BEYOND THE PRIMARY ENDPOINT: VALUE ADDED FROM IMPAACT LABORATORIES

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Clinical trials are costly and money is tight so we need to be efficient and glean as much information from the data and samples as possible

• Use of secondary objectives, NWCS, DACs, and Specialty Lab projects

• 3 examples:
  • Vaccine elicited envelope-specific antibody responses in P230/326
  • Pharmacogenomics (P366/377, P382, P1070)
  • Assay development
Acknowledgments

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• Debbie Persaud – JHU
• Amy Loftis – UNC IMPAACT Central Lab

Note: Some of these data are still preliminary and none of the data are mine, so if you have questions, please ask the investigators
VACCINES
Hypothesis: HIV-exposed infants vaccinated with gp120 can elicit a similar antibody response to that of the RV144 vaccine regimen despite the presence of HIV Env-specific maternal antibodies.

Method: Measure Env-specific IgG and IgA responses in HIV exposed infants from PACTG230 and PACTG326 using the same technique (binding antibody multiplex assay) and antigens used in the RV144 immune correlates analysis.
Vaccine Studies

**PACTG 230:**
- Chiron vaccine: rgp120 (SF-2 strain) with MF59 adjuvant (n=47)
- Vaxgen: rgp120 (MN strain) adsorbed onto alum (n=49)
- Placebo (n=19)

**PACTG 326:**
- ALVAC-HIV vCP1452 vaccine +AIDSVAX B/B (rgp120 from MN and GNE8 absorbed onto alum) (n=10)
- Placebo (n=11)
Broad gp120-specific binding IgG responses present in infant vaccines following the decline of passive maternal antibodies

*The cutoff was determined the mean MFI +3SD of 60 HIV uninfected adults

**Decline of maternal antibodies (gp41 IgG)**

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<th>Week</th>
<th>Log MFI</th>
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<tr>
<td>0</td>
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<td>24</td>
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**Cutoff**

*Only values above cutoff are presented*

**MN gp120**: PACTG 230/326 vaccine strain
**4403 BMC5**: postnatal clade C T/F Env
**GNE8**: PACTG 326 vaccine strain
**B con gp140**: Consensus clade B Env
**A244 gp120**: RV144 vaccine strain
**92TH023 gp120**: RV144 vaccine strain
High magnitude and frequency of Env-V1/V2 IgG response elicited by infant gp120 vaccination

The antigen used (gp70 B case A2 V1/V2) is the same as in the RV144 immune correlate analysis (Haynes et al, 2011).
No detectable vaccine elicited HIV gp120-specific IgA

* Cutoff determined as the mean MFI +3SD of HIV uninfected infants at birth
PHARMACOGENETICS
Host Genetic Variants alter Nevirapine Drug Levels – Protocol P366/P377
Effect of CYP2B6-G516T on Nevirapine AUC

Saitoh et al AIDS 2007
Increased Nevirapine AUC Associated with CYP2B6-516-T allele is Associated with an Improved CD4% Response at 12 and 24 Weeks following Initiation of Therapy
Host Genetic Variants can alter Antiretroviral Drug Levels – Protocol P382: Effect of CYP2B6-G516T on Efavirenz AUC

Saitoh et al AIDS 2007
Host Genetic Variants and Age can alter Antiretroviral Drug Levels – Protocol P382: Effect of CYP2B6-G516T on Efavirenz AUC

Saitoh et al AIDS 2007
P1070 – Strong Influence of CYP2B6 Genetic Polymorphisms on EFV PK in HIV-infected < 3 years and implications for dosing

- 26 subjects (median age 25 months); 19 CYP2B6 GG/GT and 7 TT
- Median EFV AUC was significantly higher in subjects with TT genotype (490 mg*h/mL) than GG/GT (106 mg*h/mL) ($p = 0.0005$)
- 13/26 met the week 2 AUC target (13 of 19 GG/GT, 0 of 7 TT); 5 were below target and 8 were above
- Possibly treatment-related toxicities ≥grade 3 occurred in 2 of 7 TT subjects and in 1 of 19 GG/GT subject, all of whom had excessive EFV levels
- P1070 was amended to add a screening CYP2B6 genotype so that a genotype appropriate dose could be used

(Bolton, 2012 CROI)
ASSAY DEVELOPMENT
Development of assays to measure latent viral reservoirs in infants

- IMPAACT P1030 showed that the latent reservoir for HIV can be quantified even with small blood volumes obtained from infants, and remained detectable through two years of age even in infants starting HAART at a median of two months of age.
Restricted latent reservoir if treated before six weeks of age (red circles)

Reservoir decays over the first two years of life but remains detectable; half-life of 11 months

[95% CI: 6 to 30 months]
Development of assays to measure latent viral reservoirs in infants

• **IMPAACT P1059** is the first clinical trial to show that boosting HIV-specific immunity leads to a transient decrease in the size of the latent reservoir in HIV-infected youth on suppressive HAART.
Therapeutic HIV Vaccines Led to a Transient Decrease in the Latent Reservoir in HIV-Infected Adolescents

Persaud et al. AIDS 2011
Specimens at BRI

- Liquid Nitrogen Total: 105,143 vials
- Non Liquid Nitrogen Total: 286,316 vials
- Protocols with more than 10,000 vials: 076, 152, 219/219C, 300, 316, 338, 381, P1020A, P1025 and P1060

Investigators are urged to come up with fresh ideas on how to use these specimens that IMPAACT is storing.
Summary

• Infants and children are not just little adults and continued study of pharmacokinetics, metabolism, and the immune response to HIV are crucial

• Much has been learned about HIV pathogenesis through studies of stored specimens from our trials

• Get creative and write a NWCS or DACS to use the wealth of data and specimens available from the PACTG and IMPAACT
QUESTIONS