

## Interim BHIVA guidance on long-acting cabotegravir/rilpivirine (LA-CAB/RPV) for antiretroviral therapy

### Introduction

LA-CAB/RPV is already in use in Scotland and imminently so in other UK nations. In lieu of the formal 2022 BHIVA treatment guidelines, due for consultation and completion by the BHIVA Spring Conference 2022, we have developed interim guidance on the use of injectables in response to enquiries from members and people living with HIV.

For comparison, virological failure rates of monthly injectables and the oral arms of FLAIR and ATLAS are shown in the Appendix.

A non-technical summary is in development.

This guidance will be superseded by the 2022 BHIVA treatment guidelines and retired.

### Summary of key recommendations for the use of LA-CAB/RPV

#### We recommend that LA-CAB/RPV can be used in people who:

1. Have a significant need for injectable antiretroviral therapy (ART) *and*
2. Have been virally suppressed to <50 copies/mL for at least 6 months *and*
3. Have no known or suspected non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INSTI) resistance *and*
4. Have no history of virological failure or unplanned treatment interruption on NNRTI- or INSTI-containing ART *and*
5. Have no history of INSTI monotherapy *and*
6. Can tolerate and commit to 2-monthly attendance for injections *and*
7. Accept the risk of virological failure despite complete adherence (approximately 1 in 70 at year 1 and 1 in 60 at year 2) *and*
8. Have a BMI <30 kg/m<sup>2</sup> AND non-A1/6 subtype if baseline resistance is unavailable *and*
9. Do not need a tenofovir-containing regimen for the treatment or prevention of hepatitis B

#### We recommend that LA-CAB/RPV can be continued in people who:

1. Have received LA-CAB/RPV in a clinical trial
2. Are on LA-CAB/RPV as part of a compassionate access or named patient programme

#### We recommend the following viral load monitoring:

1. HIV-RNA quantification at every visit
2. Prompt recall for repeat testing and resistance testing if viral rebound occurs

### Background

The initial registrational trials compared monthly LA-CAB/RPV with continued oral therapy in virally suppressed people (ATLAS and FLAIR). Both trials demonstrated non-inferiority of injectable therapy for the primary endpoint of virological failure and key secondary endpoint of virological success. ATLAS-2M compared monthly LA-CAB/RPV to a 2-monthly dosing schedule, demonstrating non-inferiority for the same primary and secondary endpoints at weeks 48 and 96. There are no direct comparisons of 2-monthly LA-CAB/RPV versus oral therapy. HIV-RNA quantification was performed at each visit in the trial so, until trial and/or real-world evidence emerges to support otherwise, we

recommend viral load monitoring at all visits and prompt recall for repeat testing and resistance testing if viral rebound occurs.

The European Medicines Agency granted approval to both the monthly and 2-monthly LA-CAB/RPV schedules, however the manufacturer is marketing only the 2-monthly option.

The advent of long-acting treatment is an important milestone in the evolution of ART. It is, however, important to acknowledge that LA-CAB/RPV has been investigated only in the context of viral suppression in a highly selected population and that data in more complex populations, including those with a history of virological failure or treatment interruption, are absent. Identifying people with adherence difficulties plus viral suppression may be challenging.

### **Service capacity**

The introduction of LA-CAB/RPV will have major implications for services, in term of staffing and the time required to support people to follow the strict dosing schedules. Although impact on services was included in the cost-effectiveness analyses undertaken by national approval bodies, there will be no extra funding for those costs, nor for the provision of pre-emptive supplies of oral bridging therapy should these be deemed necessary. It is worth noting that the estimated staff resource used to model costs in the National Institute for Health and Care Excellence technology appraisal was 15 minutes of band 5 nurse time.

*We recommend a careful approach to initial use of LA-CAB/RPV, recognising:*

1. The lack of data in a real-world setting
2. The consequences of virological failure (and the likelihood of dual-class resistance when it occurs)
3. The variable capacity of services to deliver 2-monthly injections at a time when many are still relatively constrained secondary to the impact of COVID-19

Services should therefore prioritise people most in need of injectable ART, who also meet the appropriate criteria, and ensure staff are suitably trained to discuss the key data and support people living with HIV in making decisions about the suitability of LA-CAB/RPV for them. Identifying people who struggle to manage daily pill taking but have managed to maintain viral suppression may be challenging. Patients should be confident that they can commit to 2-monthly injection appointments. We suggest that clinical services carefully consider how to deliver injectable treatment, given the likely gradual accrual of people using this treatment and the need to schedule regular visits.

