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Use of long-acting injectable cabotegravir and rilpivirine in HIV maintenance therapy

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Abstract

Objective: To determine if long-acting injectables cabotegravir and rilpivirine are non-inferior to oral antiretroviral therapy at maintaining viral load suppression below 50 copies per milliliter of serum. *Design:* Systematic literature review. *Methods:* A search was done in PubMed using the terms "HIV + cabotegravir" or "HIV + cabotegravir, rilpivirine drug combination." Limitations included non-randomized control trials, comparison of injectable regimens directly or injectables to placebo, studies that evaluate compliance or side effects only, and studies with small sample sizes. *Results:* Meta-analysis revealed that continued use of injectables was sufficient in maintaining viral suppression at 93.6%, 92.5%, and 94% in each of the respective studies. This demonstrated non-inferiority to oral therapy. *Conclusion:* Overall, the three studies randomized participants in oral or long acting therapies after an oral induction period. Long-acting injectable formulations were proven to be non-inferior in the maintenance of viral load suppression. Use of monthly injectable antiretrovirals offers an alternative for increased compliance to many people living with HIV. Efficacy of long-acting injectables as initial therapy and their use in the pediatric population need further study.

Introduction

Human Immunodeficiency virus (HIV) remains a global health concern with an estimated 37.7 million people living with HIV.[1] HIV is an RNA virus that enters primarily through anogenital mucosa and then acts by targeting dendritic cells, macrophages, and CD4+ T cells. Risk factors for transmission include men who have sex with men, IV drug users, blood product recipients, and needle-stick exposure among healthcare workers. The natural course if the disease progresses to a chronic infection characterized by a depletion of CD4+ T cells; this results in an inability to mount an immune response to pathogens.[2]

Prior to the introduction of antiretroviral therapy, HIV was a death sentence due to the acquisition of opportunistic infections that are terminal. However, improvements in therapy have drastically improved the life expectancy and quality of life for those living with HIV, allowing these individuals to achieve a lifespan approaching that of the general population. Despite the advancements made in treatment, typical regimens involve daily intake of two to three orally administered drugs requiring a high degree of medication adherence in order to sustain suppression of the virus. Elements including dosing frequently, food considerations, other drug-drug interactions, as well as the emotional burden of taking multiple pills each day have

precipitated the issue of non-compliance and viral resistance to the therapy.[3] Alternate methods to combat these obstacles have started the pursuit for more acceptable and appealing options.

Long-acting injectable antiviral therapy has shown to be a promising alternative to the daily oral antiviral regimen. Injectable therapy lessens the concern of dietary modifications as well as the stringent compliance required to follow a daily oral medication regimen. The integrase inhibitor cabotegravir and the non-nucleoside reverse-transcriptase inhibitor rilpivirine both have long-acting injectable formulations that have recently been released onto the market. Cabotegravir and Rilpivirine already have shown long-standing success in their oral formulations for HIV infection and their use as injectables is currently under evaluation.[4] Clinical question: among adults aged 18 and older that are currently living with HIV, is the use of long-acting monthly injectable Cabotegravir more tolerable and efficient in medication adherence as well as maintenance of HIV suppression to reach undetectable status (<50 copies per mL of serum) compared to the current standard oral antiretroviral therapies?

Methods

An initial search of PubMed was performed in Fall of 2021 using the search terms "HIV + cabotegravir" or "HIV + cabotegravir, rilpivirine drug combination." These search terms yielded 48 articles. Upon screening these articles, a limit was then placed to eliminate all non-randomized control trials, reducing the number of articles to 12. Furthermore, articles were then excluded for reasons including comparing injectable regimens to other injectables instead of to oral regimens, studies only looking at patient tolerance and preference rather than efficacy of treatment, studies only looking at side effects, comparing the injectables to placebo, and studies with small sample sizes. The three articles remaining were used in the qualitative synthesis.

