV clinic more often than with current oral ARTs because it is administered in the clinic. The clinical and community experts stated that cabotegravir with rilpivirine could be an effective alternative when treatment adherence to a daily oral regimen is affected either by side effects, when oral intake is impaired, or when lifestyle interferes with following a daily regimen. This is particularly important because people with HIV-1 need to maintain their medication regimen to prevent viral rebound or developing



resistance to ART. The community experts stressed that there is a huge appetite for an injectable treatment because taking tablets every day can be challenging. The committee noted that to be eligible for cabotegravir with rilpivirine, people must already have virological suppression on a stable antiretroviral regimen, so it may not be appropriate for people who have poor adherence. The company explained that long-acting treatments have improved adherence in other disease areas, so it is plausible that this would also be true for HIV. It considered that cabotegravir with rilpivirine would be particularly valuable for people with good levels of adherence but who might struggle to maintain this over time. The committee concluded that cabotegravir with rilpivirine would be a valuable treatment option for people who have adequate levels of adherence but who find daily tablets challenging or who would prefer an injectable regimen.

## Comparators

### Choice of oral ART depends on regional availability and individual need

- 3.4 There is currently no NICE technology appraisal guidance on treating HIV. [NHS England's guide on best practice in HIV prescribing and multidisciplinary teams](#) provides support to clinicians in treating HIV and managing multidisciplinary team discussions. It aims to provide access to antiretroviral therapy to anyone living with HIV, promote informed choice, help with shared decision making, and support therapy. The clinical expert explained that the clinical management of the condition is led by standard principles. The expert said that people living with HIV-1 have treatment at commissioned hospitals with specialist HIV clinics. In these clinics, people are given an antiretroviral regimen and are regularly seen until their HIV-1 is stable on a treatment routine. Once the viral load is suppressed, people would normally visit the HIV clinic 2 or 3 times per year for a routine follow up. The clinical and commissioning experts added that there is regional variation in antiretroviral prescribing, and that there are different prices for each drug in each region. Consequently, prescribing depends on individual need, and regional cost and availability. The committee concluded that the choice of oral ART

depends on regional availability and individual need.

## The company included relevant oral antiretroviral therapies

3.5 The comparator in the scope was 'antiretroviral treatment (established clinical management such as integrase inhibitors)'. The company chose the oral ARTs that most people living with HIV-1 switch to when they have virological suppression, because these would be the treatments used by the people who could potentially use cabotegravir with rilpivirine. It considered these treatments as a group (sometimes referred to as a 'basket' comparator) rather than comparing cabotegravir and rilpivirine with each oral antiretroviral individually. Given the variability in ART used across the country, the committee considered this approach to be appropriate, because the oral ARTs are all considered similar in efficacy (see [section 3.6](#)). The regimens included in the company's comparator group were:

- emtricitabine with tenofovir alafenamide plus dolutegravir
- emtricitabine with tenofovir alafenamide plus raltegravir
- abacavir, dolutegravir and lamivudine
- dolutegravir with lamivudine
- dolutegravir with rilpivirine
- bictegravir, emtricitabine and tenofovir alafenamide
- doravirine, lamivudine and tenofovir disoproxil fumarate
- darunavir, cobicistat, emtricitabine and tenofovir alafenamide
- emtricitabine, rilpivirine and tenofovir alafenamide.

The company explained that it selected these treatments based on treatment switches captured by market data. The clinical experts confirmed that these treatments are normally used in NHS practice for people who have virological suppression and need to switch treatment for non-virological reasons, and therefore it was appropriate for the company to include them. However, a clinical expert was concerned that dolutegravir plus tenofovir and emtricitabine

was excluded, because it is widely prescribed. In its submission, the company explained that people normally switch away from this treatment because of toxicity concerns. The committee concluded that the oral ARTs included in the group of comparators were relevant.

## All oral antiretroviral therapies have similar efficacy

3.6 The company assumed that all oral ART regimens have similar efficacy. It explained that the large number of non-inferiority studies available on this subject supports this, and that this assumption was confirmed by a clinical expert. Also, the company's pivotal trials used 2 NRTIs and an INSTI plus an NNRTI or PI (ATLAS), and an NRTI, INSTI and an NRTI (FLAIR), so it considered the treatment efficacy to be generalisable to the NHS. The ERG was satisfied that, given the very high efficacy of current oral ARTs, the company's assumption that they all have similar efficacy was appropriate. There was a general agreement among the clinical experts that all oral ARTs have similar efficacy. The committee concluded that all oral ARTs have similar efficacy.

