

# Trizivir (Abacavir/Lamivudine/Zidovudine) plus Lopinavir/Ritonavir Induction Therapy Followed by Trizivir-Alone Maintenance for HIV-1-Infected Patients: A 96-Week Pilot Treatment Simplification Study

Joseph C. Gathe<sup>1\*</sup>, Dean T. Martin<sup>2</sup>, M. Keith Rawlings<sup>3</sup>, Benjamin Daquioag<sup>1</sup>, John E. Fuchs<sup>4</sup>,  
Vanessa C. Williams<sup>4</sup>, Katrina L. Oie<sup>4</sup>, Gary E. Pakes<sup>4</sup>

<sup>1</sup>Therapeutic Concepts P.A., Houston, USA; <sup>2</sup>Cigna Healthcare Corp., Phoenix, USA; <sup>3</sup>Peabody Clinic, Dallas, USA; <sup>4</sup>GlaxoSmithKline, Research Triangle Park, Durham, USA.

Email: \*DrGathe@JosephGathe.com

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## ABSTRACT

**Objective:** The purpose of this study was to investigate whether switching HIV-infected patients stabilized on Trizivir (abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg) plus lopinavir/ritonavir 400 mg/100mg twice daily to Trizivir alone affects clinical efficacy and tolerability. **Methods:** This phase 4, open-label, pilot study was conducted over 96 weeks in 23 antiretroviral-naïve, HIV-infected patients. Initially, these patients received induction therapy with Trizivir plus lopinavir/ritonavir 400 mg/100mg twice daily. Patients who achieved a viral load < 50 copies/mL at week 36 or 44 started maintenance therapy with Trizivir alone at week 48 and continued this regimen through week 96. **Results:** The study population was a median of 37 years of age, predominantly male (78%) and African American (61%, with 39% Caucasians), and had a baseline mean viral load of 5.45 log<sub>10</sub> copies/mL and CD4+ count of 232 cells/mm<sup>3</sup>. Nineteen patients completed induction; of the four who did not, three were lost to follow-up and one withdrew due to gastrointestinal adverse events. In 14 induction completers who had viral load measurements taken at week 48, intent-to-treat: observed analysis showed a week 48 viral load < 400 copies/mL attained in 100% (14/14) and <50 copies/mL attained in 71% (10/14). Median week 48 CD4+ cell count was 192 cells/mm<sup>3</sup> higher than the baseline count. Twelve patients completed the subsequent 48-week Trizivir-alone maintenance phase, of whom 11 (92%) achieved viral loads of both <400 and <50 copies/mL at week 96. Median week 96 CD4+ cell count was 208 cells/mm<sup>3</sup> above baseline. Trizivir-only maintenance was associated with fewer adverse events than the Trizivir-lopinavir/ritonavir induction phase and with improvement in total cholesterol, LDL-cholesterol, and triglycerides. **Conclusions:** Trizivir-alone maintenance after Trizivir-lopinavir/ritonavir induction maintained virologic and CD4+ cell response, and was associated with an improved adverse event and lipid profile.

**Keywords:** Abacavir/Lamivudine/Zidovudine; HIV-1 Infection; Induction-Maintenance Strategy; Kaletra; Lopinavir/Ritonavir; Trizivir

## 1. Introduction

The induction-maintenance antiretroviral treatment strategy involves giving HIV-infected patients induction therapy with multiple antiretroviral agents to achieve virologic suppression, then follow this by deletion of an agent of one class to simplify the regimen. In HIV care, the induction-maintenance strategy was first explored in the late 1990s using different combinations of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease

inhibitors (PI) [1]. Antiretroviral induction-maintenance regimen sequences investigated in clinical trials to date have included switching a double NRTI/double PI regimen to a double PI-alone or a single NRTI/single PI combination [2]; a double NRTI/single PI regimen to either a double NRTI-alone or double PI-alone regimen [3]; a ritonavir-boosted PI/double NRTI regimen to a boosted PI-alone regimen [4-9]; and a triple NRTI/single NNRTI combination to a triple NRTI-alone regimen [10,11].

The triple NRTI fixed-dose combination Trizivir (GlaxoSmithKline, Research Triangle Park, North Carolina, USA), which contains abacavir 300 mg, lamivudine

\*Corresponding author.