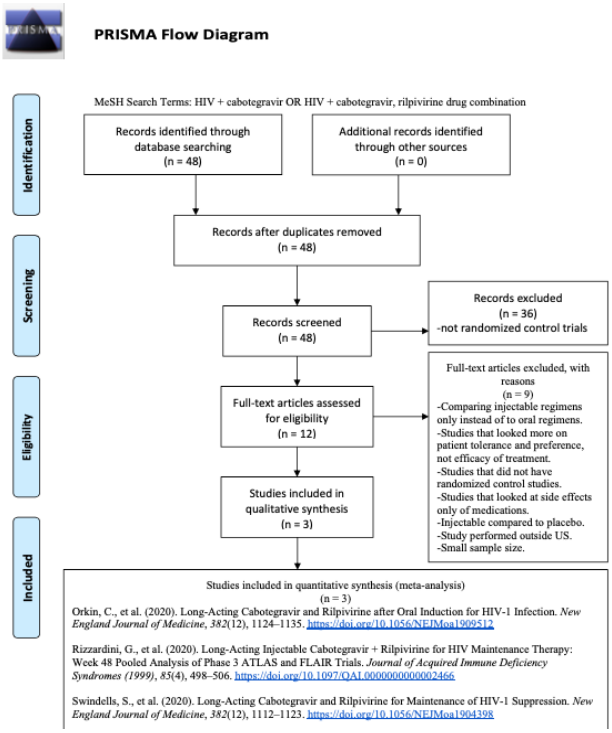

Figure 1: PRISMA flow chart indicating the inclusion and exclusion criteria of literature selection.

Results

Study #1: *Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. Orkin, et. al.*[5]

Objective: To investigate if the use of long acting cabotegravir and rilpivirine is non-inferior to standard oral therapy in patients that are antiretroviral therapy naive.

Study Design

A phase 3 randomized control trial of 809 HIV-positive participants that had not previously been treated with antiretroviral therapy was conducted. Eligible participants were 18 years of age or older and had a plasma HIV1-RNA level of 1000 copies/mL or greater at screening. These individuals were given 20 weeks of daily oral induction therapy with fixed combination dolutegravir–abacavir–lamivudine (50mg/600mg/300mg). Following the 16th week, participants with less than 50 copies of HIV1 RNA per mL of serum were then randomly divided in a 1:1 ratio to either continue their current oral regimen or switch to oral cabotegravir plus rilpivirine for 1 month followed by monthly injections of long acting cabotegravir plus rilpivirine.

Participants that were randomized into the injectable trial were given 4 weeks of oral lead in therapy with 30mg of cabotegravir and 25mg of rilpivirine once daily to confirm the safety and side-effect profile of the drugs prior to initiation of long-acting injectable therapy. At week 4, these participants received a loading injection of 600mg of cabotegravir and 900mg of rilpivirine (3mL each), administered into the gluteus muscle. Subsequent injections of 400mg of cabotegravir and 600mg of rilpivirine (2mL each) were administered within 21 to 28 days after the previous injection for the second and third injections and a window of 21 to 35 days thereafter. Participants unable to attend the visit for an injection were given oral bridging therapy with cabotegravir. This study was not blinded.

The primary endpoint was the percentage of participants who had a plasma HIV-1 RNA level of 50 copies per milliliter or higher at week 48 of the maintenance phase. The secondary endpoint was the percentage of participants who had a plasma HIV-1 RNA level less than 50 copies per at week 48 of the maintenance phase.

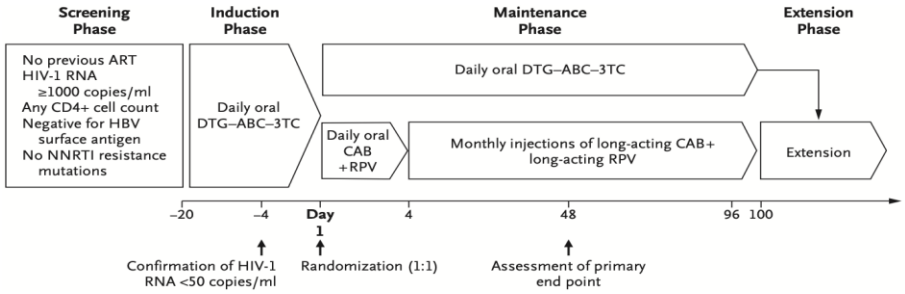

Figure 2: Orkin et. al randomization of HIV positive patients with no prior ART after screening and oral induction therapy into continued oral therapy or monthly injectable long-acting therapy.

