HIV Treatment Scientific Committee

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June 18, 2015
HIV Treatment Scientific Committee

Objectives

• In HIV-infected neonates (including preterm), infants, children and adolescents
  – Safety and pharmacokinetics (PK)
    • New ARVs and formulations
    • Novel ARV drug combinations
  – Drug-drug interactions (ARVs, TB drugs)

• In HIV-infected pregnant women
  – Safety and PK
    • New ARVs and formulations
    • Novel ARV drug combinations
  – Drug-drug interaction (ARVs, TB drugs, contraceptives)
The context is evolving globally

• In settings with good ARV access:
  • Aging population of drug-experienced pediatric and adolescent populations
  • Diminishing ARV-naïve pediatric and maternal populations
  • Increasingly numbers of pregnant women conceiving on and initiating new ARVs
  • MTCT increasingly rare
The context is evolving globally

• In settings with limited ARV access
  • Improved maternal ART coverage
  • Decreasing MTCT rates
  • Increasing prevalence of HIV DR, transmitted and acquired
• Aging up of the pediatric population
• Substantial challenges in retention and adherence
• New emphasis on pediatric case finding and treatment (ACT initiative)
Pregnant and breast feeding women

• How do we optimize use of antiretroviral drugs during pregnancy, breast feeding and newborn period?
  – Determine that standard dose for non-pregnant adults is appropriate during pregnancy
  – Preliminary safety data on new agents
  – Determine kinetics of trans-placentally transferred ARVs to neonate
Opened in 2003, now on version 9.0

Opportunistic design
- Enroll pregnant/postpartum women receiving selected ARV’s, TB drugs and/or postpartum contraceptives as part of clinical care

Pregnant subjects – PK sampling of ARV’s, TB drugs
- During pregnancy: 2\textsuperscript{nd} trimester, 3\textsuperscript{rd} trimester and postpartum
- At delivery: maternal plasma and cord blood samples
- After birth: washout pk samples from neonate

Postpartum subjects – ARV’s plus contraceptives

Target sample size – 25 evaluable subjects per arm
<table>
<thead>
<tr>
<th><strong>P1026s Arms – Version 9</strong></th>
<th><strong># enrolled</strong></th>
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<tbody>
<tr>
<td><strong>ARV’s in Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>Darunavir (twice daily 800/100 mg bid)</td>
<td>17</td>
</tr>
<tr>
<td>Darunavir (twice daily 900/100 mg bid)</td>
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<tr>
<td>Dolutegravir</td>
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<tr>
<td>Efavirenz</td>
<td>7</td>
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<tr>
<td>Dolutegravir/cobicistat</td>
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<tr>
<td>Etravirine</td>
<td>14</td>
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<tr>
<td>Tenofovir alafenamide fumarate</td>
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<tr>
<td><strong>ARV’s plus TB Drugs in Pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz plus TB drugs</td>
<td>4</td>
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<tr>
<td>Lopinavir/rtv plus TB drugs</td>
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</tr>
<tr>
<td>Nevirapine plus TB drugs</td>
<td>0</td>
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<tr>
<td>TB drugs without ARV’s</td>
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<tr>
<td><strong>ARV’s plus Postpartum Contraceptives</strong></td>
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<tr>
<td>Efavirenz plus oral contraceptives</td>
<td>1</td>
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<tr>
<td>Efavirenz plus implanted etonogestrel</td>
<td>14</td>
</tr>
<tr>
<td>Atazanavir/rtv plus oral contraceptives</td>
<td>17</td>
</tr>
<tr>
<td>Atazanavir/rtv plus implanted etonogestrel</td>
<td>25</td>
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</table>
P1026s Future Plans

• Continue to study pk of drugs used to treat HIV and related infections in pregnant women.
  – New arms:
    • cobicistat/atazanavir
    • cobicistat/darunavir
    • doravirine
• Continue to study ARV drug-drug pk interactions in pregnant and postpartum women
• Continue to study newborn washout to inform pediatric dosing
• Use accumulated pregnant and postpartum pk data to develop models of drug disposition in pregnancy and for simulations of drug exposures with new drugs and doses in pregnancy
Pregnant and breast feeding women

• Dosing and safety of new ARVs rarely studied during pregnancy
  – 1026s provides opportunistic PK data for new agents as use increases among pregnant women

• Are there specific ARVs or ARV combinations that warrant more than PK analysis?
  – Do we need additional prospective and long term data about maternal and neonatal outcomes for new agents?
    • Integrase inhibitor-base ART, TAF?
Neonates

• New assays offer prospect of same day HIV nucleic acid testing
• New interest in the potential benefit of initiating very early treatment within the first hours of life
  – Mississippi Baby and CURE agenda
• Limited number ARVs with the defined dosing and approval for use in infancy
Neonates

