Article

Overton ET, Richmond G, Rizzardini G, et al. **Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study**. *Lancet*. 2020;396(10267):1994-2005. https://doi.org/10.1016/S0140-6736(20)32666-0

Study Summary

The ATLAS-2M study is a randomized, multi-center, open-label, phase 3b, non-inferiority trial that assessed the efficacy and safety of maintenance treatment with long-acting intramuscular cabotegravir plus rilpivirine administered every eight weeks versus every four weeks in adults living with HIV.

Study Setting

- Clinical trial sites in Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the United States of America.

Methods

- Eligible participants were enrolled from two groups. The first group was enrolled directly from the ATLAS study, and the second group included newly recruited participants receiving an oral standard-of-care antiretroviral (ART) regimen.
- The ongoing phase 3 ATLAS study is comparing long-acting cabotegravir and rilpivirine dosed every 4 weeks as maintenance therapy to daily oral ART, and found that cabotegravir plus rilpivirine was non-inferior to oral ART at maintaining viral suppression over 48 weeks.
    - Participants were recruited into ATLAS-2M from both the oral standard-of-care group and the long-acting group of the ATLAS study, after completing the 52-week comparison phase.
- Newly recruited individuals must have received an uninterrupted first or second line oral standard-of-care regimen for at least 6 months, without previous virological failure (≥400 copies/mL), and have no known integrase strand transfer inhibitors (INSTI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance-associated mutations, except for K103N.

- All participants had to have a HIV-1 viral load of <50 copies/mL at study entry, and newly recruited participants were required to have at least two additional viral load measurements of <50 copies/mL in the previous year.
- Participants were randomly assigned (1:1) to receive long-acting cabotegravir plus rilpivirine maintenance dosing of either every 8 weeks (cabotegravir 600 mg plus rilpivirine 900 mg) or every 4 weeks (cabotegravir 400 mg plus rilpivirine 600 mg). Both agents were given separately as single 3 mL (every 8 weeks) or 2 mL (every 4 weeks) injections into the gluteal muscle.
- Randomization was stratified by previous cabotegravir plus rilpivirine exposure (0 weeks, 1-24 weeks and >24 weeks) to account for individuals entering from the ATLAS study.
- Participants with no previous exposure to cabotegravir plus rilpivirine initially received 4 weeks of once-daily oral lead-in treatment with cabotegravir 30 mg plus rilpivirine 25 mg to assess tolerability before long-acting administration, followed by initial loading injections (cabotegravir 600 mg plus rilpivirine 900 mg) before maintenance injections every 8 weeks or every 4 weeks.
- Phenotypic and genotypic resistance testing for HIV-1 reverse transcriptase, protease, and integrase was done at suspected virological failure (SVF), defined as the visit prior to confirmed virological failure (CVF). Baseline peripheral blood mononuclear cells (PBMCs) were collected and assessed in individuals with confirmed virologic failure (CVF) using genotypic testing. CVF was defined as two consecutive viral load measurements ≥200 copies/mL.
- A questionnaire at week 48 assessed participants' preference for cabotegravir plus rilpivirine every 8 weeks dosing versus 4 weeks dosing or previous daily oral dosing.
- Blood samples for pharmacokinetic assessment of cabotegravir and rilpivirine plasma concentrations were drawn before the first intramuscular injection and pre-dose in both groups at weeks 8, 16, 24, 32, 40, and 48, or at withdrawal.
- The primary efficacy endpoint was the proportion of participants with a viral load ≥50 copies/mL at week 48. The key secondary efficacy endpoint was the proportion of participants with viral load <50 copies/mL at week 48.
- Other secondary efficacy endpoints included the proportion of participants with CVF at week 48 and incidence of treatment-emergent genotypic and phenotypic resistance in participants with CVF.
- Secondary endpoints included plasma pharmacokinetic parameters for long-acting cabotegravir and rilpivirine, regimen preference and safety, including the incidence and severity of adverse events after 48 weeks.

- The primary analysis was based on the intention-to-treat exposed (ITT-E) population and the non-inferiority margin for every 8 weeks dosing, compared to 4 weeks dosing, was set at 4%.

