The BATAR Study

Boosted **A**tazanavir **T**ruvada vs. **A**tazanavir **R**altegravir

A Pilot Study of the Novel Antiretroviral Combination of Atazanavir and Raltegravir in HIV-1 Infected Subjects with Virologic Suppression on a Standard Regimen of Boosted Atazanavir, Tenofovir and Emtricitabine

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Background

- Patients virologically suppressed on ATV/r + TDF/FTC may require alternative regimens that maintain suppression while addressing specific drug related side effects.
- We explored two alternative regimens that replace continued ritonavir and/or TDF/FTC.
- This open-label exploratory pilot trial enrolled 43 patients virologically suppressed on ATV/r + TDF/FTC.

Methods-1

- **Subjects:** HIV-1-positive virologically suppressed adults (HIV RNA < 50 copies/ml) on a "preferred" regimen of ritonavir-boosted atazanavir plus tenofovir and emtricitabine.
- **Primary Objective:** to compare virologic outcomes of three regimens in patients with virologic suppression on ritonavir-boosted atazanavir plus tenofovir and emtricitabine.
- At baseline, subjects randomly assigned (1:1:1) to one of the three study arms:
  - **ATV/rtv/RAL:** atazanavir/ritonavir 300/100 mg once daily plus raltegravir 400 mg twice daily [stop TDF/FTC]
  - **ATV/RAL:** atazanavir 300 mg twice daily plus raltegravir 400 mg twice daily [stop TDF/FTC and rtv]
  - **ATV/rtv/TDF/FTC:** continue atazanavir/ritonavir 300/100 mg once daily plus co-formulated tenofovir and emtricitabine

Methods-2

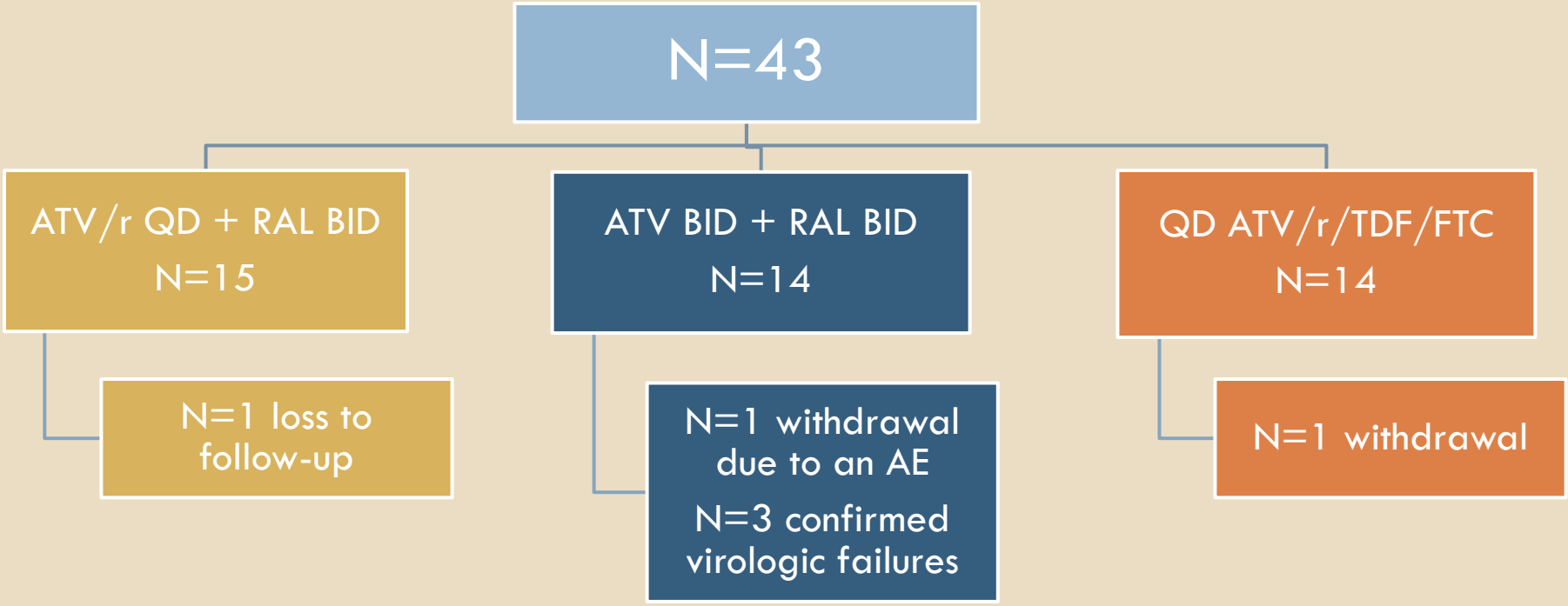
- **Secondary Objectives:** to compare the safety, tolerability, and satisfaction of the three study regimens.
- **Measures**
  - HIV viral load: Abbott Real Time HIV-1 assay (<40 c/mL)
  - Safety: clinical and lab adverse events (ACTG toxicity grading scale)
  - ECG: 12 lead ECG conducted at screening, week 2, week 4, and week 24
  - QOL: self-report on 100 point Numerical Rating Scale
  - Adherence: three day self-report of missed and taken doses
- **Definition of Virologic Failure:** HIV RNA level > 200 confirmed on consecutive, repeat measurements.

