

Quadruple Nucleoside/tide Regimen of Trizivir (TZV) + Tenofovir (TDF) is Effective Following Early Virologic Failure on an Initial Regimen Containing a Thymidine Analog + Lamivudine in Combination with a Protease Inhibitor (PI) or Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) (ESS30005, ZIP)

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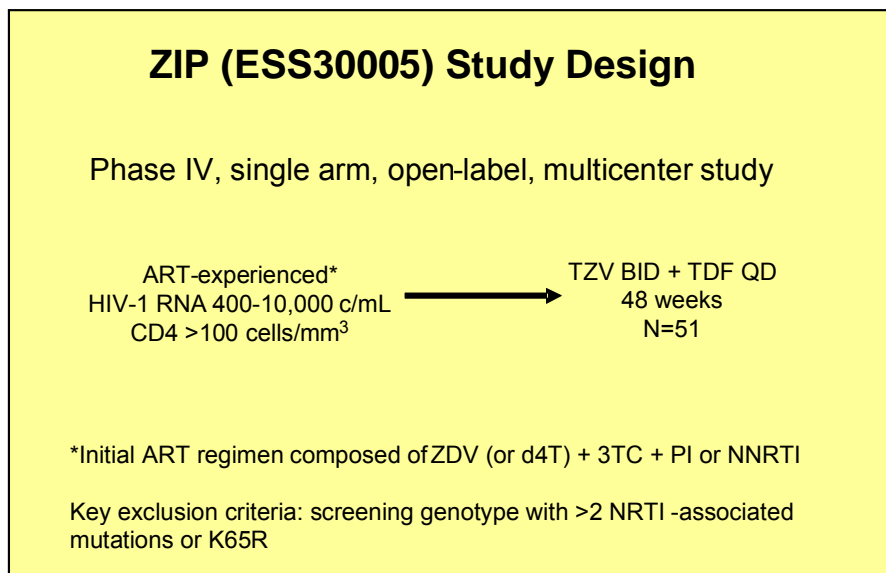
Introduction

The goal of antiretroviral therapy (ART) is undetectable HIV-1 RNA. Unfortunately, no single regimen has proven to provide life-long viral suppression in all patients. Multiple strategies have been employed upon treatment failure, including single drug substitution, addition of other antiretroviral agent(s), and changing the entire regimen. Although various approaches have been investigated, there is no consensus regarding the best treatment strategy for patients experiencing early virologic failure (HIV-1 RNA between 400 and 10,000 copies/mL).

A single class quadruple regimen of abacavir/lamivudine/zidovudine (Trizivir[®]; TZV) and tenofovir (Viread[®]; TDF) offers an attractive strategy for the management of patients experiencing early virologic failure because of its potential to preserve future treatment options with other ART classes.

Methods

The study was originally designed to enroll 100 patients and was powered based on comparing the intent-to-treat observed proportion of patients with HIV-1 RNA <400 copies/mL at Week 48 to historical controls. However, due to slow enrollment the protocol was amended to a target enrollment of approximately 50 patients.



Patient-reported adherence was assessed at baseline and Weeks 24 and 48 using the Patient Medication Adherence Questionnaire version 3W (PMAQ-3W), which includes 4 questions evaluating whether or not ART pills were missed on each of the previous 3 days and prior weekend. At each assessment time point, patients were classified as being perfectly adherent to the study regimen if no pills were missed over the past 3 days and prior weekend; otherwise they were classified as not perfectly adherent. In addition to self-report, TZV adherence was evaluated using Medication Event Monitoring Systems (MEMS) SmartCaps™ (AARDEX), which recorded the date and time of each bottle opening. TZV adherence was calculated by dividing the number of bottle openings by the number of expected doses over the time period. The adherence rate was defined as the percentage of prescribed doses taken.

Analysis Populations:

- **Intent-To-Treat (ITT):** Included all patients enrolled in the study who completed at least the baseline study visit. This is the primary population for efficacy analyses.
- **Safety:** Included all patients enrolled in the study that were exposed to at least one dose of study drug.

Analysis Methods:

- **Missing=Failure (M=F):** Responders were those with HIV-1 RNA below 400/50 copies/mL. Patients who had missing values at a given time point were considered failures.
- **Observed (Obs):** Responders were those with HIV-1 RNA below 400/50 copies/mL. Patients with missing data were excluded.

Virologic Failure Definition:

Virologic failure was defined in the protocol as:

- Failure to achieve HIV-1 RNA <400 copies/mL by Week 24 OR
- Confirmed rebound of HIV-1 RNA ≥ 1265 copies/mL ($0.5 \log_{10}$ increase over 400 copies/mL) following suppression to <400 copies/mL.