150 mg, and zidovudine 300 mg per tablet, has been available for twice-daily treatment of HIV infection since the late 1990s [12]. Use of Trizivir was expected to preserve antiretroviral agents of other classes for later use, thereby potentially delaying resistance development. Trizivir also offered dose symmetry with other agents similarly administered twice daily. Although current antiretroviral treatment guidelines from the Department of Health and Human Services and IAS-USA do not recommend monotherapy with a triple NRTI combination like Trizivir for initiating antiretroviral therapy [13,14], Trizivir-alone maintenance could be considered by clinicians desiring to avoid particular adverse events sometimes associated with recommended drug regimens.

Induction with a triple NRTI plus a boosted PI, followed by deletion of the PI has undergone little study [15-17]. In view of this data gap, the focus of the present study was to evaluate the efficacy and tolerability of induction with Trizivir as the triple NRTI component and lopinavir/ritonavir (LPV/r) as the PI component, followed by a maintenance period of Trizivir alone.

## 2. Methods

This phase 4 multicenter, open-label, single-arm, pilot study was conducted at three US-based treatment sites: Therapeutic Concepts P.A. (Houston, Texas), Cigna Healthcare Corp (Phoenix, Arizona), and the Peabody Clinic (Dallas Texas). Patients could be enrolled if they were HIV-infected, as documented by HIV-1 antibody enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot or HIV plasma viremia, were aged 13 years or older, had screening HIV-1 RNA  $\geq$  20,000 copies/mL, and were antiretroviral-naïve (defined as having  $<$ 2 weeks of prior treatment with any NRTI and no exposure to PIs). Women of child-bearing potential could be considered for the study if they had a negative serum pregnancy test ( $\beta$ -human chorionic gonadotropin) at screening and practiced birth control (used double barrier method of contraception or intrauterine device, or were abstinent) throughout the study. There were no CD4+ cell count restrictions on eligibility.

Key exclusion criteria included: active AIDS-defining opportunistic infection or disease (CDC Category C) or pre-existing mental, physical, or substance abuse disorder which, in the opinion of the investigator, would preclude the patient from participation; use of immunomodulators, systemic cytotoxic chemotherapy, or radiation therapy within 4 weeks prior to study entry; exposure to an HIV vaccine within 3 months prior to study entry; clinically relevant hepatitis within 6 months prior to screening; or concurrent use of any agent known to have a pharmacologic interaction with the boosted PI. All patients provided written informed consent to participate in the

study, and the protocol was approved by the institutional review boards for the study sites. The study was conducted according to Good Clinical Practice and the 2000 Helsinki Declaration.

During the induction phase of the study (baseline through week 48), the patients received one Trizivir tablet plus one LPV/r 400/100 mg fixed-dose combination capsule (Kaletra<sup>®</sup>, Abbott Laboratories, North Chicago, Illinois) twice daily. Patients achieving a viral load (HIV-1 RNA)  $<$  50 copies/mL at weeks 36 and 44 were eligible to enroll in the maintenance phase, during which LPV/r was discontinued at week 48 and Trizivir alone was continued through week 96.

Patients were evaluated during the induction phase at weeks 1, 2, 4, 8, 16, 24, 36, 44, and 48, and during the maintenance phase at weeks 56, 64, 72, 84, and 96. Routine biochemistry, hematology, and immunology tests were conducted at each assessment. The severity of adverse events was graded according to DAIDS criteria [18]. If any patient were to develop a suspected abacavir-related hypersensitivity reaction, Trizivir was to be discontinued immediately. Median lipid values were assessed as to whether they exceeded the National Cholesterol Education Program (NCEP) cutoff levels at which hypolipidemic drug therapy would be indicated [19]. Viral load was measured using the Roche Amplicor MONITOR Ultrasensitive assay (version 1.5; lower limit of quantitation [LLOQ] 50 copies/mL) (Roche Diagnostics, Branchburg, New Jersey) and HIV-1 MONITOR Version 1.0 polymerase chain reaction (PCR) assay (LLOQ, 400 copies/mL) (Roche, Nutley, New Jersey). CD4+ lymphocyte cell count was assessed by flow cytometry. Adherence was monitored by a self-administered questionnaire, the PMAQ3 [20].

The primary endpoint of the study was the proportion of patients with plasma HIV-1 RNA  $<$  50 copies/mL at the end of the maintenance phase (week 96). Treatment failure was defined as either virologic failure (repeated [consecutive] detection of plasma HIV-1 RNA  $>$  500 copies/mL after having achieved an HIV-1 RNA  $<$  50 copies/mL) or discontinuation because of toxicity, clinical disease progression, or death. For virologic response, both intent-to-treat: missing equals failure (ITT: M = F) and observed analyses were performed. All other parameters were reported using observed analyses only. Descriptive-only statistical analyses were applied to efficacy and safety data and comparisons.

