



# Effect of Nucleoside (NRTI) Intensification on Prevalence of Morphologic Abnormalities (MoAs) at Year 5 of Ritonavir (RTV) Plus Saquinavir (SQV) Therapy in an HIV-Infected Cohort

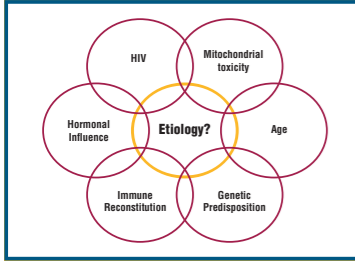
Poster 683-T

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## BACKGROUND

### Potential Etiology of Metabolic and/or Body Composition Changes



### NRTI-Associated Mitochondrial Toxicity Hypothesis

- Lipodystrophy has been characterized in patients only receiving NRTIs
- NRTIs inhibit mitochondrial DNA polymerase  $\gamma$  to varying degrees
- Mitochondrial toxicity may partly explain body composition changes<sup>1</sup>
- Muscle and adipose biopsies demonstrate decreased mitochondrial DNA content, mitochondrial respiratory chain dysfunction, and ultrastructural abnormalities<sup>2</sup>

1. Brinkman K, et al. Lancet. 1999; Kakuda TN, et al. AIDS. 1999.  
2. Gomez Zaera M, et al. AIDS. 2001; Shikuma CM, et al. AIDS. 2001; Walker UA, et al. JAMA. 2002.

## MATERIALS AND METHODS cont.

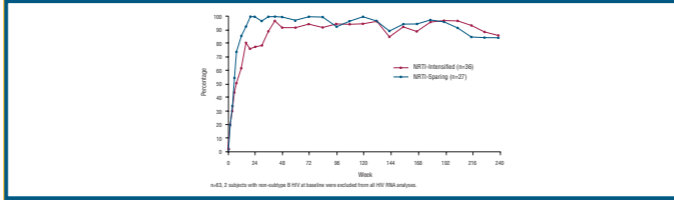
### NRTI Intensification for Subjects Ongoing at Year 5

- 37/65 (57%) subjects intensified their RTV/SQV regimen with NRTIs
- 13 of 37 subjects intensified prior to Week 48

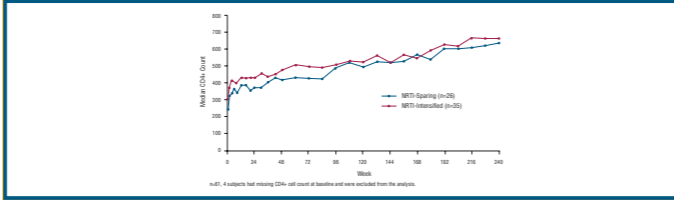
| Initial Intensification Regimen | N (%)    |
|---------------------------------|----------|
| 3TC/d4T                         | 32 (86%) |
| 3TC/AZT                         | 2 (5%)   |
| 3TC/ddI                         | 1 (3%)   |
| d4T/ABC                         | 1 (3%)   |
| ddI                             | 1 (3%)   |

## RESULTS

### HIV RNA Level <200 copies/mL for Subjects Ongoing at Year 5



### CD4+ Cell Count (cells/mm<sup>3</sup>) for Subjects Ongoing at Year 5



### Grade 3 or 4 Laboratory Abnormalities Prevalence Through 5 Years

| Laboratory Variable                     | NRTI-Intensified (n = 37) | NRTI-Sparing (n = 28) |
|---|---------------------------|-----------------------|
| AST >180 mg/dL or ALT >215 mg/dL        | 4/37 (11%)                | 1/28 (4%)             |
| With baseline abnormality*              | 2/14 (14%)                | 0/8 (0%)              |
| Without baseline abnormality*           | 2/23 (9%)                 | 1/20 (5%)             |
| Triglycerides (>750 mg/dL) <sup>1</sup> | 11/37 (30%)               | 8/28 (29%)            |
| Cholesterol (>300 mg/dL) <sup>1</sup>   | 9/37 (24%)                | 10/28 (36%)           |

N=65  
\* Defined as greater than the upper limit of normal for AST/ALT, hepatitis B Ag+ or hepatitis C Ab+ at baseline.  
<sup>1</sup> Regardless of fasting or non-fasting conditions.

### Body Composition Survey

- Administration of a body composition survey completed by subjects at the end of Year 3 and then every 6 months thereafter
- Physical exam for body composition abnormalities conducted at the end of Year 3 and then every 6 months thereafter
- Results have been summarized at Year 5 for each survey item by the proportion of subject-reported, exam-confirmed body composition abnormalities

### Body Composition Survey Items

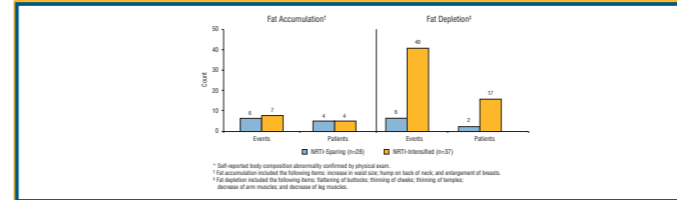
#### Fat Accumulation

- Increase in waist size
- Hump on back of neck
- Enlargement of breasts
- Lumps on body
- Weight gain ( $\geq 10\%$ )