Study Population and Follow-up

- In total, 1,149 individuals were screened between October 2017 and May 2018, of whom 1,045 were included in the ITT-E population; 522 in the every 8 weeks group and 523 in the every 4 weeks group.
- Participants were mostly white (73%), with a median age of 42 years (interquartile range [IQR] 34–50), 27% were female at birth, and the median CD4+ count at baseline was 661 cells/μL (IQR 508–849).
- Overall, 37% of participants had previously received long-acting cabotegravir plus rilpivirine every 4 weeks in ATLAS, of whom most (65%) had >24 weeks of previous exposure.
- There were 78 treatment discontinuations overall, representing 7% of participants in the every 8 weeks group and 8% in the every 4 weeks group.
- Injections were administered within the protocol-specified 7 days of the planned visit 98% of the time in the every 8 weeks dosing group and 99% of the time in the every 4 weeks dosing group.

Efficacy Outcomes

- At week 48, nine (2%) participants in the every 8 weeks dosing group and five (1%) in the every 4 weeks dosing group had a viral load ≥50 copies/mL, with an adjusted treatment difference in proportions of 0.8 (95% CI -0.6-2.2), thus meeting the pre-specified non-inferiority criterion of the primary endpoint.
- Similarly, the non-inferiority criterion was met for the key secondary efficacy endpoint of viral load <50 copies/mL, with 94% of participants in the every 8 weeks group and 93% in the every 4 weeks group maintaining viral suppression at week 48 (adjusted treatment difference in proportions 0.8; 95% CI -2.1-3.7).
- There were ten cases of CVF through to 48 weeks: eight in the every 8 weeks group and two in the every 4 weeks group.
    - Seven of these participants had no exposure to cabotegravir plus rilpivirine before enrolling in the study. The remaining three participants with CVF (all every 8 weeks group) had a cumulative exposure to cabotegravir plus rilpivirine at the SVF visit for 16, 33, and 61 weeks, respectively.
    - Five of the eight participants with CVF in the every 8 weeks dosing group had archived NNRTI resistance-associated mutations to rilpivirine in baseline PBMC samples, either alone (n=4) or in combination with an archived major INSTI resistance-associated mutation (n=1). Neither of

the two every 4 weeks participants with CVF were found to harbor baseline INSTI or NNRTI mutations.
    - Plasma cabotegravir and rilpivirine concentrations for participants with CVF were within the range of concentrations for the overall study population at the time of SVF.
    - Nine out of ten participants with CVF achieved viral re-suppression on oral ART with protease inhibitor-based or INSTI-based regimens. All nine participants who had CVF and available INSTI integrase phenotype data retained phenotypic susceptibility to dolutegravir.

Other Secondary Outcomes

- Adverse events were common, with 77% in the every 8 weeks group and 84% in the every 4 weeks group reporting at least one adverse event, excluding injection site reactions (ISR). However, the majority (91%) of adverse events were grade 1 or grade 2 in severity, and only 2% of participants discontinued treatment due to an adverse event.
- ISR, particularly injection site pain, were the most common adverse events.
    - There were 5,659 ISR in total, 44% of which occurred with every 8 weeks dosing, and 56% occurred with every 4 weeks dosing.
    - Overall, ISR occurred with 30% of all injections in the every 8 weeks group, with 76% of participants having at least one ISR (median 3, IQR 1-8). ISR occurred with 20% of all injections in the every 4 weeks group, with 75% of participants experiencing at least one ISR (median 3, IQR 1–9).
    - The severity and duration of ISR was similar in both groups, with the majority being grade 1 or 2 (98%), and most (86%) resolving within 7 days (median 3 days). Discontinuation for injection-related reasons occurred in 1% of participants in the every 8 weeks group and 2% of participants in the every 4 weeks group.
    - Fewer participants in the every 8 weeks group with previous cabotegravir plus rilpivirine exposure in ATLAS reported ISR after the first injection, compared to those without previous exposure (34% vs. 70%).
    - ISR reporting decreased with time in both groups and, by week 48, the proportion of participants reporting ISR was similar in the two groups (20% in every 8 weeks, 19% in every 4 weeks group).
- At week 48, concentrations of cabotegravir were approximately ten times the cabotegravir protein-adjusted concentration required for 90% virus inhibition (PA-IC_{90}) in the every 8 weeks groups and 17 times the PA-IC_{90} in the every 4

weeks group. Rilpivirine concentrations were six times the rilpivirine PA-IC_{90} in the every 8 weeks group and eight times the PA-IC_{90} in the every 4 weeks group.

