The START Trial: 
On the Shoulders of SMART

5 years after SMART 
INSIGHT Satellite Session 
WAC, Washington DC, July 2012
Rationale for START

• Considerable variation in time from infection to progression to CD4 count < 350 cells/µL
• Lack of data from randomized controlled trials - and conflicting findings from observational studies - to assess benefit:risk ratio for ART in early HIV infection
• ART reduces infectiousness and public health would argue for early ART
• Pathogenesis studies suggest potential benefit of suppression of viral replication
• ART associated with potential side effects, risk of resistance and challenge of long term adherence
Hypothesis: ART reduces risk of non-AIDS events by dampening inflammation and coagulation

HIV

† inflammation
† coagulation activation

No ART:
† risk*

ART:
↓ risk*

*: magnitude of absolute risk † or ↓ depends on demographics, lifestyle, co-morbidities, host genetic
The case why START may show net harm from early ART

• Incidence of morbidity and mortality in early HIV without ART low
  – In particular among younger persons
    • Overrepresented among those with early HIV
• ART may adversely affect
  – Kidney function
  – Bone formation
  – Liver function
  – Cardiovasvular disease
  – Neurocognitive function
  – Pulmonary function
  – (Cancer ?)
• If scenario turns out to correct (will know in next 3 yrs) – major implications for persons already started early ART
First, do no harm

• *Primum non nocere*

• The doctor should not prescribe medications unless s/he knows that the treatment is unlikely to be harmful

Doctor oath, year 1200
Areas of consensus and of controversy

• Consensus
  – Continued substantial transmission remains Achilles heel in overcoming the HIV pandemic
  – Initiation of ART makes persons less infectious
  – ART is of net health benefit to HIV+ persons with HIV-related symptoms or with CD4<350 cells/µL

• Controversy
  – Is ART of net health benefit to the asymptomatic HIV+ person if started at a CD4 count>350 cells/µL (i.e. early ART)?
Recent guidelines favouring use of early ART

- **US DHHS guidelines, March 2012**
  - Argue that early ART is of benefit to the HIV+ person = all should be treated
  - Quality of evidence: < 350 (AI), 350-500 (AII), > 500 (BIII)
- **WHO Couples HIV testing and counselling, April 2012**
  - Recognises uncertainty in benefit:risk ratio from early use of ART for the HIV+ person
  - Recommend that ART is offered to prevent transmission in heterosexual couples as long as
    - the HIV+ person is told that there is no evidence of benefit – and there maybe harm - to his/her health
    - [assume also: the person makes the decision autonomously and without pressure from his/her partner]
RCTs to inform "earlier start" of ART

- Focus interpretation on deferral strategy
  - Median CD4 count and outliers (those allowed to progress to even lower CD4 counts)

- 3 completed RCT’s –
  - Haiti trial (NEJM 2010): 280 versus 166
  - SMART subgroup (JID 2008): 477 versus 236
  - HPTN 052 (NEJM 2011 + IAS 2012): 442 versus 225

- In START
  - Current: 644 vs deferred?
While SMART was conducted:
Several smaller size RCT's and observational studies suggested that interruption of ART was safe!

GRADE criteria for assessing evidence: used widely and adopted by WHO:

- "Observational studies [...] only yield low quality evidence; in unusual circumstances [...] classified as moderate/high. E.g. if [...] magnitude of treatment effect provides extremely large and consistent estimates"
- Whether to start ART in early HIV infection
  - 3 observational studies
    - Results not large nor consistent (RH close to 1 in two and in one > 2)
    - GRADE classification: C (A is best)
Survival after ART initiated at different CD4 count levels between 200-500 cells/µL: ”causal” modelling

Proportion surviving

**Implication**
Randomized, controlled trials are needed to better define the optimal time of initiation of combined antiretroviral therapy in HIV infection.

---The Editors---

Absolute risk differences:
Death: -0.02%
AIDS/death: 2.1%
START Design

HIV-infected adults, ART-naive with CD4+ cell counts > 500 cells/mm³

Early ART Group
Immediately initiate ART
N=2,000

Deferred ART Group
Defer ART until CD4+ < 350 cells/mm³ or symptoms develop
N=2,000

Primary endpoint: Serious AIDS & serious non-AIDS disease (375)

Current Status: 2700 randomised; randomisation ends < 2012 / study < 2015.
**START Design**

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- 235 sites in 31 countries and involving 1000+ experienced HIV clinicians
- 100-140 persons randomised / month

This reflects clinical equipoise in clinical research community globally.
Key current statistics of START

• N=2693 – enrollment complete in 1Q2013

• Demographics
  – Age=35 (38% above 40 yrs), 19% females
  – 56% white, 22% black
  – 65% MSM, 31% heterosexual – 1 year since HIV diagnosis

• Clinical status
  – 5% HCV and 2% HBV co-infected
  – CD4 count = 644 (IQR:580-748); HIV-RNA = 14,110
  – 11% TDR (of 699 tested sofar)
  – 37% smokers, 20% hypertension

• Median follow-up: 13 months (38% > 18); 3.1% LTFU

• 8 substudies (organ dysfunction (pulmonary, neurology, CVD, bone) + host gene & informed consent)
Importance of defining balance of risk:benefit to individuals versus prevention benefit in resource constrained regions

• No observational data on risk:benefit of early ART (to date, all published to date from high resource countries)
• Limited data from HPTN 052
  – Deferral strategy lead to initiation of ART @ CD4 count considerably below current WHO recommendations (350)
  – composite clinical endpoint,
  – benefit restricted to extrapulmonary TB,
  – no benefit in pulmonary TB (surprising !)
  – no benefit on survival
Thank you