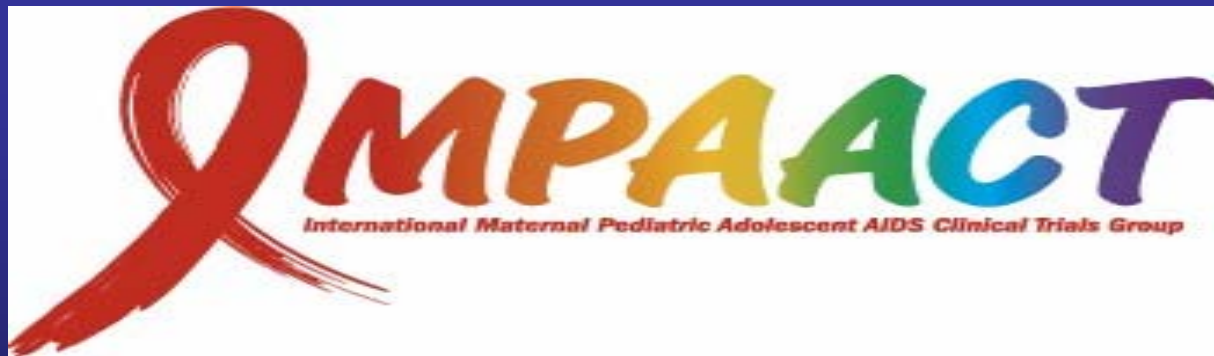


# State of the IMPAACT Network

May 7, 2009

*Brooks Jackson*



# Specific Aims

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1. Develop and evaluate safe, cost effective approaches to interrupt mother-to-child transmission (MTCT)
2. Evaluate treatments for HIV-infected children, adolescents, and pregnant women, including treatment and prevention of co-infections and co-morbidities
3. Evaluation of vaccines for prevention of MTCT and sexual transmission among adolescents, and for therapeutic use

# **Overarching Goal:** **End the Pediatric HIV Epidemic**

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**Scientifically we know how to do this:**

- **Identify HIV infected women early in pregnancy**
- **Start maternal HAART early and throughout pregnancy**
- **Formula feed infant**

