NIH AIDS Clinical Trials Group (ACTG) Network Therapeutic Research in Resource-Limited Settings

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The NIH AIDS Clinical Trials Group Network

• Established in 1986 as a U.S. research network
  – Network Principal Investigator/Chair; Executive Committee
  – Coordinating and Operations Center (OPS)
  – Statistical and Data Management Center (SDMC)
  – Six Scientific Committees
  – 14 Network Specialty Laboratories (Virology, Immunology, Pharmacology, central DNA and specimen repository)

• Multicenter clinical trials units and clinical research sites
  – 26 U.S. CTUs with 53 clinical research sites
  – 15 International CTUs with 24 clinical research sites
ACTG International HIV/AIDS Clinical Trials Program

- 1999-2002: Initial planning and funding development
- 2003: Initial international/U.S. partner site selection
- 2003-4: Infrastructure and capacity development & training; development of international scientific agenda
- 2005: Implementation of first international clinical trials and expansion of international research sites
- 2006-2010: Completion of initial clinical trials; revision of international research agenda; second wave of studies initiated
International ACTG Clinical Trials Units

- Univ KwaZulu-Natal (Durban - 2)
- Duke/Kilimanjaro (Tanzania)
- UCSD/Chennai (Chennai, India)
- Johns Hopkins/BJMC (Pune, India)
- UCLA/Rio de Janeiro (Brazil)
- UCSF/Zimbabwe (Harare)
- Harvard/Molepolole (Botswana - 2)
- Fundação Oswaldo Cruz (Rio de Janeiro)
- Case Western Reserve/Makerere Univ (Uganda)
- WITS Health Consortium/Perinatal Research Unit (Soweto, South Africa)
- National AIDS Research Institute (Pune, India)
- GHESKIO (Haiti)
- IMPACTA/INMENSA (Lima, Peru - 2)
- Univ. of WITS (Johannesburg, SA)
- Chiang Mai Univ RIHES (Chiang Mai, Thailand)
- UAB/Zambia (Zambia)
- Johns Hopkins/Malawi (Blantyre)
- UNC/Malawi (Lilongwe)
- Walter Reed/KEMRI/MOI (Kericho & Eldoret, Kenya - 2)
Initial International Clinical Trials

- A5175/PEARLS (alternative first line ART regimens)
- HPTN 052/A5245 (how to use ART to prevent HIV transmission and when to start ART in RLS)
- A5190 (long-term followup of infants exposed to ARVs in resource-limited settings)
- A5199 (neurocognitive and neurologic complications of HIV and ARVs)
- A5207 (alternative ART regimens for PMTCT)
- A5208 (1st line ART in women exposed to sdNVP)
- A5221 (when to start ART in pts with active TB)
Accrual to International Studies by Site and Protocol
PEARLS: DSMB Findings

1A = ZDV/3TC + EFV; 1B = ddI-EC + FTC + ATV; 1C = TDF/FTC + EFV

Favors Arm 1B
ddl + FTC + ATV

Favors Arm 1A
ZDV/3TC + EFV

Primary Endpoint
1.67 (1.02, 2.75) Virologic Failure
1.77 (1.04, 3.03) AIDS Progression
3.00 (0.61, 14.87) Death
0.99 (0.23, 4.26)

Hazard Ratio (+/- 99.8% CI)
ACTG A5208/OCTANE

• Rationale: High rate of NVP resistance after sdNVP exposure → what to do in 1st line ART
  • HIV-infected women, CD4+ cell counts < 200 cells/µL, with or without previous exposure to single dose nevirapine for PMTCT
    – Two parallel strata
• Randomization:
  – Arm A: Tenofovir/Emtricitabine/Nevirapine (or Efavirenz)
  – Arm B: Tenofovir/Emtricitabine/Lopinavir-RTV (Kaletra)
DSMB Findings October 8, 2008

- Women in Stratum 1 (previous sdNVP) who were randomized to TDF/FTC/NVP were significantly more likely to experience virologic failure or die than those who received TDF/FTC/Kaletra
  - 29/123 (24%) vs. 8/120 (7%)
- Of those who started the trial with evidence of NVP resistance, 5/13 (38%) failed on the NVP arm vs. 0 on the Kaletra arm
- Differences were most evident in women entering the study 6 mos – 2 years after last NVP exposure
- Stratum 2 (no previous sdNVP) continues
Final Results: A5208/OCTANE

• Trial 2 results – 500 ARV-naïve women with CD4 < 200 and no prior sdNVP
  – Randomized to same regimens

• Results:
  – At 48 weeks, the proportions of women alive without virologic failure were 85.7% and 86.3% for the NVP and LPV/r arms (HR 0.85, 95% CI 0.56-1.29); i.e. equivalent virologic efficacy
  – However, premature ART discontinuation due to an AE occurred in 32% randomized to NVP arm and 22% to LPV/r arm

• Inferiority of NVP arm in Trial 1 likely related to NVP resistance resulting from prior sdNVP exposure
ACTG A5221

• Rationale: When to start ART in persons with active TB and CD4+ counts < 200 cells/µL unknown

• Randomization:
  – Arm A: Immediate ART (within 2 weeks of starting TB treatment) with TDF/FTC/EFV
  – Arm B: Deferred ART (after 8 weeks of intensive TB treatment) with TDF/FTC/EFV

• N=800 enrolled; f/u completed 8/2010
  – Substudies: Intensive PK of EFV and RIF; intensive TB case finding; TB IRIS incidence/pathogenesis
Additional Studies

• ACTG 5225:
  – Alternative treatment for cryptococcal meningitis – dose ranging up to 2400 mg/d high dose fluconazole

• 2\textsuperscript{nd} and 3\textsuperscript{rd} Line ART Studies:
  – 2 RCTs developed comparing regimens with novel drugs/new drug classes for use in drug-resistant HIV in RLS

• ACTG A5263, A5264:
  – International studies evaluating different strategies for treatment of limited or advanced Kaposi’s sarcoma
Challenges of Therapeutic Intervention Research in RLS

• Limited and competing resources for care, treatment and prevention

• Limited “investment” in research
  – Developing a research culture and infrastructure
  – Training of researchers and faculty/mentor development
  – Statistical training, data management and IT systems

• Logistical and regulatory challenges

• For clinical trials, access to new drugs during and after the trials

• Coordination with multiple “donors”
Thank you for your attention