All patients who met the definition of virologic failure were withdrawn from the study.

Results

Study Population:

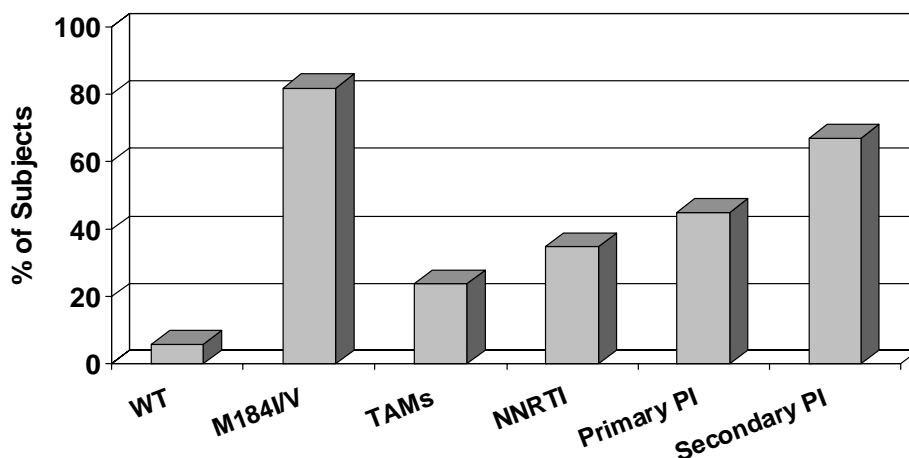
A total of 51 patients were enrolled in the study and initiated treatment with TZV + TDF.

Table 1. Demographics and Baseline Characteristics

	TZV + TDF (N = 51)
Median Age (range), years	39 (20-68)
Gender, n (%)	
Male	40 (78%)
Female	11 (22%)
Race, n (%)	
Black	26 (51%)
White	20 (39%)
Hispanic	5 (10%)
Baseline plasma HIV-1 RNA	
Median (range), log ₁₀ copies/mL	3.30 (1.77-4.88)
<400 copies/mL, n (%)	4 (8%)
>400-10,000 copies/mL, n (%)	40 (78%)
>10,000 copies/mL, n (%)	7 (14%)
Median baseline CD4+ cell count (range), cells/mm³	436 (142-1291)
Baseline CDC Classification for HIV infection, n (%)	
Category A = Asymptomatic	32 (63%)
Category B = Symptomatic, not AIDS	13 (25%)
Category C = AIDS	6 (12%)

The study enrolled a diverse study population with >20% female and >50% non-white. At baseline, median HIV-1 RNA was 1972 copies/mL and median CD4 cell count was 436 cells/mm³.

Figure 1. Genotypic Mutations at Screen



TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

NNRTI mutations: L100I, K103N, V106M, V108I, Y181C/I, Y188C/L/H, G190A/S, P225H, M230L, P236L

Primary PI mutations: D30N, M46I/L, G48V, I50V, A71V/T, V82A/F/T/S, I84V, L90M

Secondary PI mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M36I, I47V, F53L, I54L/M/V, G73S/A, V77I, N88D/S

Potential patients were excluded if viral genotype at screen indicated more than 2 NRTI-associated mutations (M41L, A62V, D67N, T69D/S, K70R, L74V/I, V75I, F77L, Y115F, F116Y, Q151M, M184V, L210W, T215Y/F, K219Q/E) or the K65R mutation. Only 1.4% (2/140) of patients screened were excluded due to genotypic restrictions.

Table 2. Prior Antiretroviral Therapy at Study Entry

	TZV + TDF (N = 51) n (%)
Nucleoside reverse transcriptase inhibitor (NRTI)	51 (100%)
Combivir	30 (59%)
Lamivudine	21 (41%)
Stavudine	20 (39%)
Zidovudine	1 (2%)
Protease Inhibitor (PI)	31 (61%)
Nelfinavir	19 (37%)
Indinavir	7 (14%)
Ritonavir	3 (6%)
Saquinavir	3 (6%)
Amprenavir	2 (4%)
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	20 (39%)
Efavirenz	10 (20%)
Nevirapine	10 (20%)

Table 3. Patient Disposition

	TZV + TDF (N = 51)
Completed study, n (%)	38 (75%)
Prematurely discontinued on or before Week 48	13 (25%)
Adverse events*	4
Lost to follow-up	4
Virologic failure	2
Protocol violation†	2
Other‡	1

* Adverse events leading to discontinuation included nausea, fatigue, and cancer.