## Clinical effectiveness

### It is unlikely that including case control studies in the company's systematic review would affect the cost-effectiveness results

3.7 The company did a systematic review to identify literature on clinical effectiveness and safety outcomes. The company included evidence from randomised control trials and excluded case-control studies. The ERG was concerned that relevant data might have been missed by excluding case-control studies. The company stated that given the high volumes of literature on HIV, priority was given to randomised controlled trials, which are the gold standard in the evidence hierarchy. The company also stressed that including case-control studies would not have led to a different conclusion. The clinical experts agreed with the company and expressed no concerns, because the available evidence came from randomised controlled trials. The ERG explained that it had other concerns about the company's search strategy, including language and date limits, and search sensitivity. It would have preferred searches

specifically for safety data but agreed that given the large amount of HIV literature about safety, it is unlikely that anything new would have been identified. The committee considered there to be minor limitations associated with the company's systematic review, but it was unlikely that important studies were missed. The committee concluded that it is unlikely that including case-control studies would have affected the cost-effectiveness results.

## **The comparator ARTs in the ATLAS and FLAIR clinical trials are generalisable to the NHS**

3.8 The company's key clinical evidence for long-acting cabotegravir with rilpivirine came from ATLAS, FLAIR and ATLAS-2M. These were phase 3 randomised, controlled, open-label, non-inferiority trials in people living with HIV-1. ATLAS and FLAIR compared monthly cabotegravir and rilpivirine with daily oral ARTs. ATLAS included 618 adults who had virological suppression on a stable regimen containing 2 NRTIs plus an INSTI, an NNRTI or a PI for at least 6 months. The comparator in ATLAS was 2 NRTIs plus an INSTI, 2 NRTIs plus a PI, or 2 NRTIs plus an NNRTI. FLAIR included 566 adults who had no previous experience of ART. There was a 20-week induction with current oral ART (abacavir /dolutegravir/lamivudine), then people were randomised to have monthly cabotegravir with rilpivirine or continue the induction regimen. The ERG noted that the oral ARTs used in the comparator arms of ATLAS and FLAIR may not be fully representative of the drugs normally used in the NHS in England. The company explained that the regimens used as comparators in ATLAS and FLAIR are considered to have comparable efficacy to currently used regimens in the NHS. It supported this by explaining that non-inferiority trials are the norm for ART in HIV (see [section 3.6](#)). To further support its assumption of generalisability to the NHS, the company submitted information about how the components used in the ATLAS oral ART arm were similar to drugs prescribed in the UK. The company had consulted an expert who stated that he had no reservations about the generalisability of the results of the company's trials to the NHS. At technical engagement, a representative from a professional organisation explained that most individuals would take an NRTI with either an NNRTI, INSTI or PI. This was similar to the comparator arm of ATLAS (in ATLAS, people in the comparator arm took

2 NRTIs plus an INSTI and an NNRTI or a PI). The committee concluded that the comparator ARTs in the ATLAS and FLAIR clinical trials are generalisable to the NHS.

## **Long-acting cabotegravir with rilpivirine is non-inferior to oral ARTs**

3.9 ATLAS and FLAIR aimed to show non-inferiority to oral ARTs with a pre-specified non-inferiority margin of 4%. The primary outcome in both trials was the proportion of people with HIV-1 RNA 50 or more copies/ml at week 48. The company presented results from a pre-specified pooled analysis of ATLAS and FLAIR, explaining that the trials had similar designs. The primary end point was met in this pooled analysis, with 11 of 591 people (1.9%) in the monthly cabotegravir with rilpivirine arm, and 10 of 591 people in the oral ART arm, with HIV-1 RNA 50 or more copies/ml at week 48. The adjusted difference in the proportion of people with HIV-1 RNA 50 or more copies/ml at week 48 was 0.16% (95% confidence interval [CI] -1.35 to -1.67). The clinical experts confirmed that cabotegravir with rilpivirine is considered similar in effectiveness to the current oral ARTs. The committee concluded that long-acting cabotegravir with rilpivirine is non-inferior to oral ARTs.

