AIDS CLINICAL TRIALS GROUP ACTG

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From Research to the Real World: Sharing Science Symposium
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CFAR CENTER FOR AIDS RESEARCH Baylor-UTHouston

Houston Department of Health and Human Services

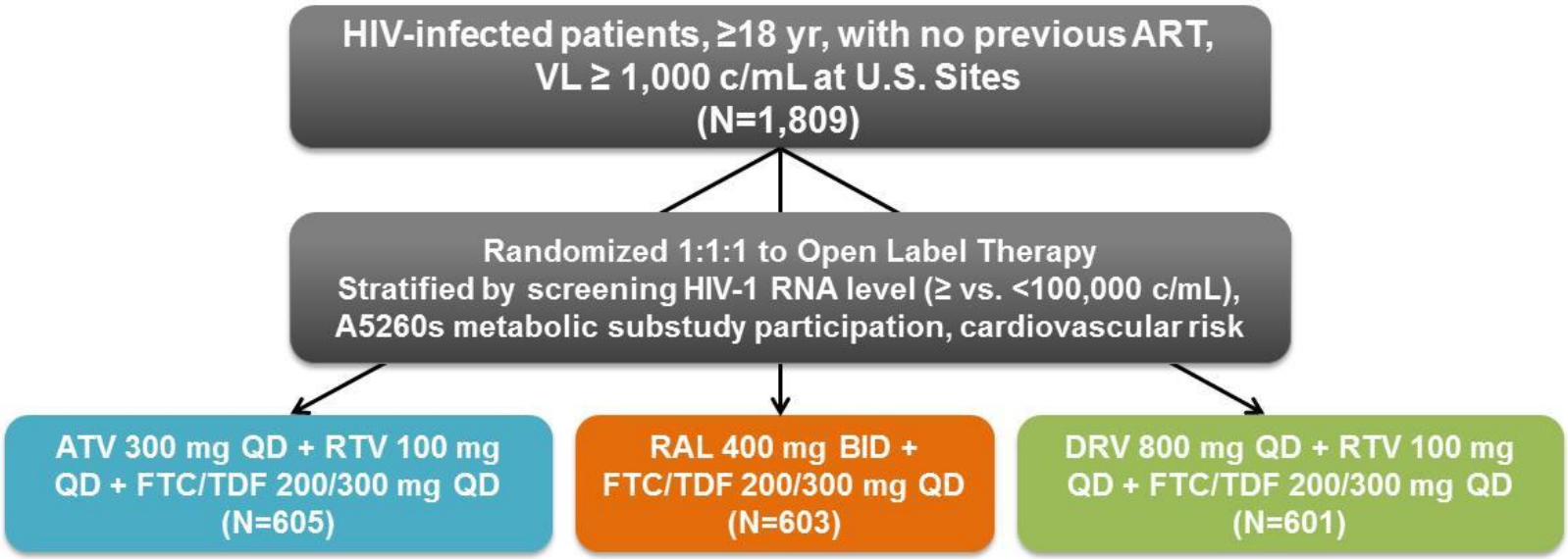
Why We Did A5257 ARDEN

- The most commonly prescribed and successful regimen contains the medication efavirenz. However, this regimen has been shown to cause undesirable side effects for some patients and is therefore not an option. Alternative regimens are needed for these patients

- This study looked at how well different combinations of anti-HIV drugs work to decrease the amount of HIV in the blood (viral load) of and allow immune system recovery in people who have never received anti-HIV therapy

- This study also examined drug tolerability and safety for the various drug combinations

What We Did: A5257 ARDEN

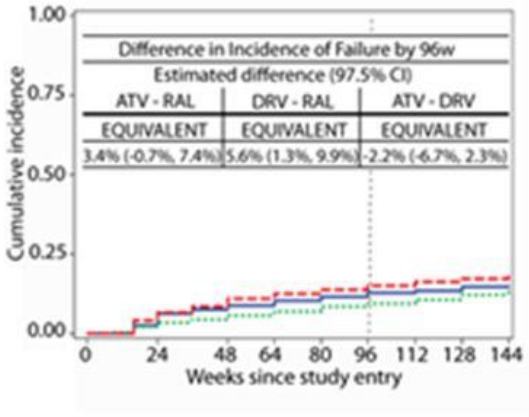


- Primary Endpoints*
  - Time to HIV-1 RNA >1000 c/mL wk 16 to before wk 24, or >200 c/mL at or after wk 24 (VF)
  - Time to discontinuation of randomized component for toxicity (TF)
- Pre-planned Composite Endpoint
  - The earlier occurrence of either VF or TF in a given participant

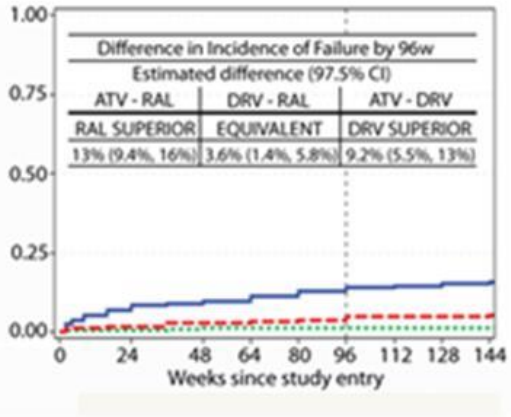
Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