† Protocol violations leading to discontinuation were nonadherence and unauthorized ART.

‡ Other reason for discontinuation was site closure.

Efficacy:

Figure 2. Virologic Response (HIV-1 RNA <400 copies/mL)

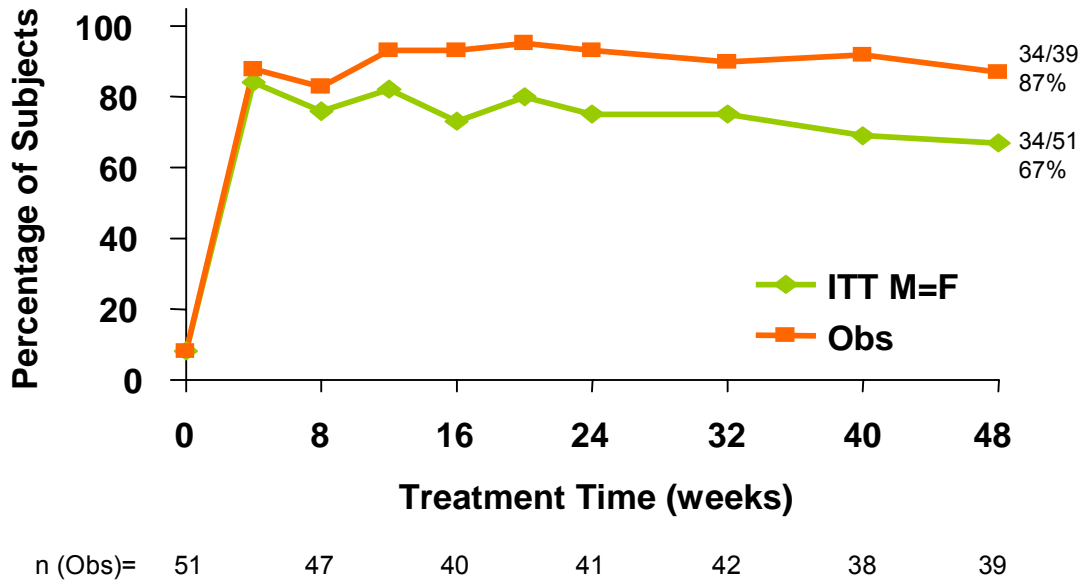
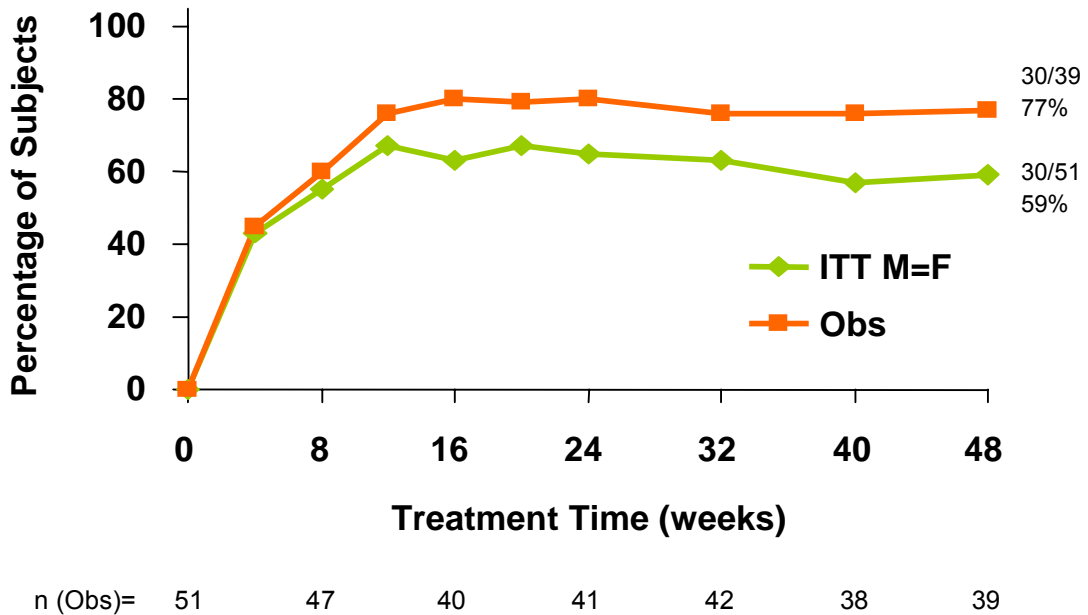


Figure 3. Virologic Response (HIV-1 RNA <50 copies/mL)



Overall, a high proportion of patients experiencing early virologic failure on an initial ART regimen achieved viral suppression with the quadruple nucleoside regimen of TZV + TDF over 48 weeks (Figures 2 and 3). In an exploratory analysis, patients were grouped according to the following screen NRTI resistance-associated mutation profiles: no NRTI mutations (n=7), 1 TAM (n=2), M184V/I (n=32), M184V/I + □1 TAMs (n=10). Median Week 24 and 48 HIV-1 RNA was <50 copies/mL for all screen mutation profiles. Good immunologic response was seen with a median increase of 71 CD4 cells/mm³ from baseline (436 cells/mm³) over 48 weeks.