## **Long-acting cabotegravir with rilpivirine is as effective when taken every 2 months compared with when taken every 1 month**

3.10 The ATLAS-2M clinical trial aimed to show that cabotegravir with rilpivirine every 2 months is non-inferior to cabotegravir with rilpivirine every 1 month. The trial included 1,020 adults who had virological suppression. People were randomised to have long-acting cabotegravir with rilpivirine either monthly or bi-monthly (every 2 months) for 100 weeks. About half of the people enrolled were from the ongoing ATLAS study and the rest were new. The primary outcome was met at week 48. The results showed that 5 of 523 (1.0%) in the monthly cabotegravir with rilpivirine arm, and 9 of 522 (1.7%) in the bi-monthly arm had HIV-1 RNA 50 or more copies/ml at week 48. The adjusted difference in the proportion of people with HIV-1 RNA 50 or more copies/ml at week 48 was 0.8% (95% CI -0.6 to 2.2). The pre-specified non-inferiority margin assigned to note the difference between the

2 interventions was 4%. The clinical experts were satisfied that cabotegravir with rilpivirine every 2 months is non-inferior to monthly cabotegravir with rilpivirine. The committee recognised that long-acting cabotegravir with rilpivirine is as effective when taken every 2 months compared with when taken every 1 month.

## **An indirect treatment comparison is appropriate in the absence of head-to-head trial data**

3.11 The company submitted an indirect treatment comparison (ITC) of long-acting cabotegravir with rilpivirine every 2 months compared with oral ARTs. The ERG stated that the lack of a head-to-head comparison restricts the comparability of the 2 interventions. The company agreed with the ERG in that an ITC cannot replace evidence from head-to-head studies but explained that there are no head-to-head trials of cabotegravir with rilpivirine every 2 months and oral ARTs. A stakeholder at technical engagement said that the efficacy of cabotegravir with rilpivirine every 1 month is already established as being non-inferior to oral ARTs, so it is uncertain if a direct comparison would add value. The committee concluded that there is no direct evidence comparing long-acting cabotegravir with rilpivirine every 2 months with oral ARTs, so an ITC was appropriate.

## **Results of indirect treatment comparisons using pooled data and meta-analysed data are similar**

3.12 The company combined results from ATLAS and FLAIR in a pre-specified pooled analysis and used the pooled results in an ITC. The outcomes included in the company's ITC were the relative risk of having more than 50 HIV RNA copies/ml, the relative risk of having fewer than 50 HIV RNA copies/ml, and the relative risk of having an adverse event leading to stopping treatment. The relative risk of having more than 50 HIV RNA copies/ml with cabotegravir and rilpivirine compared with oral antiretroviral treatments was 1.10 (95% CI 0.25 to 4.90). The relative risk of having fewer than 50 HIV RNA copies/ml was 1.01 (95% CI 0.95 to 1.06). The ERG considered there to be substantial differences between the ATLAS and FLAIR studies and explained that the studies should have been meta-analysed rather than pooled. After technical engagement, the

company submitted results of an ITC in which the ATLAS and FLAIR data had been combined in a meta-analysis, then used in an ITC. The relative risks of having a viral load of fewer than 50 copies/ml and more than 50 copies/ml were very similar across the ITC using the meta-analysed ATLAS and FLAIR data and the analysis using the pooled data. However, the ERG highlighted that the relative risk of having an adverse event leading to stopping treatment was higher with cabotegravir and rilpivirine compared with oral ART in the non-pooled data analysis. The committee concluded that the results of the ITCs using pooled data and meta-analysed data are similar.

## **The ERG disagrees with the company's interpretation of non-inferiority for the ITC, but this has no implications for cost-effectiveness results**

3.13 The company considered that cabotegravir and rilpivirine every 2 months is non-inferior to current ARTs. However, the ERG noted that the ITC was imprecise and not designed as a non-inferiority analysis with defined non-inferiority margins, and non-significance cannot be interpreted as non-inferiority. The ERG's interpretation of the ITC results was that there is no evidence that cabotegravir with rilpivirine every 2 months is inferior to current ART, and it is uncertain whether cabotegravir with rilpivirine every 2 months is non-inferior to current ART. However, the ERG clarified that this issue relates only to the wording and interpretation, rather than the estimation of results, so there would be no effect on the cost-effectiveness results. The company claimed that guidance on the interpretation of non-inferiority within the context of ITC methodology is still under development and that there is no single accepted method. Furthermore, the company stated that the conclusions on comparative effectiveness had been interpreted correctly in the context of HIV regimens and the basis for their efficacy. The committee concluded that the ERG disagreed with the company's interpretation of non-inferiority, but that this has no implications for the cost-effectiveness results.