- Of surveyed participants in the 8 weeks dosing group without previous exposure to cabotegravir plus rilpivirine, 98% preferred every 8 weeks dosing over daily oral dosing of cabotegravir plus rilpivirine. Of participants in the 8 weeks dosing group with previous exposure to cabotegravir plus rilpivirine, 94% of respondents preferred every 8 weeks dosing over both daily oral and every 4 weeks dosing.

Critical Analysis

The randomized, multi-center, open-label, phase 3b, non-inferiority ATLAS-2M study found that long-acting intramuscular cabotegravir plus rilpivirine dosed every 8 weeks was highly efficacious and non-inferior to dosing every 4 weeks in maintaining viral suppression after 48 weeks. Although ISR were common, there were no significant differences in safety and tolerability between the two dosing groups. Most participants in the 8 weeks dosing group greatly preferred this schedule to oral or every 4 weeks dosing.

The following points should be considered when interpreting the study findings:

- The study population was predominantly recruited from high-income countries and pregnant or breastfeeding women were excluded, which may limit generalizability of these findings to populations in sub-Saharan Africa. The study also excluded those with known INSTI or NNRTI mutations at baseline, which further limits generalizability of CVF results in resource-constrained settings where baseline genotyping is not done routinely.
- The larger injection volume (3 mL) could explain the greater proportion of ISR relative to the number of injections given in the every 8 weeks group compared with the every 4 weeks group. However, this finding should be considered along with the fact that every 8 weeks dosing requires half the injection frequency.
- Participants adhered well to the planned treatment schedule, with few injections administered outside of the allowable treatment window (±7 days), and the few participants with a planned interruption in injection dosing were covered with oral cabotegravir plus rilpivirine bridging. It remains to be seen if this level of adherence and coverage can be maintained in real-world settings.
- The study design did not allow for blinding and the absence of an oral standard-of-care control group prohibits direct comparison to oral ART. Therefore, outcomes were inferred by referencing other ongoing phase 3 trials that found non-inferiority of long-acting cabotegravir plus rilpivirine dosed every 4 weeks versus the standard of care.

- The study enrolled individuals who had achieved viral suppression through adherence to oral ART. Long-acting cabotegravir plus rilpivirine may be a more attractive option for those who struggle to adhere to daily medication, however this population has thus far been excluded from studies of this regimen.

Implications

The randomized, multi-center, open-label, phase 3b, non-inferiority ATLAS-2M study found that long-acting intramuscular cabotegravir plus rilpivirine given every 8 weeks is as efficacious and well-tolerated as every 4 weeks dosing for maintaining HIV-1 viral suppression and could be considered as a therapeutic alternative to daily oral ART. The study regimen dosed every 8 weeks was highly preferred by participants and has the potential to improve treatment convenience, adherence, and quality of life for people living with HIV. Since this article was published, the U.S. Food and Drug Administration approved a combined long-acting cabotegravir plus rilpivirine regimen given every 4 weeks for maintenance therapy, making it the first long-acting injectable approved for ART.[1] While populations with adherence challenges may benefit the most from long-acting ART, they have yet to be included in clinical trials of such regimens, and use of long-acting ART in resource-limited, real-world settings necessitates further implementation planning. Nonetheless, the option of a long-acting form of ART is an important development and an additional tool to provide person-centered care that meets the needs of people living with HIV.

Reference

1) U.S. Food and Drug Administration. *FDA Approves First Extended-Release, Injectable Drug Regimen for Adults Living with HIV*. FDA New Release; January 21, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-extended-release-injectable-drug-regimen-adults-living-hiv

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