*Initially it is reasonable for services to focus on the following groups for access to LA-CAB/RPV:*

1. Those most in need:
  - a. People who express a major psychological impact of daily pill taking
  - b. People with physical barriers to pill taking
  - c. People who describe a concerning adherence pattern but remain virally suppressed
  - d. People who describe a real risk of stopping ART if they continue oral therapy
2. Those already receiving LA-CAB/RPV as part of a clinical trial or compassionate access programme
3. Clinics that have capacity and staffing to ensure that repeated, safe administration is possible (i.e. where individual services cannot meet the necessary requirement, they should work within their clinical networks to ensure equitable access) and have robust processes to manage and recall people who miss scheduled injection appointments

### **Recommended criteria for LA-CAB/RPV use**

*Based on the entry criteria for the ATLAS-2M trial, we recommend the following criteria for LA-CAB/RPV use:*

1. Viral suppression to <50 copies/mL for at least 6 months *and*
2. No known or suspected NNRTI or INSTI resistance *and*
3. No history of virological failure on an NNRTI- or INSTI-containing regimen *and*
4. No use of INSTI monotherapy *and*
5. Ability to tolerate and commit to 2-monthly attendance for intramuscular (IM) injections *and*
6. Acceptance of a small risk of virological failure and resistance (approximately 1 in 70 at year 1 and 1 in 60 at year 2) *and*
7. In the absence of baseline resistance test availability, BMI <30 kg/m<sup>2</sup> AND non-A1/6 subtype *and*
8. No requirement for a tenofovir-containing regimen for the treatment or prevention of hepatitis B

*People should be counselled that:*

1. Known or suspected resistance to the either drug a detectable viraemia are exclusions
2. They will require an oral lead-in and then two deep IM injections 1 month apart followed by deep IM injections every 2 months in clinic
3. Implementation work shows they can expect to spend 30–60 minutes in clinic at each visit
4. Adherence is critical with a **maximum** of +/- 7 day window for early/late administration; oral bridging can be used but should be considered an exception rather than routine
5. In clinical trials, about 1 in 70 people on 2-monthly LA-CAB/RPV experienced viral rebound at year 1, and 1 in 60 at year 2, despite 100% adherence, and most of those also developed resistance to one or both drugs

### **LA-CAB/RPV and pregnancy**

There is limited information about injectable treatment in pregnancy so it is not a recommended option. Individuals wishing to conceive can remain on LA-CAB/RPV. Those becoming pregnant on LA-CAB/RPV should consult with their physician.

Please contact [bhiva@bhiva.org](mailto:bhiva@bhiva.org) with any enquiries.

### Appendix. Virological failure rates

ATLAS-2M (2-monthly [2M] vs monthly [1M] injectable) risk of failure (mostly with resistance):

- 2M arm
  - 1 in 70 after 1 year on 2M
  - 1 in 60 after 2 years on 2M
  - 1 in 40 after 3 years on 2M
- 1M arm
  - 1 in 100 on 1M with no more failure after year 1

FLAIR (1M vs oral) where people were started on abacavir/dolutegravir/lamivudine and had to be suppressed at week 20:

- Oral arm (abacavir/dolutegravir/lamivudine) - adherence not reported
  - 1 in 94 at year 1 with no resistance
  - 1 in 70 at year 2 with no resistance
- 1M arm
  - 1 in 70 at year 1, 75% with two-class resistance
  - No more failure after year 1

ATLAS (1M vs ORAL):

- Oral arm
  - 1 in 80 at year 1  
Of the failures (n=4): one failed lamivudine/zidovudine + efavirenz with M184V + G190S NNRTI; one failed elvitegravir/cobicistat/emtricitabine/tenofovir with M184I; one failed elvitegravir/cobicistat/emtricitabine/tenofovir with M230I NNRTI; and one failed elvitegravir/cobicistat/emtricitabine/tenofovir with no resistance
  - No additional confirmed virological failures at year 2
- 1M arm
  - 1 in 100 at year 1, all (n=3) with NNRTI resistance, one also with INSTI resistance
  - No additional confirmed virological failures at year 2