## **Cabotegravir with rilpivirine is generally well tolerated in clinical trials, but is associated with injection site reactions**

3.14 The most commonly reported adverse events in ATLAS-2M for long-acting cabotegravir with rilpivirine were injection site pain, injection site nodule and induration. Most people with injection site reactions reported them as being mostly mild (grade 1 or 2). The median duration for injection site reactions was 3 days, but in some cases, they lasted more than 14 days (monthly 6% and bi-monthly 4%). In this trial, drug-related adverse events leading to withdrawal were slightly higher in the monthly arm (11%) than in the bi-monthly arm (8%). In the pooled ATLAS and FLAIR analysis, the findings showed that adverse events were more prevalent in people who had monthly injections of cabotegravir and rilpivirine than in people who had oral ARTs (86% and 75%, respectively). The most frequently reported adverse event related to cabotegravir with rilpivirine was injection site pain (pooled ATLAS and FLAIR, monthly injections 76%). The rate of adverse events leading to withdrawal from treatment in ATLAS and FLAIR (pooled) was similar for cabotegravir with rilpivirine and oral ARTs (3% and 2%, respectively). The committee concluded that cabotegravir with rilpivirine was generally well tolerated in the clinical trials but is associated with injection site reactions.

## **Cost-effectiveness analysis**

### **The company's model is acceptable for decision making**

3.15 The company presented a hybrid Markov state-transition model with a decision tree process. The model used clinical data from ATLAS-2M for virological response (HIV RNA fewer than 50 copies/ml) and immunological response (increase in CD4+ cell count) for both cabotegravir with rilpivirine and oral ART. In the model, people with HIV were at risk of experiencing treatment failure, reaching or maintaining virological suppression, or having an adverse event that could lead to viral resistance or withdrawal from therapy. It also included an internal decision tree process that differentiated between individuals who stopped treatment because of virological reasons and those who stopped for non-virological reasons. The treatment switching process



was allocated by the model's decision tree. This informed the overall cohort results once individuals had transitioned through the appropriate subsequent treatments. Clinical efficacy was driven by virological response (HIV RNA fewer than 50 copies/ml), immunological response (increase in CD4+ cell count) and whether there was a change in therapy line use or resistance development. The company assumed there was no difference in efficacy between cabotegravir and rilpivirine and oral antiretroviral therapy, but assumed differences in adherence and utility values between the treatments. In the model, the adherence input affected viral suppression, which then affected the monthly probability of viral rebound. The impact of reduced adherence translated into experiencing a higher probability of viral rebound and switching to a different treatment each month. The committee noted that the company's model structure appropriately represented the natural history of the disease. But, it was concerned that if the assumptions about the consequences of non-adherence were not appropriate, the benefit of cabotegravir with rilpivirine may have been overestimated (see section 3.16). The committee concluded that the structure of the model was acceptable for decision making.

## **The model should not include a reduction in adherence for oral antiretroviral therapy**

3.16 In its original base case, the company assumed that 25.6% of people do not adhere to treatment with oral ARTs. It explained that this value was obtained from the SWEET study. The company updated this assumption to 17.85% after technical engagement because this is a mid-point value between the company's original value and the ERG's preferred estimate of 10.1%. The ERG obtained its estimate from Sherr et al. (2010). The ERG explained that a range of 87% to 93% for average lifetime adherence is plausible. Regarding adherence to long-acting cabotegravir with rilpivirine, the company used the adherence rate of 98% at 96 weeks from the ATLAS-2M clinical trial. The company assumed that adherence to cabotegravir with rilpivirine would not differ in clinical practice to that seen in the trial setting. It explained that it is difficult to estimate adherence to HIV treatment regimens, especially because people's adherence varies through their lifetime. The clinical expert agreed with the company that it is difficult to calculate adherence, but suggested