## 3. Results

### 3.1. Patient Characteristics

A total of 23 patients were enrolled at the three study sites. Most of the patients (18 [78%]) were males and

African American (14 [61%], with 9 [39%] Caucasians). The median age was 37 years (range, 20 to 74 years). Median baseline plasma HIV-1 RNA level was 5.45 log<sub>10</sub> copies/mL (range, 4.28 to 5.88 log<sub>10</sub> copies/mL). Nine patients (39%) had an HIV-1 RNA < 100,000 copies/mL, and 14 (61%) an HIV-1 RNA ≥ 100,000 copies/mL. Median baseline CD4+ cell count was 232 cells/mm<sup>3</sup> (range, 19 to 504 cells/mm<sup>3</sup>), with 12 (52%) ≥ 200 cells/mm<sup>3</sup> and 11 (48%) < 200 cells/mm<sup>3</sup>. The baseline CDC classification was Category A in 16 patients (70%), Category B in six (26%), and Category C in one (4%).

### 3.2. Virologic and Immunologic Response

Of the 23 patients who started induction, 19 completed it, three were lost to follow-up, and one withdrew due to grade 2 adverse events (combination of diarrhea/fatigue/nausea/vomiting). Of the 19 induction completers, 14 had viral load measurements done at week 48 (five patients missed their week 48 study visit). Week 48 ITT: observed analysis indicated viral load < 400 copies/mL in 100% of the 14 induction completers and < 50 copies/mL in 71% (10) (Figure 1). ITT: M = F analysis showed these levels of viral load suppression in 14/23 (61%) and 10/23 (43%), respectively. As Figure 1 indicates, a drop in percentage of patients with viral load < 50 copies/mL occurred between week 32 and week 48 that may possibly have been due to non-adherence in a few patients. Median CD4+ increase above baseline was 192 cells/mm<sup>3</sup> at week 48 (Figure 2).

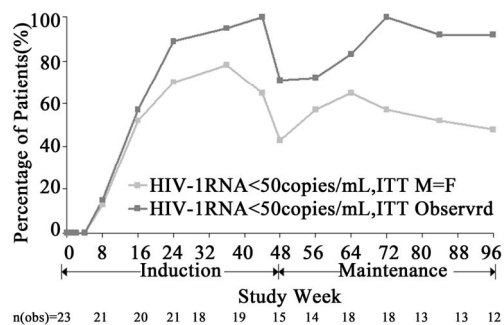


Figure 1. Proportion of patients with HIV-1 RNA < 50 copies/mL.

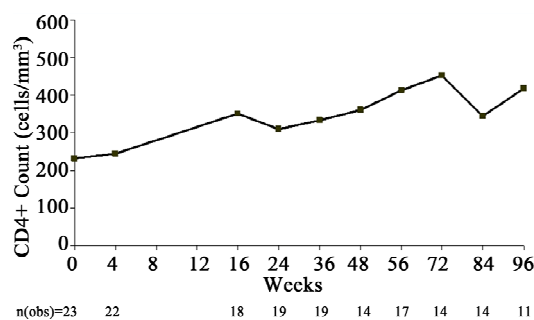


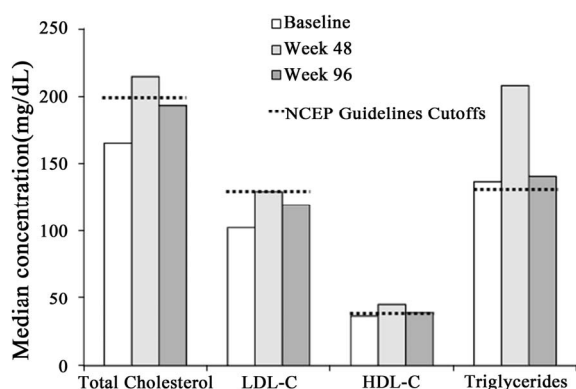
Figure 2. Changes in CD4+ cell count.

Nineteen patients entered the maintenance phase of the study. Twelve patients completed the entire maintenance phase through week 96, of whom 92% (11/12) achieved viral loads of < 400 and < 50 copies/mL in the ITT: observed analysis and 48% (11/23) in the ITT: M = F analysis (Figure 1). One of the 12 maintenance completers had an insufficient viral load at his last two study visits (470 copies/mL at week 84 and 2000 copies/mL at week 96), and non-adherence may have been a causal factor for this. Of the seven patients who dropped out of the maintenance phase prematurely, one had met the criteria of virologic failure with two consecutive viral load measurements of > 500 copies/mL (at weeks 64 and 72), three had missed their week 96 study visit (all had had a viral load < 50 copies/mL at every maintenance visit through week 84), and three had had a single insufficient viral load at one study visit and subsequently withdrew from the study. Median change from baseline in CD4+ cell count was +208 cells/mm<sup>3</sup> at week 96 (Figure 2).