• How can we safely dose use new ARVs in the neonatal period?
  – Washout PK
    • RAL (low birth weight) [1097 v.2]
    • Many ... [1026s v.9]
  – Dosing PK
    • NVP and LPV/r (> 34 wks GA) [P1115]
    • RAL (> 2kg and > 37 wks GA) [P1110]
    • MVC (> 2kg and > 37 wks GA) [IMPAACT 2007]
    • ARV in low birthweight infants [P1106]
Objectives

Primary Objectives:

1. To evaluate the safety and tolerability of MRV solution when administered with local standard of care PMTCT ARV prophylaxis during the first 6 weeks of life to HIV-1 exposed infants at risk of HIV infection.

2. To evaluate the pharmacokinetics of MRV solution during the first 6 weeks of life when given with standard PMTCT ARV prophylaxis.

3. To determine an appropriate dose of MRV solution for prophylaxis during the first 6 weeks of life.
Study Design

• Phase 1 safety and pharmacokinetics study with 2 sequential dosing cohorts:
  – Cohort 1, N= 6-18: Single doses of MRV administered between 0 and 72 hours and on day 7-14 of life with PK sampling around each dose
  – Cohort 2, N=12-18: Daily dosing with MRV initiated within 72 hours after birth through 6 weeks of life with PK sampling around two doses, one administered between day 7-14 and the other day 21-35
Study Population

- Full-term neonates <72 hours old born to HIV infected mothers at **moderate** risk of HIV-1 transmission and begun on single or combination antiretroviral therapy with standard of care antiretrovirals that do not include a potent cytochrome P450 CYP3A4 inhibitor or inducer.
  - *Nevirapine is not considered a potent cytochrome P450 CYP3A4 inducer in regards to MVC*
  - *Under discussion*
    - Inclusion of infants exposed to EFV across placenta and/or via breast milk
    - Inclusion of ‘low’ risk infants
Young children

• How do we safely dose new agents with better resistance profiles in young children?
  – **EFV** (3 to 36 months) [P1070]
  – **ETR** (2 to 6 years) [P1090]
  – **RAL** (3 to 12 years) [P1101]
  – **DOL** (2 months to 12 years) [P1093 and ODYSSEY]
  – **LPV/r, 3TC, ZDV** (6 to 36 months, malnourished) [P1092]

• What is the best 1st line regimen for HIV-infected children < 3 years old?
  – PI vs INSTI? [IMPAACT 2006]
IMPAACT 2006
NextGen Strategy Trial comparing Lopinavir/ritonavir- versus Raltegravir-based ARV Treatment in Children < 3 years of age
IMPAACT 2006: RATIONALE

• Addresses the urgent need to identify better treatment options for infants and young children

• Takes advantage of new opportunities:
  – New LPV/r formulation
    • Pellet formulation approved by FDA (DNDI/Cipla)
  – New drug class with pediatric formulations – integrase inhibitors
    • Raltegravir (Merck), approved in December 2013 for use in infants and children ≥ 4 weeks of age and available as liquid and chewable tablet formulations
    • RAL recently added to the MPP Patent Pool
IMPAACT 2006: OBJECTIVES

• **Primary Objectives:**
  – Establish relative performance of LPV/r- vs RAL-based regimens among children < 3 years of age
    • (VL at 24 weeks; safety; tolerability)

• **Secondary Objectives:**
  – Longer term performance characteristics (48+ weeks)
  – Resistance characteristics at enrollment and at treatment failure
  – Adherence
  – Cost effectiveness
  – Effort to capture multiple endpoints simultaneously to establish relative performance
IMPAAACT 2006: DESIGN

• Population (N=200):
  – HIV-infected children between 1 months and 3 years of age and either antiretroviral treatment naïve or NNRTI treatment experienced.

• Design:
  – HIV-1 infected children will be randomized to either LPV/r-based antiretroviral treatment (ART) or RAL-based ART.
  – Randomization stratified by treatment experience: those who are antiretroviral naïve (Naïve) and those who are failing an NNRTI-based regimen (NNRTI-experienced).