that viral suppression could be a reliable surrogate marker. The expert further explained that people in the UK have extremely high rates of virological suppression and that recent studies have shown that undetectable viral blood levels can be maintained even if adherence to oral ARTs is reduced to 75%. The clinical experts also noted that the company's analysis modelled a pessimistic adherence scenario for oral ART, compared with an optimistic scenario for cabotegravir with rilpivirine. The committee agreed it was problematic that the company had used randomised clinical trial data to inform the model adherence input for cabotegravir with rilpivirine but had assumed that oral ARTs would have lower rates of adherence than seen in the trials. The clinical experts highlighted that individuals who would take long-acting injectable ARTs could also experience difficulties adhering to it and that the consequences of not adhering may be worse. This is because long-acting injectable doses have a much longer gap in between administrations. Nevertheless, this was not captured in the company's model. The clinical experts explained that individuals who miss doses of injections are at higher risk of developing drug resistance and virological failure than people who miss a tablet. The committee also expressed concerns about the fact that differences in adherence assumptions drive differences in life years gained in the model. It considered it unrealistic that somebody would live longer if they have cabotegravir and rilpivirine injections compared with oral ART, especially given the high rates of treatment success with modern oral ART. The committee understood the difficulties with obtaining adherence inputs for the model, but considered it had not seen any evidence to convince it that there is a difference in adherence between cabotegravir with rilpivirine and oral ART. The committee concluded that the model should not include a reduction in adherence for oral ART compared with long-acting injectable ART.

## **Modelling a linear relationship between adherence and risk of virological failure may not be appropriate**

3.17 The company explained that, once it had obtained its estimate for the level of adherence, it used this in a direct linear regression equation from a published paper by Ross et al. (2015). From this formula, an adjustment factor was derived, which was then applied to the trial-reported viral suppression rate, thereby linking rates of adherence with rates of viral

suppression in the model. The company confirmed that this approach means that there is a direct linear relationship between viral suppression and adherence in the model, and people begin to lose effect if they do not adhere perfectly to treatment. A clinical expert responded that a linear relationship between adherence and risk of virological failure does not happen in real life. They explained that in clinical practice, there is a threshold effect, which is getting progressively lower with modern treatments. However, the committee recalled that the model should not include a reduction in adherence for oral antiretrovirals compared with long-acting injectables (see [section 3.16](#)). It considered that updating the model to incorporate its preference for a threshold effect would be unlikely to affect decision making if the adherence reduction for oral antiretrovirals was removed. The committee concluded that modelling a linear relationship between adherence and risk of virological failure may not be appropriate.

## The company's approach to costing the grouped comparator is acceptable

3.18 The company used a simple average of the prices of the individual treatments to calculate the overall cost of the grouped comparator (see [section 3.5](#) for a list of included treatments). For decision-making purposes, Commercial Medicines Unit prices were used to cost the comparators, which included a confidential discount and better reflected the cost incurred by the NHS than the list prices. When different regional prices were available for a comparator, 3 scenarios were considered to explore the uncertainty:

- using a simple average of the prices across the regions
- using the single lowest of the regional prices
- using the single highest of the regional prices.

These different pricing scenarios for the comparators were then used to calculate the average price for the grouped comparator. When deciding on the most appropriate regional pricing scenario, the committee considered variations in the availability and pricing of ARTs across regions in England. It had not seen evidence on antiretroviral therapy use within the different

regions. For this reason, the committee decided that a simple average of the Commercial Medicines Unit prices across regions best reflected the price paid by the NHS in England. By contrast, the lowest and highest regional price scenarios would unlikely represent the true price paid by the NHS due to the regional variations. The committee queried whether the annual cost of the comparator (when using a simple average of the prices across the regions) was similar to the annual costs seen in the NHS. The clinical expert confirmed that the approximate annual cost of therapy used in the NHS was similar to the average price of the comparator when using a simple average of the prices across the regions (the prices are confidential so cannot be reported here). The committee considered that the company's approach to costing the comparator was appropriate, and the average of the regional Commercial Medicines Unit prices should be used. The committee concluded that the company's approach to costing the grouped comparator is acceptable.

## **The assumption of a utility advantage for cabotegravir with rilpivirine is uncertain**

3.19 The company's modelled health states were stratified by CD4+ cell count. The utility values defined by CD4+ cell count were retrieved from the literature. The company used published values from Kauf et al. (2008), which were derived from 5 open-label studies in 1,327 individuals who had treatment with oral ART. The company explained that it was unable to use utility values from the clinical trials for these health states because of the CD4+ cell stratification boundaries used in each health state. It also explained that it would not have been possible to collect health-related quality-of-life data for all the health-state categories in the model. The company clarified that SF-12 health questionnaires were collected in the ATLAS and FLAIR clinical trials. Although these could not be used to estimate health-state utilities, it was possible to use them to estimate a difference in utility between cabotegravir with rilpivirine and oral ARTs. The company used mapping to generate SF-6 data from SF-12 data, then derived a utility advantage for cabotegravir with rilpivirine. The value is confidential so cannot be reported here. This was then applied to the health-state utility values in the economic model. The ERG added that the utility advantage in the model is applied continuously for as long as people are on the treatment and that although it is a small value, it has a large impact on the results. The committee expressed its concerns