### 3.3. Safety and Tolerability

During the study, all 23 patients experienced at least one adverse event that was grade 1 to 2 (mild to moderate) in severity. Adverse events that investigators considered to be treatment-related were reported by 13 patients (57%); these included diarrhea (two), nausea (four), fatigue (four), rash (two), abdominal pain (two), vomiting (two), and alopecia, abdominal distention, upper abdominal pain, hyperlipidemia, dizziness, erectile dysfunction, and upper respiratory tract infection (one case each). Most of these adverse events were reported within the first 30 days of the induction period, with the exceptions being one report each of diarrhea (at 62 days), fatigue (at 43 days), rash (at 96 days), and upper respiratory tract infection (at 385 days—the only adverse event reported during the maintenance phase). No suspected abacavir-related hypersensitivity reactions occurred.

Median values of all lipids increased above baseline values during the Trizivir-LPV/r induction phase and generally decreased during the Trizivir-only maintenance phase (Figure 3). Median lipid concentrations at base-line, end of induction (week 48), and end of maintenance (week 96) were 165.5, 215.0, and 194.0 mg/dL, respectively, for total cholesterol; 102.5, 129.5, and 119.5 mg/dL, respectively, for LDL-cholesterol; 36.5, 45.0, and 39.0 mg/dL, respectively, for HDL-cholesterol; and 137.0, 208.5, and 141.0 mg/dL, respectively, for triglycerides. Although median total cholesterol and triglyceride concentrations exceeded the NCEP cutoff levels at the end of induction, the medians for these lipids fell below the cutoffs during maintenance. Of the 12 patients who completed both phases of the study, the number whose total cholesterol exceeded the NCEP cutoff (200 mg/dL) at baseline, end of induction, and end of



**Figure 3. Median fasting lipids at baseline, week 48, and week 96. The cut-off levels established by the NCEP are shown with dotted lines.**

maintenance was five, nine, and six; for LDL-cholesterol (130 mg/dL), the number was five, seven, and three; for HDL-cholesterol (40 mg/dL), the number was four, eight, and five; and for triglycerides (150 mg/dL), the number was four, nine, and five. All patients whose lipids fell below the NCEP cut-off levels were able to avoid the need for hypolipidemic agents.

#### 4. Discussion

This study showed that in HIV-infected patients who have attained a reduction in viral load to <50 copies/mL with a Trizivir-LPV/r induction regimen, the deletion of LPV/r from the regimen with maintenance of Trizivir alone results in continued virologic suppression, enhanced CD4+ cell counts, and improved tolerability. The efficacy results of our clinical trial are consistent with those of two other studies that have evaluated the same regimen for induction and maintenance [15,16]. Thus, van Raalte *et al.* [15] found that 19 (95%) of 20 antiretroviral-naïve patients with viral loads < 50 copies/mL after Trizivir-LPV/r induction for a mean of 19 weeks (range, 6 - 39 weeks) retained this level of virologic suppression over a mean of 36 weeks (range, 6 - 73 weeks) after LPV/r deletion and Trizivir-alone continuation. The one patient who did not achieve < 50 copies/mL during maintenance was found to be non-adherent. No CD4+ cell data were presented in the report of this study. Similarly, Mallolas *et al.* [16] observed that 48 of 60 patients (80%) with viral loads < 50 copies/mL after 24 to 36 weeks of Trizivir-LPV/r induction were able to maintain viral loads ≤ 200 copies/mL and achieve a 274-cell/mm<sup>3</sup> median gain in CD4+ count 48 weeks after deleting LPV/r (no data on proportion < 50 copies/mL presented). It is noteworthy that in both of these studies, a variable time for induction was allowed. In contrast, in our study we specifically chose week 36 (with confirmation at week 44) to assess eligibility for maintenance therapy (HIV-1

RNA < 50 copies/mL) because this time period is at least nine times longer than the half-life of the second phase of viral decay [21].