Inclusion Criteria

- **Inclusion Criteria**
  - CD4 count ≥ 200/mm^3 at screening
  - Undetectable HIV RNA (<40 c/mL) at screening *and* no HIV RNA >200 c/mL during the 180-day period prior to screening
  - Stable on a regimen of once-daily ATV 300mg + rtv 100mg + TDF/FTC at screening and for at least 90 days prior to screening
  - History demonstrates either lack of evidence of resistance to any of the drugs that were used in any of the three arms, or treatment history consistent with atazanavir sensitive virus
  - Raltegravir naïve
  - No acute or chronic hepatitis B infection
  - No ECG demonstrating atrioventricular block, prolonged QRS interval > 12ms or known complete bundle branch block

Results: Disposition

- **Baseline characteristics were generally similar in the three study arms**
  - 88% male; mean age 46 years
  - 74% white; 21% African American; 5% other race
  - Mean CD4: 532 cells/mm^3



Results: Primary Endpoint

Outcomes through Week 48

N=43	Enrolled N	Virologic Response N (%)	Confirmed Virologic Failure N (%)	Withdrawal due to AE; VL <50 N (%)	Other Withdrawal; VL <50 N (%)
ATV/rtv/ RAL	15	14 (93%)*	0	0	1 (7%)
ATV/RAL	14	10 (71%)	3 (21%)	1 (7%)	0
ATV/rtv/ TDF/ FTC	14	13 (93%)^	0	0	1 (7%)

*One subject on prohibited medication (phenytoin) but responded.
^One subject with elevated viral load at week 48 but <50 on consecutive draw after week 48.

Results: Quality of Life

- **Quality of Life:** change from baseline by self-report on 100 point Numeric Rating Scale

  No difference in QOL change across arms

N=31*	ATV/rtv/RAL		ATV/RAL		ATV/rtv/ TDF/ FTC		Total	
	mean	sd	mean	sd	mean	sd	mean	sd
Baseline	77.4	16.1	82.5	11.6	92.9	8.6	84.2	14.1
Week 48	78.2	22.6	81.3	17.5	90.5	11.1	83.3	18.2
Change	0.8	20.0	-1.3	12.7	-2.5	8.2	-0.9	14.4

*Note: Results only for patients on study through week 48; all other data censored.