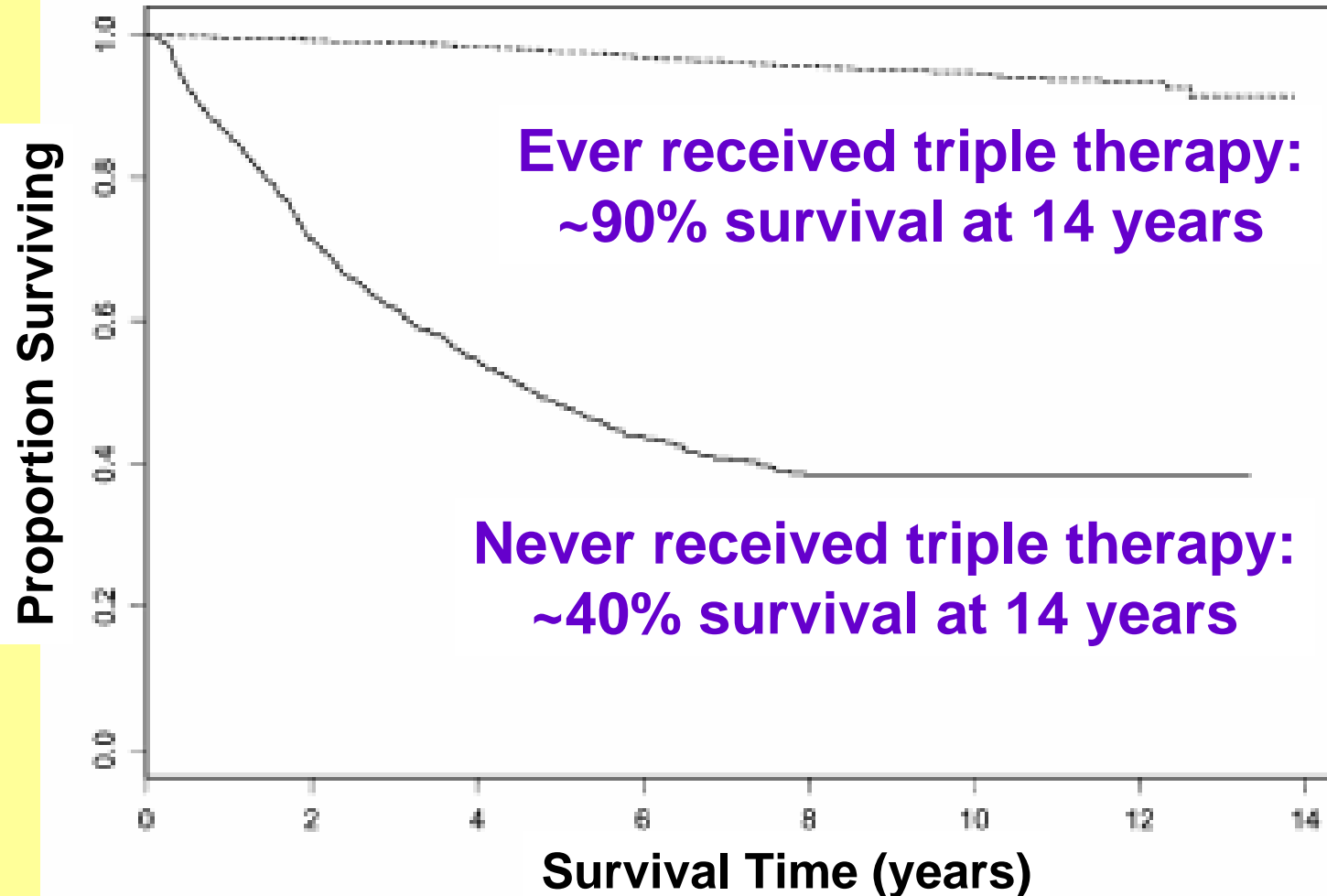


# Treatment of Pediatric HIV Infection



# HAART is Associated with Improved Survival in HIV-Infected Children in the U.S.

*McConnell M et al. JAIDS 2005;38:488*



US Pediatric Spectrum of Disease Project

## Early ART reduces risk of AIDS/death in HIV infected infants

- European Infant Collaboration Group conducted an observational study in Europe of 210 perinatally infected infants free of AIDS before 3 mo who received (n=124) or did not receive ART (n=86) before 3 months of age
- Similar baseline characteristics in both groups
- Risk of developing AIDS/death at 1 yr was 1.6% and 11.7% respectively. Adjusted Hazard ratio – 3.0



## Progress in Treatment of HIV-Infected Children

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- Clinical trials have led to incremental improvements in health of the estimated 4400 children <15 yo living with HIV in North America.
- Combination therapy is now standard treatment for children at an early age.
- Cases of pediatric AIDS and mortality have significantly decreased, but long term HIV and ARV complications are a concern.
- Some new drugs are being approved for adults and children, but PK/safety data in young children (esp infants) is lacking for majority of ARVs.

## Priorities for Pregnant Women

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- **PK/safety data of approved ARVs for treatment needed for pregnant women**
- **Efficacy and safety of continuing HAART or not after delivery in women with high CD4**

# Domestic Agenda – Scientific priorities

1. Phase I/II trials of new drugs (ARVs and drugs for complications) for PK and safety in children and pregnant women

P1066 (Raltegravir), P1071 (Vicriviroc), P1026s (PK of new drugs in pregnancy), P 1080 (Psychiatric and ARV medication interactions)

2. Phase I/II trials for testing new ARV combination therapies esp in drug experienced children and treatment naïve and experienced adolescents

P1020A (ATV), P1021 (FTC+EFV+ddI), P1058 (Tenofovir), A5241 (OPTIONS protocol), ATN 061/071 (immune preservation and neuro cognitive assessment following HAART deintensification)

# Domestic Agenda - Scientific priorities

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## 3. Protocols for treatment of HIV complications and drug related toxicities