• Treatment Regimens:
  – Best available formulations of LPV/R (BID) and raltegravir (BID).
  – Partnered with either AZT/3TC or ABC/3TC.
IMPAACT 2006: ENDPOINTS

• Primary endpoint:
  – Proportion experiencing virologic failure (VF) or off drug by week 24
  – Proportion experiencing VF by week 24

• Secondary endpoint:
  – Safety
  – Time to VF or death
  – Time to VF or off drug
  – Composite clinical endpoint
Older children & adolescents

• Can we simplify and decrease toxicity in context of life-long ARV treatment?
  • Tenofovir alafenamide (TAF)
  • NRTI-sparing simplified regimens (CAP 513)
  • Doravirine under discussion

• What is the role for novel formulations that promise to facilitate adherence and minimize resistance?
  • Long acting formulations (rilpiverine and cabotegravir)
HIV and Tb Co-treatment

• How do we appropriately dose ARVs in context of Tb treatment in children?
  – EFV (3 months to < 36 months) [P1070]
  – RAL (3 years to < 12 years) [P1101]
  – many (low birth weight neonates) [P1106]
## IMPAAACT Treatment Studies: Closed to Accrual or Follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Accrual</th>
<th>Target Accrual</th>
<th>Status</th>
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<tbody>
<tr>
<td>P1020a</td>
<td>Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, Reyataz) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and Experienced HIV-infected Infants, Children, and Adolescents</td>
<td>195</td>
<td>157</td>
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<tr>
<td>P1058a</td>
<td>Intensive Pharmacokinetic Studies of New Classes of Antiretroviral Drug Combinations in Children, Adolescents, and Young Adults</td>
<td>89</td>
<td>85</td>
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<tr>
<td>P1060</td>
<td>Phase II, Parallel, Randomized, Clinical Trials Comparing the Responses to Initiation of NNTRI-based Versus PI-based Antiretroviral Therapy in HIV-infected Infants who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother-to-Child HIV Transmission</td>
<td>452</td>
<td>315</td>
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<tr>
<td>P1066</td>
<td>A Phase I/II, Multicenter, Open-Label, Noncomparative Study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents</td>
<td>153</td>
<td>160</td>
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<tr>
<td>P1083</td>
<td>A Phase II/III Trial of Lopinavir/Ritonavir Dosed According to the WHO Pediatric Weight Band Dosing Guidelines</td>
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<td>Study</td>
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<tr>
<td>P1026s</td>
<td>PK of ARVs &amp; Related Drugs During Pregnancy &amp; Postpartum</td>
<td>85</td>
<td>350 (V9)</td>
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<tr>
<td>P1070</td>
<td>Dose-Finding &amp; PK of Efavirenz in HIV-infected &amp; HIV/TB Co-infected Infants &amp; Children ≥3 months to &lt;36 Months of Age</td>
<td>66</td>
<td>155</td>
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<tr>
<td>P1090</td>
<td>Phase II/III Open-Label Trial to Evaluation Safety, Tolerability, PK &amp; Antiviral Activity of Etravirine in ARV Treatment-Experienced HIV-1 Infected Infants and Children, Aged ≥2 Months to &lt;6 Years</td>
<td>6</td>
<td>50 (V4)</td>
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<tr>
<td>P1093</td>
<td>Phase I/II, Multi-Center, Open-Label PK, Safety, Tolerability &amp; Antiviral Activity of Dolutegravir, Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents</td>
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<td>120</td>
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<tr>
<td>P1097 Cohort 2</td>
<td>Raltegravir PK &amp; Safety in Neonates</td>
<td>1 pair</td>
<td>20 pairs</td>
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<td>P1101</td>
<td>Phase I/II Dose-Finding, Safety, Tolerance, Drug-Drug Interaction &amp; PK Study of Raltegravir-Containing ART Regimen in ART-Naïve HIV-Infected and TB Co-Infected Children ≥ 3 Years to &lt; 12 Years of Age</td>
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<td>P1110</td>
<td>Phase I Trial to Evaluate Safety &amp; PK of Raltegravir in HIV Exposed Infants at High Risk</td>
<td>13 pairs</td>
<td>50 pairs</td>
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<td>P1092</td>
<td>Phase IV Evaluation of the Study State Pharmacokinetics of Zidovudine, Lamivudine, and Lopinavir/ Ritonavir in Severely Malnourished HIV-1-Infected Antiretroviral-Naïve Children Who Are Initiating HAART</td>
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# IMPAACT Treatment Studies: Pending & In Development

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<tr>
<td><strong>P1106</strong></td>
<td>Pharmacokinetic Characteristics of Antiretrovirals and Tuberculosis Medicines in Low Birth Weight Infants</td>
<td>NA, 158</td>
<td>Pending</td>
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<tr>
<td><strong>IMPAACT 2007</strong></td>
<td>Phase I Safety and Pharmacokinetics of Maraviroc in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection</td>
<td>NA, TBD</td>
<td>In development</td>
</tr>
<tr>
<td><strong>IMPAACT 2006</strong></td>
<td>NextGen Strategy Trial comparing Lopinavir/ritonavir- versus Raltegravir-based ARV Treatment in Children &lt;3 Years of Age</td>
<td>NA, TBD</td>
<td>In development</td>
</tr>
</tbody>
</table>
THANKS EVERYONE!

- 90% diagnosed
- 90% on treatment
- 90% virally suppressed