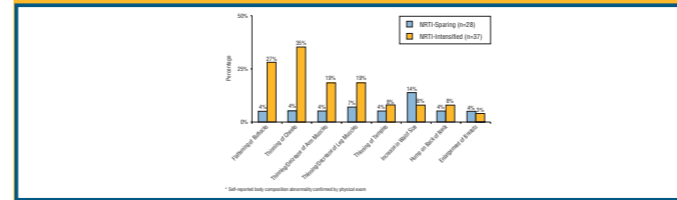
#### Fat Depletion

- Flattening of buttocks
- Thinning of cheeks
- Thinning of temples
- Thinning/decrease of arm muscles
- Thinning/decrease of leg muscles
- Weight loss ( $\geq 10\%$ )

### Summary of Body Composition Survey\* Results at Year 5



### Summary of Individual Items from the Body Composition Survey\* at Year 5



### Risk Factor for Body Composition Abnormality\*: Logistic Regression Models

| Risk Factor**                           | Unadjusted Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio <sup>1</sup> (95% Confidence Interval) |
|---|---|--|
| Intensification with NRTIs <sup>3</sup> | 4.514 (1.142 – 17.847)                          | 4.710 (1.172 – 18.933)                                     |

\* Defined as at least two body composition abnormalities reported by subject and confirmed by physician.  
\*\* Other factors including age, gender, baseline HIV RNA, baseline CD4+ cell count, duration of prior RTIs and lipid measurements were not found to be statistically significant for at least two body composition abnormalities.  
<sup>1</sup> Odds ratio adjusted for weight gain (>10%); <sup>2</sup> Intensification with NRTIs occurred in 37/65 (57%) of the subjects.

### Assessment of Risk Factors for Most Prevalent\* BCAs

| Risk Factor                           | Unadjusted Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio** (95% Confidence Interval) |
|---------------------------------------|---|---|
| <b>Buttock wasting</b>                |   |   |
| Intensification with NRTIs            | 10.000 (1.196 – 83.611)                         | 9.484 (1.125 – 79.953)                          |
| <b>Thinning of cheeks<sup>1</sup></b> |   |   |
| Baseline CD4+ cell count              | 0.991 (0.984 – 0.998)                           | 0.991 (0.984 – 0.998)                           |
| Intensification with NRTIs            | 14.625 (1.778 – 120.265)                        | 16.669 (1.947 – 142.751)                        |

\* Two most common body composition abnormalities reported by subject and confirmed by physician.  
\*\* Odds ratio adjusted for weight gain (>10%).  
<sup>1</sup> Neither baseline CD4+ cell count nor intensification with NRTIs were significant in the multiple regression analysis.

## CONCLUSIONS

- Ritonavir/Saquinavir with or without NRTI intensification provided durable virologic and immunologic response through 5 years of therapy.
- The most prevalent body composition abnormalities, signs of lipodystrophy, were more common among NRTI-intensified subjects compared to subjects on NRTI-sparing regimens
  - Buttock wasting: 27% vs. 4%,  $p < 0.05$
  - Cheek thinning: 35% vs. 4%,  $p < 0.01$
- NRTI-intensification was identified as a potential risk factor for at least two body composition abnormalities. In addition, baseline CD4+ cell count may be a risk factor for development of body composition abnormalities.
- Age, gender, baseline RNA viral load, duration of prior RTIs before study participation and lipid measurements were not identified as potential risk factors.

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## STUDY OVERVIEW

### Objectives

In subjects receiving a RTV/SQV-based regimen, with and without NRTI-intensification, during a 5-year treatment period

- To determine the prevalence of body composition abnormalities (BCAs)
- To assess potential risk factors associated with the occurrence of BCAs

### Study Design

- Open-label, multicenter, randomized study of four RTV/SQV dose regimens (400/400 BID, 600/400 BID, 400/400 TID, 600/600 BID) with specific criteria for treatment intensification with RTIs
- Inclusion criteria: HIV+, CD4+ 100-500 cells/mm<sup>3</sup>, PI-naïve
- Cross-Sectional Body Composition Survey beginning at Week 144
- Treatment intensification with NRTIs allowed for HIV RNA >200 copies/mL at 12 weeks, virologic rebound at any time, or investigator's discretion after 48 weeks

## MATERIALS AND METHODS

### Baseline Characteristics of Study Population Ongoing at Year 5 (N = 65)

|   | NRTI-Intensified (n = 37) | NRTI-Sparing (n = 28) |
|---|---------------------------|-----------------------|
| Mean age, years                                   | 39                        | 39                    |
| Male, %   | 89                        | 75                    |
| Median HIV RNA level, log <sub>10</sub> copies/mL | 4.9                       | 4.5                   |
| Median CD4+ count, cells/mm <sup>3</sup>          | 250*                      | 312                   |
| Median number of previous ARVs                    | 2                         | 2                     |
| ARV-naïve subjects                                | 3                         | 5                     |
| Median duration of prior NRTI use, months (range) | 47.5 (0-89.6)             | 25.5 (0-80.2)         |

\*  $p = 0.028$