**P1047** long term immunogenicity of HPV vaccine

**ATN 024, ATN 052** (Immune response to HBV)

**P1063** (Safety of atorvastatin for PI associated high Chol)

**P1076** (Impact of alendronate on BMD)

**ATN 063** (Vit D supplement to improve phosphate resorption and decrease bone turnover)

**P1074** Long Term Follow-up registry

**A5240** (HPV vaccine immunogenicity in young adults)

## 4. Phase I/II/III trials of HIV therapeutic vaccines

**P1049** (Safety/Immunogenicity of DermaVir)

## Domestic Agenda – Scientific priorities

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5. Safety and Efficacy of continued or cessation of HAART after delivery in women with high CD4 counts  
P1077HS

## Urgency of Research to Identify Relevant Prevention and Treatment Regimens for Resource-Poor Countries

WHO Pediatric HIV/AIDS in 2007	Global Estimate	Sub-Saharan Africa	Resource-Rich Countries
Children Living with HIV/AIDS	2.0 million	1.8 million	6,800
New Infant HIV Infections	370,000	330,000	<700
Deaths in Children with HIV/AIDS	270,000	240,000	<400

# IMPAACT International Priorities

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- Evaluate efficacy of both simple and more complex **PMTCT regimens** in order to enhance maternal health and minimize infant HIV transmission in breastfeeding populations, and decrease infant mortality and ARV resistance
- Evaluate more simple, less toxic, and efficacious **ARV, TB, and malaria treatment regimens** to provide more complete treatment options and minimize resistance

## International Agenda – ARV Treatment priorities

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- > Phase I/II/III trials for testing new ARV combination therapies, formulations, and FDCs esp in treatment naïve children, adolescents, and women

**P1069** (PK of GPO-VIR AZT+3TC+NVP tablets vs liquid Thailand)

**P1070** (PK of EFV in TB infected infants)

- > Phase III trials of different HIV treatment strategies (ie, using different drug combinations, sequencing regimens, new formulations) to maximize viral suppression and minimize resistance esp in treatment naïve children and women

**P1060** (NNRTI vs PI for initial therapy in infants 6-36mos of age ± sd-NVP PMTCT exposure)

# International Agenda – Co-infection Treatment Priorities

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➤ **Tuberculosis**

➤ **Malaria**

## IMPAACT TB studies

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- **P1041** - Phase III trial INH Prophylaxis in HIV exposed children in Africa
- **P1070** - PK study of EFV in HIV/TB co-infected children <36 mo of age
- **P1078** - Safety and Efficacy of INH preventive therapy among HIV+ pregnant women with latent TB

## Malaria

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- **P1068s** - Evaluate effect of PI vs NNRTI based ART to suppress malaria parasitemia
- **P1079** - PK study to investigate drug interactions between artemesinin based combination therapy (ACT) for malaria and NNRTI treatment for HIV in children co-infected in resource limited settings.

# Challenges to Effective PMTCT in Resource Poor Settings

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1. Lack of access to HAART and if available should it be continued after delivery
2. Inability to safely formula feed or breastfeed

# **Proposed IMPAACT PROMISE Strategy Clinical Trial P1077**

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- **Large trial designed to address multiple questions with overall goal to maximize maternal and infant survival.**
  - **What is optimal and most effective PMTCT regimen antenatally and in breastfeeding infants which is cost-effective and implementable**
  - **How to improve HIV-free survival in infants after weaning (does CTX help)**
  - **Maternal survival and morbidity – can HAART be stopped after prophylaxis (does duration of prophylaxis make a difference)**

# International Agenda – PMTCT priorities

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Phase I/II/III trials of effective interventions and (ARVs, vaccines, other) to further reduce MTCT during the antenatal, postnatal or breastfeeding periods