Study Results

At 48 weeks, greater than 50 copies/mL HIV1 RNA were found in 6 participants (2.1%) of the long-acting injectable therapy and in 7 participants (2.5%) who received continued oral therapy. Therefore, regarding the primary endpoint, the long-acting injectable formulation was found to be non-inferior to the oral therapy.

The secondary endpoint of HIV1 RNA level less than 50 copies per mL at 48 weeks were found in 93.6% of long-acting therapy participants and in 93.3% of participants receiving oral therapy with a 95% confidence interval of −3.7 to 4.5. This endpoint also meets the criteria of proving non-inferiority of the injectable formulation compared to the oral.

Adjuvant endpoints were also measured. Grade 3 adverse events or higher were seen in 11% in the injectable and 4% in the oral formulation. Liver-related stop criteria were found in 2% in the injectable and 1% in the oral formulation. Treatment satisfaction in the injectable formation participants was 91%.

Study Critique

The strength of this study was the use of previously untreated participants and use of a standardized induction medication to minimize potential resistance to antivirals from previous regimens that could alter the results of the study. Efficacy results in this trial using the long-acting therapy were similar to those seen in the ATLAS trial, which had a similar switch design but consisted of participants that had longer-term viral suppression. Overall, potential clinical use of long acting regimen remains to be a viable option for a spectrum of HIV-1 infected individuals.

Study #2: *Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. Swindells, S., et al.*[6]

Objective: To compare the efficacy of standard oral antiretroviral therapy to that of intramuscular injections of long-acting cabotegravir and rilpivirine at maintaining viral suppression of less than 50 copies per milliliter after 48 weeks in HIV-1 positive patients.

Study Design

This was a randomized open-label trial that enrolled patients aged 18 and older with HIV-1 infection and viral load documented as less than 50 copies per milliliter within 6 to 12 months before screening. Participant's current antiretroviral regimens included two nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs) plus either an integrase strand transfer inhibitor (INSTI), non-nucleoside reverse-transcriptase inhibitor (NNRTI), protease inhibitor (PI), or unboosted atazanavir. Exclusion criteria included active hepatitis B infection, previous virologic failure, INSTI or NNRTI resistance mutations, or interruption to their current regimen within 6 months prior to screening or any interruption greater than 1 month in duration.

Qualified participants were randomly assigned in a 1:1 ratio to one of two groups; they either continued their current oral therapy or were switched to the long-active therapy regimen. Groups were stratified based on the class of the third antiretroviral drug as well as sex at birth. The long-acting therapy group received 30mg of oral cabotegravir plus 25mg of rilpivirine once daily with food for the first 4 weeks for assessment of safety and side effects. Next, they were given initial doses of 3mL injection of cabotegravir and 3mL injection of rilpivirine into the gluteus muscle followed by 2mL injections of cabotegravir and 2mL injections of rilpivirine every 4 weeks through week 52 of the maintenance phase.

Participants attended monthly clinic visits to obtain a physical exam, address any adverse events, collect blood samples for clinical evaluation, assess viral load, and give long-acting injections within that respective group. The primary endpoint of the study was the percentage of participants with plasma HIV-1 RNA levels of greater than or equal to 50 copies per milliliter at week 48 and the secondary endpoint was the percentage with plasma HIV-1 RNA levels of less than 50 copies per milliliter at week 48. Patient satisfaction of antiretroviral therapy was assessed at baseline as well as at weeks 24 and 44 via the 12-item HIV Treatment Satisfaction Questionnaire (HIVTSQs). Lastly, a single-item question regarding preference for long-acting or oral therapy was assessed in the long-acting therapy group at week 48.