Virologic Failure:

Two patients met virologic failure criteria during study, only one of which had treatment emergent mutations. This patient had no detectable resistance mutations at baseline but acquired M184V and thymidine analogue mutations (TAMs; D67N + K70R + K219Q) at the time of confirmed virologic failure (Week 32). The patient's PMAQ responses indicated incomplete adherence at multiple prior visits. The other patient had no additional resistance mutations at confirmed virologic failure (Week 32). PMAQ data indicated suboptimal adherence prior to study discontinuation.

Adherence:

Table 4. Patient-Reported Adherence (PMAQ-3W)

Regimen	N	Perfect Adherence*
ART regimen at study entry		
patients with data available at baseline	49	71%
patients with data at both baseline and Week 48	33	68%
TZV + TDF at Week 48	33	85%

* Perfect adherence = missed no pills in the prior 3 days or prior weekend.

As assessed by MEMS, median adherence to Trizivir was 76% over the 48-week study period and 63% at Week 48.

Safety/Tolerability:

Table 5. Most Commonly Reported Adverse Events (All Grades)

Adverse Event (AE)	TZV + TDF (N=51)	
	n (%)	Drug-Related AEs n (%)
Nausea	18 (35%)	16 (31%)
Fatigue	13 (25%)	12 (24%)
Depression	7 (14%)	0
Diarrhea	7 (14%)	3 (6%)
Headache	7 (14%)	4 (8%)
Vomiting	7 (14%)	4 (8%)
Bronchitis	6 (12%)	0
Insomnia	5 (10%)	3 (6%)
Rash	5 (10%)	0
Upper respiratory tract infection	5 (10%)	0

Four patients discontinued study due to adverse events. None of the 6 serious adverse events reported were determined to be treatment-related. No abacavir (ABC) hypersensitivity reactions occurred in this ABC-naïve population.

Discussion

This study evaluated the feasibility of quadruple nucleoside/tide therapy for patients experiencing early virologic failure on a thymidine analogue containing PI- or NNRTI- based regimen. The target enrollment for this study was 100 patients; however, finding patients experiencing early virologic failure on a regimen that included Combivir (or d4T+3TC) was more difficult than anticipated. The majority of screen failures (76%, 68/89) were due to HIV-1 RNA <400 copies/mL at the screening visit.

Virologic failure was rare (2/51) despite the presence of M184V and/or limited TAMs at entry. Suboptimal adherence was documented for both patients meeting virologic failure criteria. Only one of these patients developed new genotypic mutations at failure. The low rate of virologic failure supports the efficacy of a quadruple NRTI regimen composed of Trizivir and tenofovir in this population of patients experiencing early virologic failure.

The reported rate of perfect adherence to TZV + TDF at Week 48 was observed to be higher than the rate of perfect adherence to the previous failing regimen at the time of study entry.

Conclusion

- **Patients experiencing early virologic failure on an NNRTI- or PI- based regimen containing a thymidine analogue and 3TC can be effectively managed with TZV+TDF, even in the presence of M184V and limited TAMs.**
- **Virologic response to TZV BID + TDF QD was high: 87% with HIV-1 RNA <400 copies/mL and 77% with HIV-1 RNA <50 copies/mL at Week 48 (ITT Obs).**
- **Only 2 patients met virologic failure criteria on regimen of TZV + TDF through Week 48.**
- **TZV + TDF was generally well-tolerated in this treatment experienced population; the most common treatment-related AEs were nausea and fatigue. In this abacavir-naïve population, no hypersensitivity reactions were reported.**
- **Based on the PMAQ-3W, the proportion of patients who reported perfect adherence to TZV+TDF at Week 48 (85%) was observed to be higher than the proportion who reported perfect adherence to their prior regimen (71%).**
- **TZV+TDF helps preserve other ART classes for future treatment while offering an effective, tolerable, and simple (three pills/day) alternative for patients.**

Acknowledgements

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