RCT: TEMPRANO ANRS: A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

TAKE HOME MESSAGE: Starting both antiretroviral therapy **and** isoniazid preventative therapy immediately after a new diagnosis of HIV independently led to lower rates of death and serious illness in an African country with high prevalence of tuberculosis.

EXECUTIVE SUMMARY: The TEMPRANO ANRS trial was a 2x2 RCT conducted at multiple centers throughout the Ivory Coast that sought to evaluate early initiation of both antiretroviral therapy (ART) and isoniazid prophylaxis (IPT) in patients newly diagnosed with HIV with CD4 counts less than 800. Patients were either started immediately on tenofovir/emtricitabine plus efavirenz, or clinically followed until CD4 dropped to WHO treatment standards before initiating treatment, and then were either started on INH 300 mg daily or no TB prophylaxis, finishing 6 months of therapy. Patients were randomly assigned into four groups – deferred ART, deferred ART plus IPT, early ART, and early ART plus IPT. Primary outcome was a death composite; secondary outcomes were severe illnesses. A total of 2056 patients were followed for 4757 patient years (average 30 months each). The risk of composite death was lower with early ART versus deferred ART (adjusted hazard ratio 0.56; 95% CI 0.41-0.94), and lower in IPT versus no IPT (adjusted hazard ratio 0.65; 95% CI 0.48 to 0.88).

The international guidelines for CD4 levels for initiating ART have been increasing steadily over the past decade – from 200 in 2006 to 500 in 2013 -- as additional RCTs are published. The TEMPRANO ANRS trial, along with the START trial, which was previously SNAPped by my esteemed colleague Dr. Jarred McAteer, provided further evidence for early initiation of ART, and in September 2015 the WHO released new guidelines stating that ART should be started in every patient with HIV at any CD4 level. Furthermore, in high-prevalence areas, tuberculosis infection is the major cause of morbidity in patients diagnosed with HIV. IPT has been studied in the pre-ART era, and several smaller studies have recommended its use. This led 2011 WHO guidelines to recommend its use. Despite these recommendations, many countries have not adopted IPT, and in countries that do its use still remains low -- in fact, the health ministry of the Ivory Coast does not allow IPT and made a specific exception for its use in this study. TEMPRANO ANRS provides the strongest evidence yet of IPT's benefit, and shows that it can be prescribed safely.

GUIDELINES:

- WHO Guidelines: Antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count
- CDC Guidelines: Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (AI).

PRACTICE CHANGE:

Naturally, this trial is another feather in the cap of early ART initiation. In regards to isoniazid prevention therapy, this trial will not change my practice in the United States, which has a low prevalence of TB and is a fundamentally different study location. The question is more relevant after I relocate to Botswana. Botswana actually introduced an IPT program in 2008; this program involves screening questions rather than blanket treatment, as in TEMPRANO ANRS, and is targeted towards picking up active TB infection. Given the fact that all INH therapy in Botswana takes place within a pre-existing, directly-observed infrastructure I will continue to follow Botswana's current guidelines, but will advocate for an expansion of IPT to all new patients diagnosed with HIV, in particular those with low CD4 counts (less than 500)

DESIGN:

- Study design: Multi-center, unblinded 2x2 factorial randomized-controlled, 1:1 superiority trial
- Patients: n=2076, evenly distributed among 4 study groups
- Setting: Nine care centers in Abidjan, the economic capital of the Ivory Coast
- Enrollment: March 2008 – January 2015
- Analysis: Intention-to-treat
- Mean follow up: 30 months

POPULATION

- **Inclusion criteria**
    - 18 years of age or older
    - HIV 1 infection, or HIV 1 or 2 coinfection
    - CD4+ count < 800 cells per cubic millimeter
    - Written informed consent
    - Met no criteria for starting ART according to most recent WHO guidelines
- **Exclusion criteria**:
    - History of combined ART
    - Pregnancy
    - Breastfeeding
    - HIV-2 infection alone
    - Ongoing serious clinical signs leading to suspect any disease that would be an indication to start ART
    - Severe renal, cardiac, or liver disease
- **Baseline characteristics**
    - Age: 35
    - Female 78%
    - CD4-count 460
    - Plasma HIV-1 RNA level: 4.6 log10copies/mL
    - Education level: Primary school or less 54%, Secondary school or more 46%

INTERVENTIONS

- All patients had HIV-1 RNA and systemic chest radiography after undergoing randomization. The first 967 also had IGRA for TB performed.
- Patients were assigned on four groups:
    - **Early ART**
    - **Deferred ART**
    - **Early ART + IPT**
    - **Deferred ART + IPT**
- All patients received tenofovir-emtricitabine plus efavirenz. Patients with contraindications received tenofovir-emtricitabine plus lopinavir-ritonavir.
- Patients with CD4<500 received TMP-SMX prophylaxis.
- Patients receiving IPT received isoniazid 300 mg daily.

OUTCOMES

Primary Outcomes

- 30-month probability for primary end point was:
    - 11.4% -- deferred ART
    - 6.6% -- early ART
    - 10.7% -- no IPT
    - 7.2% -- IPT
- Hazard ratios:
    - Early ART vs deferred ART: 0.56 (95% CI, 0.41 to 0.76)
    - IPT vs no IPT: 0.65 (95% CI 0.48 to 0.88)

Secondary Outcomes (grade 3 or 4 event)

- 30-month probability for secondary end point was:
    - 7.7% -- deferred ART
    - 7.1% -- early ART
    - 8.2% -- no IPT
    - 6.6% -- IPT
- Hazard ratios:
    - Early ART vs deferred ART: not significant
    - IPT vs no IPT: 0.69 (95% CI, 0.38-1.27)

CRITICISMS

- The most significant criticism is that the CD4 cutoff level for the deferred ART group was changed as WHO recommendations changed, from 200 to 500. Therefore, the early initiation group is not compared to a single unchanged standard.
- The study was un-blinded – both participants and providers knew which group each patient belonged to.

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