Results: Adherence by Self Report

- **Adherence:** percent of doses reported taken during three days prior to study visit

N=35	ATV/rtv/RAL		ATV/RAL		ATV/rtv/ TDF/ FTC		Total	
	mean	sd	mean	sd	mean	sd	mean	sd
baseline	97.5	9.2	96.7	10.4	100.0	0.0	98.1	7.8
week 48	97.5	9.2	95.0	15.8	100.0	0.0	97.6	10.0
change	0.0	13.5	-1.7	19.9	0.0	0.0	-0.5	13.0

- **Summary:** ≥ 95% adherence reported by most subjects in all three arms at both baseline and week 48

Note: There were 3 virologic failures on ATV/RAL that were attributed to adherence issues. Their adherence values are discussed on the next panel; 3 early withdrawals and 2 with missing data points are excluded from the calculations.

Results:CD4 and Virology Outcomes

- **Mean CD4 count changes from baseline to week 48**

	ATV/rtv/RAL	ATV/RAL	ATV/rtv/TDF/ FTC	Total
Mean change	12.1	-31.9	75.4	21
Median change	10.5	-12.5	61.5	19.5

  - Median CD4 change was significant comparing ATV/RAL to Control (p=0.010) and comparing ATV/rtv/RAL to Control (p=0.018).

- **Virology**
  - Through week 48, there were n=3 observed virologic failures (>200 c/mL on 2 consecutive tests), all on ATV/RAL.
  - These three had self-reported 100% adherence at one or both study visits associated with viremia.
    - However, study staff documented a history of difficulty adhering to the regimen
  - Resistance testing was attempted in all subjects with confirmed virologic failure; results either did not detect resistance or were non-amplifiable.

Results: Adverse Events and Safety

- Adverse events (AE) were categorized by body system. Most AEs were transient. In this pilot, only differences of ≥ 5 events within a category between arms is summarized below.
- Frequency (n) of AEs by category regardless of assessment of causation:

Adverse Event	ATV/rtv/RAL	ATV/RAL	ATV/rtv/TDF/FTC
Neurologic	7	6	1
ENT	3	6	9
Musculoskeletal	3	7	1

- Frequency (n) of AEs by category judged *possibly related* to study drug:

Adverse Event	ATV/rtv/RAL	ATV/RAL	ATV/rtv/TDF/FTC
Neurologic	5	2	0

Results: Adverse Events and Safety

- One subject randomized to ATV/RAL discontinued due to an Adverse Event:
  - Experienced heart palpitations without chest pains starting on day 2
  - Stopped study medications and restarted the pre-study regimen prior to the week 4 visit
  - Symptoms resolved within two days of discontinuation of the study regimen
  - The subject withdrew at the week 4 visit
- No significant differences across arms were noted in lipid fractions (Total Chol, HDL, LDL, TG) or other lab tests
- There were no clinically significant ECG changes across arms

Results: Serious Adverse Events

N=5 SAEs; one judged possibly related to study:

- ATV/rtv/RAL:
  - Hospitalization for asthma; Hx of sarcoidosis
  - Prostate Cancer
- ATV/RAL:
  - Two hospitalizations for recurrent depression
  - **Deep vein thrombosis; judged possibly/probably related**
- ATV/rtv/TDF/FTC:
  - Myocardial infarction; Hx of CAD s/p stent

BATAR Study: Conclusions

- In this study, the use of ATV/rtv with either TDF/FTC or RAL was similarly successful over 48 weeks in maintaining virologic suppression.
- Unboosted twice-daily atazanavir with twice-daily raltegravir had several concerns emerge during study:
  - N=3 (21%) virologic failures without resistance detection
  - CD4 count change was significantly less than Control
  - More neurologic and musculoskeletal adverse events
- In sum, these data support the continuation of TDF/FTC with ATV/rtv when tolerated; replacing TDF/FTC with RAL maintained suppression in this pilot though an increased number of neurologic events was observed.
  - The use of twice-daily ATV instead of ATV/rtv is not recommended for use based on the observations in this pilot

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