Comparable efficacy findings during Trizivir-alone maintenance therapy have been observed in an induction-maintenance study in which a PI other than LPV/r was combined with Trizivir for induction [17]. Thus, in Trisud, 18 patients whose viral load was <50 copies/mL after 48 weeks of induction with twice-daily Trizivir plus nelfinavir 1250 mg were switched to Trizivir alone for the subsequent 48 weeks [17]. Fifteen patients completed the Trizivir-alone maintenance period, and three patients withdrew from the study for reasons investigators considered unrelated to Trizivir (pregnancy, stroke, and murder, respectively). Of the 15 completers, 11 (79%) had week 48 viral loads < 50 copies/mL, three had viral loads < 400 copies/mL, and the other patient did not have a viral load measurement at week 48 due to her missing the week 48 clinic visit (although her viral load was <50 copies/mL at week 40). Median CD4+ cell count increased from 336/mm<sup>3</sup> at the start of maintenance to 447/mm<sup>3</sup> at week 48.

Trizivir-alone maintenance also has been evaluated in clinical trials in which antiretroviral-naïve patients received ≥3 months of induction with regimens of dual nucleosides (zidovudine/lamivudine, stavudine/lamivudine, or stavudine/didanosine) plus a PI (indinavir, nelfinavir, or LPV/r) followed by Trizivir alone [22-26]. In these studies, maintenance of viral load and continued increases in CD4+ counts were generally seen over the ensuing 48-week or longer Trizivir-alone maintenance period. However, because these studies were conducted before it became standard-of-care to test for the presence of the HLA-B5701 allele (to avoid prescribing abacavir for HLA-B5701-positive, hypersensitivity-prone patients), dropouts due to suspected abacavir-related hypersensitivity reactions occurred, which confounded the efficacy results. Therefore, the applicability of the results of these older studies to current clinical practice in antiretroviral prescribing is dubious.

Almost all adverse events in our study were reported during the induction phase, with most reports during the first month. Only one adverse event (upper respiratory tract infection) was reported during the Trizivir-alone maintenance phase; this was considered unlikely to be treatment-related. Although discontinuation of LPV/r following the induction phase may have accounted for some diminution in adverse events, this diminution was also likely impacted by the natural reduction in adverse event frequency that occurs with longer term therapy [27]. A natural tendency for improved tolerance over time was also shown in the CNA3003 study of the components of Trizivir given in combination twice daily as monotherapy

[28]. Thus, in the CNA3003 comparison of total incidence of adverse events at weeks 0 (baseline) to 16 versus at weeks 16 to 48, the following frequency rates were observed: nausea, 47% vs 8%; malaise/fatigue, 37% vs 8%; headache, 31% vs 13%, and nausea with vomiting, 16% vs 5% [28].

Our study demonstrated that lipids increased during the Trizivir-LPV/r induction period, but improved after LPV/r was stopped and Trizivir alone was continued for maintenance. During induction, median concentrations for the treatment group rose above NCEP cutoffs for total cholesterol and triglycerides. Several patients in whom lipid concentrations exceeded NCEP cutoffs during induction, and hence were candidates for hypolipidemic agents at that study point, were able to obviate the need for these agents during Trizivir-alone maintenance because their lipids fell below NCEP cutoffs in the latter phase. Mallolas *et al.* [16] observed a similar pattern of change in total cholesterol, HDL-cholesterol, and triglycerides during Trizivir-LPV/r induction (median change from baseline of +30.5, +8, and +65 mg/dL, respectively) and Trizivir-alone maintenance (median change from end of induction to end of study of -25, -2.7, and -62 mg/dL, respectively). Comparable improvement in lipids has also been reported in studies of patients who have switched from Trizivir-efavirenz induction to Trizivir-alone maintenance [10,11,29].

Our study was limited by its non-randomized design, the small size of the study population, and the unavailability of resistance information in patients who had insufficient virologic response or failure. However, resistance data from the Mallolas *et al.* study of Trizivir-LPV/r induction with Trizivir-alone maintenance revealed that primary treatment-emergent mutations observed in virologic failures were either M184V alone or M184V plus a thymidine analogue-associated mutation [16]. Use of a quality-of-life measuring tool also would have been valuable to detect any changes in patient attitudes toward and satisfaction with their antiretroviral therapy following the change from the induction to the maintenance regimen.

In conclusion, in this pilot study, Trizivir-alone maintenance after Trizivir-LPV/r induction resulted in sustained virologic and CD4+ cell response and an improved adverse event and lipid profile.

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## **Appendix**

CDC: Centers for Disease Control and Prevention;  
DAIDS: Division of Acquired Immunodeficiency Syndrome (of the United States National Institutes of Health);  
LLOQ: lower limit of quantitation;

NCEP: National Cholesterol Education Program;  
NNRTI: non-nucleoside reverse transcriptase inhibitor;  
NRTI: nucleoside reverse transcriptase inhibitor;  
PI: protease inhibitor.