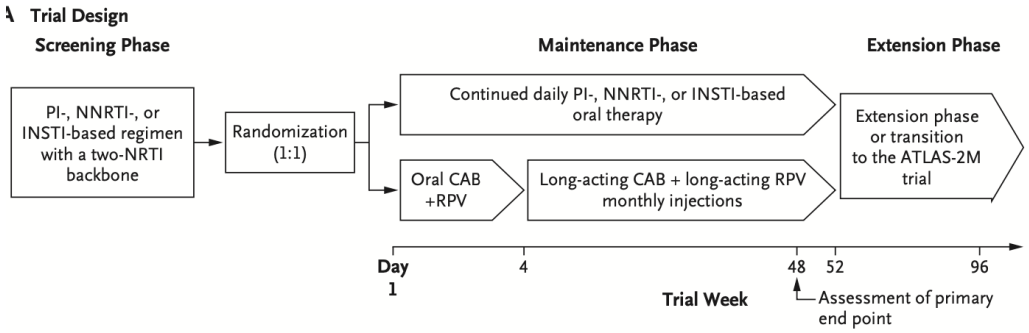

Figure 3: Swindells et. al randomization of HIV positive patients on oral ART after screening into continued oral therapy or monthly injectable long-acting therapy.

Study Results

618 patients underwent randomization in subgroups. Participants were 33% female, 32% nonwhite, and had a medium age of 42 years old. 93% of patients completed maintenance-phase treatment through week 52. 26 participants in the long-active therapy group and 18 in the oral therapy group withdrew from the trial. Intention to treat protocol was followed.

An HIV-1 RNA level of 50 copies per milliliter or higher at week 48 was found in 5 participants (1.6%) in the long-acting therapy group and 3 (1.0%) in the oral therapy group. An HIV-1 RNA level of less than 50 copies per milliliter at week 48 was achieved in 92.5% of the long-acting therapy group and 95% of the oral therapy group. Therefore, criteria was met to establish noninferiority of the long-acting injectables compared to the oral antiretrovirals for both the primary and secondary endpoints of the study. The most common adverse events in the long-acting therapy group were injection site reactions.

In regard to patient tolerability, after 44 weeks of therapy, those in the long-acting injectable group reported an average 5.68 point increase in score from baseline on the HIVTSQs. A within-group comparison also showed that 266 of 273 (97%) of participants that responded to the questionnaire selected the injectable regimen over daily oral therapy as their preferred HIV treatment.

Study Critique

Strengths of this study include demonstration of successful treatment of HIV-1 infection with an all-injectable regimen as a non-inferior alternative to daily oral regimen. This long-acting injectable therapy ultimately improves adherence, side effects, and quality of life for those living with the disease. HIV-1 suppression through 48 weeks was maintained at similar percentages within both groups, participants in the long-acting therapy group reported greater satisfaction and preferred this regimen over their prior oral therapy, and adverse events were reported in both treatment groups at a similar rate. Some limitations of the study include the requirement of suppressed HIV-1 infection with no previous virologic failure or gaps in treatment, ultimately limiting the ability to generalize findings to a broader population.

Study #3: *Long-Acting Injectable Cabotegravir + Rilpivirine for HIV Maintenance Therapy: Week 48 Pooled Analysis of Phase 3 ATLAS and FLAIR Trials. Rizzardini, G., et al.*[7]

Objective: To analyze if monthly injections of cabotegravir + rilpivirine demonstrate noninferiority to participants' current daily oral antiretroviral regimen at maintaining HIV-1 suppression below 50 copies per milliliter or less.

Study Design

This study was a randomized, open-label study comparing cabotegravir + rilpivirine with current daily oral antiretroviral treatments among 591 adults aged 18 and older with HIV-1 infection. The study consisted of a screening phase, maintenance phase, and extension phase. The screening phase functioned to achieve viral suppression of less than 50 copies per milliliter. Those whose serum HIV-1 RNA reached these levels were randomized in a 1:1 fashion to receive either cabotegravir + rilpivirine monthly IM injections or to continue their current oral regimen. Randomization was stratified by sex at birth, baseline HIV-1 RNA, and based on the third agents of each participant's prior oral regimen. Participants with virologic failure were removed from the study.