about the uncertainty around the utility gain, but it was conscious of the issues around stigma that might be reflected in the utility advantage presented. The committee recalled that some people with HIV have a negative experience with oral medication on a day-to-day basis. Individuals experience the psychological consequences of living in a society in which stigma-related issues are still prevalent, the fear of unwanted disclosure if their tablets are seen, and the burden of a constant reminder of their HIV status from their daily tablets. The committee considered that medication alone cannot reduce stigma associated with the disease but can help with the cognitive load of self-managing HIV. The committee concluded that there may be a utility advantage for cabotegravir with rilpivirine because it may be valued by people concerned about stigma and disclosure of their HIV status, and it reduces the burden of taking daily tablets. However, it also concluded that the company's modelled utility advantage is uncertain.

## **Implementation issues may need to be considered by the NHS**

3.20 The clinical experts explained that currently NHS services are not set up to offer treatment with an intramuscular long-acting antiretroviral drug, so are not ready to cope with the demand of increased visits. They emphasised that people would have to attend the clinics more frequently when having treatment with cabotegravir and rilpivirine than they would with oral ARTs. The community expert stressed that there are advantages and disadvantages associated with visiting the clinic more frequently, and that the increased number of visits with cabotegravir and rilpivirine should not be seen only as a negative. Visiting the clinic more often means there are more opportunities to signpost people to local support services. Clinical experts explained that costs of setting up additional clinics may need to be considered. They also explained there are other costs associated with cabotegravir with rilpivirine treatment. These include follow up for people who have missed appointments and providing people with oral bridging therapy to maintain viral suppression levels in the case of missed injections. The company suggested that the uptake of the new technology would not be immediate and that it would increase over several years, allowing time for its implementation. The committee understood that the company's model included the costs for an assumed 15 minutes for a nurse to administer the 2 intramuscular

injections, but did not include any other implementation or administration costs. The committee recalled that the company offered support with the implementation of this technology in clinics, but the extent of that resource was unclear. The committee considered that the NHS may need to consider implementation issues, including whether its services need to be adapted to ensure cabotegravir and rilpivirine can be administered. However, it concluded that it had not seen any evidence to suggest that the time needed for the NHS to comply with the recommendations should be amended.

## Cost-effectiveness results

### **Cabotegravir with rilpivirine is likely to be a cost-effective use of NHS resources**

3.21 [NICE's guide to the methods of technology appraisal](#) notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee agreed that an acceptable ICER would be towards the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) because of the unmet need for an alternative to daily tablets and stigma-related issues. Because of confidential commercial arrangements for cabotegravir with rilpivirine and comparator treatments, the exact cost-effectiveness results cannot be reported here. In the company's base case, which assumed a 17.85% reduction in adherence for oral ART, the cost-effectiveness estimate for cabotegravir with rilpivirine compared with oral ART for HIV-1 was within what NICE normally considers an acceptable use of NHS resources. However, the committee would have preferred to see an analysis with a 0% reduction in adherence for oral ART (see [section 3.16](#)). When the committee's preferred non-adherence assumption of 0% was applied, the cost-effectiveness estimate increased but remained below £30,000 per QALY gained. It concluded that its preferred ICER was in the range that could



be considered cost-effective.

## Innovation

### **The innovative quality of long-acting antiretroviral injections is taken into account in the cost effectiveness**

3.22 The committee considered whether cabotegravir and rilpivirine could be considered innovative, and whether the company's economic analysis had captured all associated health-related benefits. The committee was aware that cabotegravir with rilpivirine is the first long-acting antiretroviral injectable available for people with HIV and agreed with the company that there is an unmet need for an alternative to current oral ARTs. The committee considered that the dosing frequency and method of administration had been captured by the utility benefit associated with treatment. It concluded that it had taken this innovative quality into account when considering the cost effectiveness of long-acting cabotegravir and rilpivirine.