What We Found

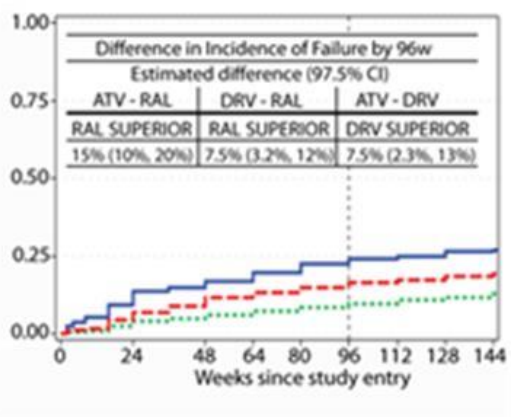
Cumulative incidence of Virological failure (VF)



Cumulative incidence of Tolerability failure (TF)



Cumulative incidence of VF/TF



Treatment arm

ATV

RAL

DRV

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What Our Results Mean and Why this Matters

- **ATV/r, RAL, and DRV/r were equivalent for virologic efficacy**
- **ATV/r was less well tolerated than DRV/r or RAL**
  - Largely due to cosmetic hyperbilirubinemia
- **RAL was superior to both Darunavir/r and Atazanavir/r regimens for combined tolerability and virologic efficacy**
  - DRV/r was superior to ATV/r
- **VF with resistance was rare**
  - Most frequently observed with RAL

A5308 BACKGROUND

- The immune activation and inflammatory responses are pivotal mechanisms by which organisms get rid of infections
- HIV-1 Infection induces a “frenzy state” in which the immune and inflammatory responses will lead to damage of target organs
- Usually, ARV treatment-naïve HIV-1-infected patients have high viral loads that lead to chronic hyper stimulation of the immune system and exacerbation of the inflammatory reaction
- Despite, the low HIV-1 viral load on HIV-1 controllers, their immune and inflammatory responses are exaggerated, increasing the incidence of cardiovascular events, kidney problems, metabolic disorders and many others

A5303 HYPOTHESES

- Starting antiretroviral therapy (ART) among ARV treatment-naïve HIV-1 controllers will result in a significant reduction of markers of immune activation
    - In treatment-naïve HIV-1 controllers starting ART, HIV-1 RNA Viral Load and the size of the HIV reservoirs will exhibit a significant decline
    - In treatment-naïve HIV-1 controllers starting ART, absolute CD4+ T-cell counts will significantly increase
    - In treatment-naïve HIV-1 controllers starting ART, will induce a reduction of the inflammatory response

BACKGROUND: A5314, A5317 and A5325

- Although ART prolongs life, it does not fully restore health. For reasons that remain controversial, HIV-infected individuals doing well on therapy have a higher than expected risk of a number of “non-AIDS” conditions, including premature CVD, renal, liver and bone diseases and non-AIDS related malignancy. Many factors likely contribute to this excess risk of premature diseases, including chronic inflammation

- Need for novel strategies to reduce inflammation in the setting of HIV infection

A5314 HYPOTHESIS and OBJECTIVES

- Reduction of HIV-associated inflammation using Methotrexate among treated and suppressed HIV-infected people on ART will be associated with a significant reduction on inflammatory markers

- To demonstrate that treatment with Methotrexate improves vascular function

- To estimate the effects of Methotrexate on cardiovascular inflammatory markers related to cardiovascular disease risk, inflammation, and coagulation

A5317 HYPOTHESES

- Telmisartan therapy will decrease lymphoid and/or adipose tissue fibrosis (scars) in HIV-infected people on ARV therapy
    - Telmisartan therapy will decrease circulating levels of biomarkers associated with inflammation, immune activation, and oxidative stress and decrease the frequency of circulating activated T cells and monocytes
    - Telmisartan therapy will increase the proportion of CD4+ T cells in lymph nodes and increase circulating CD4+ T cell counts. In treatment-naïve HIV-1 controllers starting ART, will induce a reduction of the inflammatory response

A5325 HYPOTHESES

- Isotretinoin treatment for 16 weeks will result in reduction in the levels of immune activation

- Subjects treated with isotretinoin, gut bacterial translocation, and peripheral-markers of inflammation, will decline from baseline and will be lower compared to subjects not treated with isotretinoin

- Subjects treated with isotretinoin will exhibit great reduction in the size of the HIV reservoir

A5327 BACKGROUND

- Hepatitis C virus (HCV) infection affects more than 4 million persons and causes an estimated 12,000 deaths annually in the United States

- Early identification of acute HCV infection is essential to prevent chronic infections and the long-term liver disease complications that may occur

- Early identification and treatment of HCV during the acute phase can result in significantly higher response rates with shorter durations of therapy

A5327 DESIGN and DURATION

- SWIFT-C is a Phase I, open-label, two-cohort clinical trial, in which between 44 and 50 acutely HCV-infected HIV-1 positive people will be enrolled and administered oral sofosbuvir (SOF) in combination with weight-based ribavirin (RBV)

- 32-36 weeks:
  - 8-12 weeks on-treatment followed by 24 weeks of follow-up

A5279 BACKGROUND

- The World Health Organization (WHO) estimates that in 2009, the last full year for which data collection is complete, there were 9.4 million new incident cases of TB, and 1.68 million deaths

- Among new incident cases of TB, 1.1 million were HIV-coinfected, and 35% of TB deaths were among HIV-coinfected individuals

- INH has been the cornerstone of treatment for LTBI to prevent active TB for more than 30 years; the first report of successful prevention of TB with INH was published in 1956

A5279 HYPOTHESIS and OBJECTIVES

- Ultra-short-course (4-week) daily rifapentine (RPT)/isoniazid (INH) is not inferior to a standard 9-month (36-week) daily INH regimen for the prevention of tuberculosis (TB) in HIV-infected individuals

- To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals

- To compare adherence rates in the two regimens

Acknowledgments

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