The primary endpoint of the study was evaluation of the proportion of participants with plasma HIV-1 RNA levels greater than or equal to 50 copies per milliliter. The secondary endpoint was evaluation of the proportion of participants with plasma HIV-1 RNA levels less than 50 copies/mL. Both were examined at week 48. Data was analyzed via intention to treat protocol.

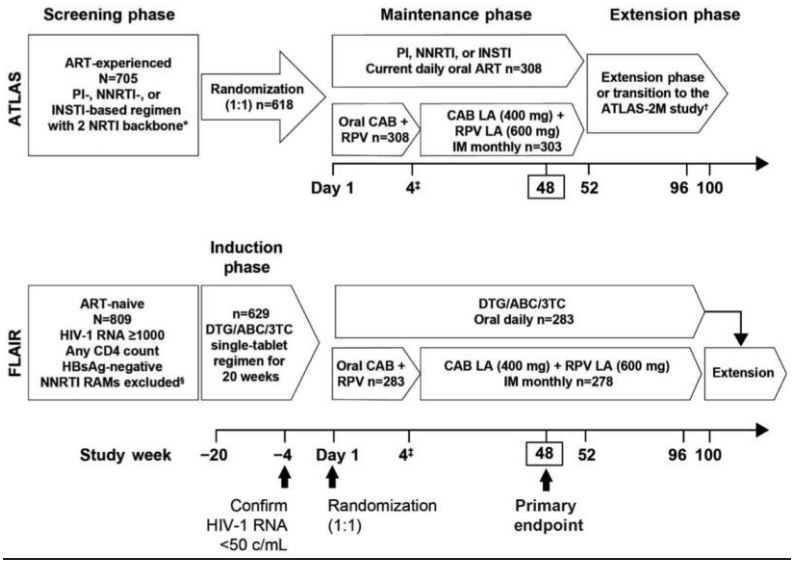

Figure 4: Rizzardini et. al randomization of HIV positive patients either on oral ART or with no prior ART after screening and oral induction therapy into continued oral therapy or monthly injectable long-acting therapy.

Study Results

At 48 weeks, greater than 50 copies/mL HIV1 RNA were found in 11 participants (2%) of the long-acting injectable therapy and in 10 participants (2%) who received current oral therapy. This trial met the noninferiority criteria for the primary endpoint, initially set at 4% margin. Additionally, the second endpoint was also met with 550 (93%) the long-acting injectable participants and 558 (94%) having HIV-1 RNA less than 50 copies/mL of serum. This also met the noninferiority margin set at 10%. Efficacy was consistent among subgroups.
At week 48, seven of the long-acting participants had achieved virologic failure. Six of these participants were found to have resistance mutations to one or both medications.

Adverse events excluding injection site reactions were reported by 506 (86%) of long-acting participants and 444 (75%) of current oral therapy participants with mostly classifications of grade 1 or 2 adverse reactions. 17 (3%) participants in the long-acting arm and 6 (1%) participants in the current antiretroviral therapy arm had ALT elevations greater than or equal to three times the upper limit of normal. Furthermore, seven of these participants were found to have hepatitis A, three with hepatitis B, two with hepatitis c, and one with hepatitis E, none of which are considered to represent drug-induced liver injury.

Study Critique

The results of the primary and secondary endpoints were generally similar between all subgroups and virologic success with long-acting therapy at week 48 in this analysis is like previous phase 3 noninferiority switch studies. Additionally, the number of participants that had virologic failure occurred in 1% of participants through week 48. This proportion is comparable to other larger switch studies that had less than or equal to 1%.