## Equalities

### **HIV-1 disproportionately affects some populations, but this cannot be addressed in a technology appraisal**

3.23 The committee noted potential equality issues raised during the NICE scoping and appraisal process. HIV-1 disproportionately affects some populations such as gay, bisexual and trans people, people of black African family background, people from countries with a high community prevalence, people who are homeless, and people who inject drugs. The company confirmed that there is no evidence of a difference in the effect of cabotegravir with rilpivirine in any population with protected characteristics and the guidance would apply equally to all groups for whom there was evidence presented. Also, the committee noted that differences in incidence of a condition in different groups cannot be addressed in this technology appraisal.

## **The committee took into account lifestyle factors that may affect people's ability to have treatment**

3.24 At technical engagement, clinical and community groups noted that lifestyle factors may affect people's ability to attend clinics or adhere to their medication. People with chaotic lifestyles (for example people who are homeless, in prison, or who use drugs) may struggle to keep up with daily oral medication because it needs to be taken at the same time each day, with food, whereas long-acting injections may not suit people who cannot easily access their clinic for appointments. The committee was not presented with evidence relating to adherence for people with different lifestyle factors, but took this issue into account in its decision making.

## **The committee took into account in its decision making that some people struggle to take oral treatments**

3.25 The committee acknowledged that some people struggle to take their oral medication because of psychological or social reasons, and some people have difficulty swallowing or absorption issues. It was unclear whether this technology would benefit these people because the committee had not been presented with the necessary information about the current comparator treatments for this population to make a decision. However, the committee took this issue into account for its decision making.

## **It is not possible to address needle phobia in this technology appraisal**

3.26 The committee noted that even though this technology is a helpful alternative to current standard of care, it might not be suitable for individuals who have needle phobia. Needle phobia was not considered in the company's clinical- or cost-effectiveness evidence. The committee did not consider this to be an equalities issue and did not consider it possible to address needle phobia in this technology appraisal.

## **The benefit of long-acting antiretrovirals for stigma related to**



## taking daily tablets for HIV is included in the modelling

- 3.27 The committee was aware of the stigma associated with HIV. It acknowledged that long-acting antiretrovirals could remove the stigma-related concerns associated with daily tablets, for example the fear of unwanted disclosure if tablets are seen, and the burden of a constant reminder of HIV status (see [section 3.2](#)). However, the committee considered this benefit had been taken into account in the modelled utility advantage for cabotegravir with rilpivirine compared with oral ART (see [section 3.19](#)).

## Conclusion

### Cabotegravir with rilpivirine is recommended for routine commissioning

- 3.28 The committee recommended cabotegravir with rilpivirine, within its marketing authorisation, for treating HIV-1 infection in adults with virological suppression (HIV-1 RNA fewer than 50 copies/ml) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no previous virological failure with, any NNRTIs or INIs. The committee acknowledged that cabotegravir with rilpivirine meets an unmet need for people living with HIV-1 by offering an alternative to daily oral regimens. There was uncertainty about the size of the utility advantage for cabotegravir with rilpivirine over daily oral ART. Despite this uncertainty, the committee considered that a utility advantage was plausible because cabotegravir with rilpivirine may be valued by people concerned about stigma and disclosure of their HIV status, and it reduces the burden of taking daily tablets (see [section 3.19](#)). The committee considered it was acceptable for the company to assume in its model that long-acting cabotegravir with rilpivirine and oral ARTs have the same efficacy. But it was not appropriate to assume that adherence is greater with cabotegravir with rilpivirine compared with oral ARTs. The committee acknowledged other factors including the innovative nature of cabotegravir with rilpivirine, the daily burden of taking tablets, the equalities issues raised (see [section 3.23](#)) and the negative impact that stigma has on the lives of people living with HIV. But it recalled that this

was captured in the cost-effectiveness calculation (see section 3.19). Using the committee's preferred adherence assumption (see [section 3.16](#)), the most plausible ICER for cabotegravir and rilpivirine compared with oral ART was lower than £30,000 per QALY gained. The committee concluded that the cost-effectiveness estimates were unlikely to exceed its acceptable maximum even though some uncertainties remained. Taking all this into account, the committee concluded that cabotegravir with rilpivirine is likely to be a cost-effective use of NHS resources for treating HIV-1, so it is recommended.

## 4 Implementation

- 4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HIV and the doctor responsible for their care thinks that cabotegravir with rilpivirine is the right treatment, it should be available for use, in line with NICE's recommendations.

## 5 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Anne Murray-Cota**

Technical lead

**Hannah Nicholas**

Technical adviser

**Gavin Kenny**

Project manager

ISBN: 978-1-4731-4385-2