The Strategic Timing of AntiRetroviral Treatment (START) trial

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Background

- Combination antiretroviral therapy (cART) has turned HIV from an uniformly fatal disease into a chronic, manageable condition

- Early initiation of cART can reduce HIV transmission between heterossexual serodiscordant couples by 96%

- However, cART exposure is not without risks and has been independently associated CNS toxicity, myocardial infarction, worsening renal function, bone demineralisation and cancer

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Evolution of CD4+ Count Criteria for Starting Antiretroviral Therapy in Asymptomatic Persons with HIV, According to Different Guidelines.

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De Cock & El Sadr NEJM 2013
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Defining the benefit:risk ratio is the critical missing link in the discussion on earlier use of cART.
Methods

START: Strategic Timing of Antiretroviral Treatment

HIV+ persons who are cART-naïve with CD4+ count > 500 cells/mm³

Early cART Group
- Initiate cART immediately following randomization
- N=2,326

Deferred cART Group
- Defer cART until the CD4+ count declines to < 350 cells/mm³ or AIDS develops
- N=2,362

Babiker Clin Trials 2013
Primary Study Endpoint
(Time to first event)

- **AIDS* or death from AIDS**
  Opportunistic events consistent with the 1993 CDC expanded surveillance definition, plus additional events. *Esophageal candidiasis and chronic *Herpes simplex* counted only if they result in death.

- **Non-AIDS**
  - Cardiovascular disease (CVD) (MI, angioplasty, CABG, stroke)
  - Chronic end-stage renal disease (ESRD) (initiation of dialysis, renal transplantation)
  - Decompensated liver disease
  - Non-AIDS defining cancers (basal and squamous cell skin cancers are not counted)

- **Death not attributable to AIDS, including death of unknown cause**

  N = 213 events
Enrollment Accomplishments by ICC

- Copenhagen ICC
  - N=889
  - Austria, Belgium, Czech Rep., Denmark, Estonia, Finland, Germany, Luxembourg, Norway, Poland, Portugal, Spain, Sweden
- London ICC
  - N=1,015
  - France, Greece, Ireland, Italy, Morocco, Switzerland, Uganda, United Kingdom
- Sydney ICC
  - N=901
  - Argentina, Australia, Chile, India, Israel, Malaysia, Mexico, Nigeria, South Africa, Thailand
- Washington ICC
  - N=1,883
  - Brazil, Mali, Peru, South Africa, United States
START Around the World

555 (11%)

1,126 (25%)

1,002 (21%)

357 (8%)

109 (2%)
Conclusion

• START is fully enrolled and on track to provide the highest evidence for a reliable assessment of the benefit:risk ratio of early initiation of cART.

• Main current focuses are:
  – Maintain excellent follow-up
  – Minimise non-adherence to allocated treatment strategy
  – Timely and appropriately reporting and documenting clinical events
Acknowledgments

START Study Team


Substudy Co-chairs: Jason V Baker, Daniel Hendel (arterial elasticity); Andrew Carr, Kathrine Lerman (bone mineral density); Brian K Agan, Moso Malo (tetani genesis); Christine Grady (informed consent); Edwina Wright, Bruce Brew, Richard W Price, Kevin Robertson (neurology). The University of Minnesota, the sponsor of START, receives royalties from the use of abacavir, one of the HIV medicines that can be used in START.

Regional Endpoints:

- European Union:
  - Belgium: Nathalie Muller, Stefano Decorte, Brussels;
  - France: Christian Grady, Olivier Bonnet, Paris;
  - Germany: Heike Jensen, Carsten Zedlack, Berlin;
  - Spain: Jose Luis Arribas, Madrid;
  - United Kingdom: Christopher Heath, London.

- Latin America:
  - Argentina: Ruben Salazar, Rafael Delgado, Buenos Aires;
  - Brazil: Alexandre de Souza, Sao Paulo;
  - Chile: Christian Grady, Santiago;
  - Colombia: Christian Grady, Bogota;
  - Mexico: Christian Grady, Mexico City.

- North America:

- Asia:
  - China: Christian Grady, Beijing; Yueshi Li, Shanghai;
  - India: Christian Grady, New Delhi.

- Africa:
  - South Africa: Christian Grady, Durban; Mark Nunn, Pretoria.

- Australia:
  - Australia: Christian Grady, Sydney.

- Canada:
  - Canada: Christian Grady, Montreal.

- Other:
  - Antje Rogowsky, University of Goteborg, Sweden.

Conflict of interest: Six pharmaceutical companies (Abbott, Gilead Sciences, GlaxoSmithKline, Merck, Tibotec, and Schering-Plough) are involved in the study's CDR. The University of Minnesota, the sponsor of START, receives royalties from the use of abacavir, one of the HIV medicines that can be used in START.
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