Limitations of this study include a relatively short duration of treatment when compared to lifelong therapy. Additionally, selection bias was present in the participants since it was shown that people living with HIV interested in injectable therapy were likely to enroll in the study. In summary, the efficacy and safety results indicate CAB + RPV long-acting can be a potential therapeutic approach to virologically suppressed HIV-1.

Pooled Outcomes of the Selected Studies			
	Orkin et. al[5]	Swindells et. al[6]	Rizzardini et. al[7]
n of LA injectables	283	308	591
HIV-1 <50 copies	265	285	550
HIV-1 ≥50 copies	6	5	11
% Undetectable	**93.6%**	**92.5%**	**93.1%**
n of Oral Regimen	283	308	591
HIV-1 <50 copies	264	294	558
HIV-1 ≥50 copies	7	3	10
% Undetectable	**93.3%**	**95.5%**	**94.4%**

Table 1: Results demonstrated that continued use of injectables was sufficient in maintaining viral suppression. Long-acting formulations are shown to be non-inferior to oral antiretroviral therapy in the maintenance of viral load suppression.

Discussion

HIV is a deadly disease that remains highly prevalent across the population. Despite major advancements in medications and treatments allowing those with HIV to reach a life span equal to that of the general population, the daily maintenance regimens still pose challenges due to the rigorous scheduling, compliance, side effect profile, drug-drug interactions, and emotional toll it takes on individuals living with HIV. New alternative methods of HIV antiretroviral therapy, such as long-acting injectables cabotegravir and rilpivirine, may act to reduce these obstacles and the emotional burden that comes with it. The purpose of this review is to determine if injectable antiretroviral agents are non-inferior to oral regimens at suppressing HIV viral load below 50 copies per milliliter of serum.

All three studies examined the use of cabotegravir and rilpivirine in their injectable formulations to maintain a virologic suppression after an induction period of oral antiretrovirals.

Following confirmation of viral suppression, participants of all three studies were randomized into groups that either continued their oral regimens or were switched to the long-acting injectable medications. Each study examined a different subgroup of people living with HIV including those who were newly diagnosed and had no prior treatment of antiretroviral therapy and those that had already been on a maintenance therapy. In all three studies, the continued use of injectables were sufficient in maintaining viral suppression at 93.6%, 92.5%, and 94%, respectively. This proved non-inferiority to oral regimens.

Limitations exist within each study that may potentially affect end results. Ultimately, the studies standardized patients with an induction period of oral therapy prior to randomization and initiation of injectable therapy. This leaves the question of if injectables are efficacious as the initial method of treatment to suppress viral load or if its effectiveness pertains solely to those that have achieved undetectable viral load status prior to initiation. Additionally the patient populations within each study were different. Study 1 evaluated those that had never taken any form of antiviral therapy prior to the induction period compared to studies 2 and 3 that selected individuals already on a daily oral regimen within undetectable viral loads. This allows for a holistic view across patient populations, however it increases the suspicion that those without prior use of oral regimens have not experienced the same challenges with regard to compliance. Ultimately, results for both subsets of populations remained equivocal in their respective studies, indicating this may only be a minute observation.

Conclusively, these studies correspond with the end result in showing that the use of injectables as long term therapy is non-inferior to oral regimens and can be offered as an alternate option for HIV positive patients that prefer single monthly dosing.

Conclusion

Question: Among adults aged 18 and older that are currently living with HIV, is the use of long-acting monthly injectable Cabotegravir more tolerable and efficient in medication adherence as well as maintenance of HIV suppression to reach undetectable status (<50 copies per mL of serum) compared to the current standard oral antiretroviral therapies?

Long-acting injectables cabotegravir and rilpivirine are well-tolerated antiretroviral therapies that provide increased patient compliance while simultaneously demonstrating non-inferiority to oral regimens at maintaining HIV virologic suppression below 50 copies per milliliter of serum. It has the potential to provide a more tolerable medication regimen to improve overall patient satisfaction and compliance. Unanswered questions remain in regard to efficacy and use of these medications in the pediatric HIV positive population as well as their effectiveness in initial viral load suppression from baseline in newly diagnosed adult patients.

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