**HPTN 027** (ALVAC HIV vaccine in newborns)

**HPTN 040/P1043** (Comparison of postpartum ARV regimens)

**HPTN 057** (PK TDV in newborns)

**HPTN 046** (6 mo NVP prophylaxis in breastfed infants)

**PROMISE P1077** and **P1084S**

**P1081** (Viral kinetics in 3<sup>rd</sup> trimester using 3 different HAART regimens)

## **Accomplishments to date**

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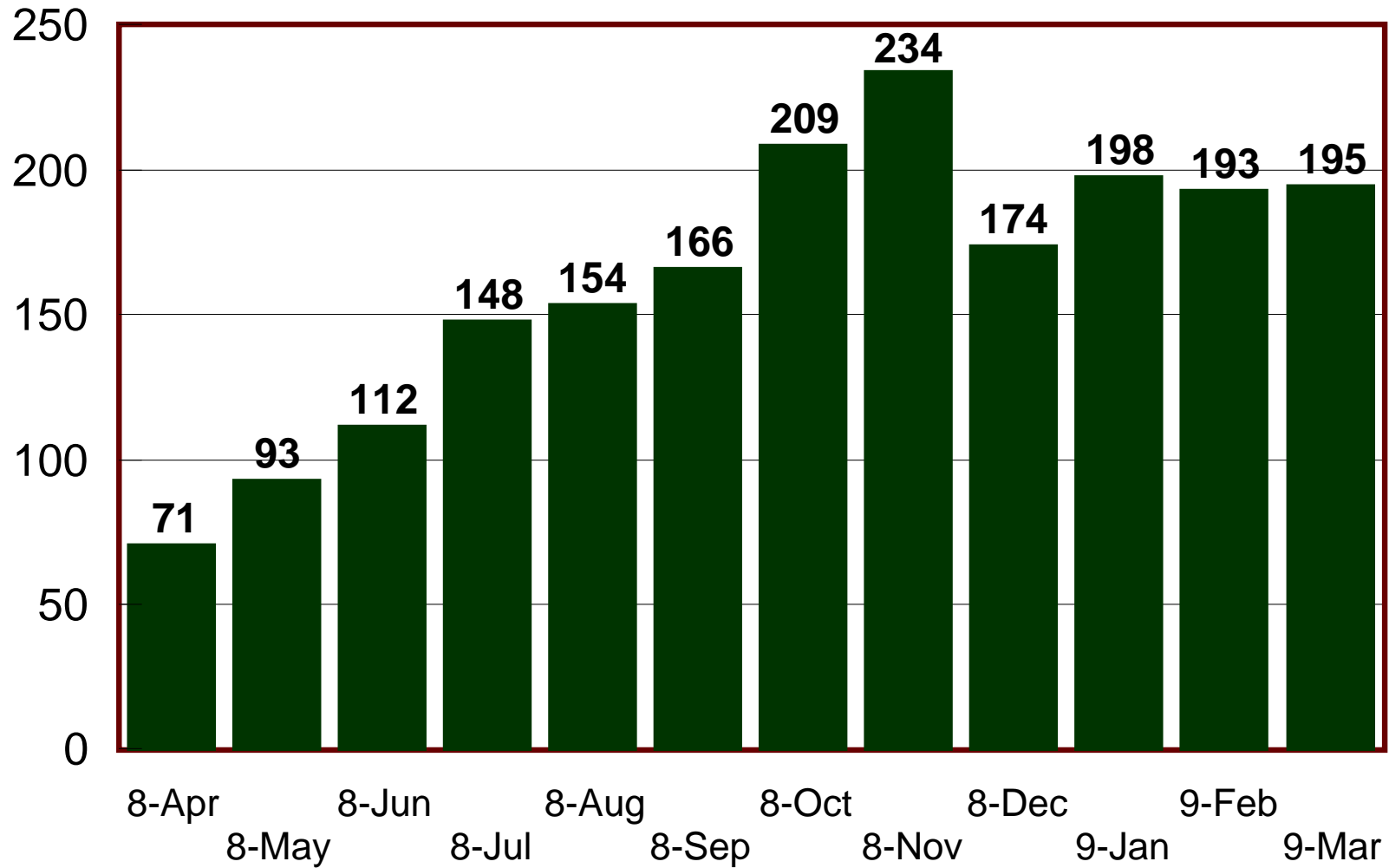
- **P1060 demonstrated that by week 24 treatment failure was significantly higher in NVP exposed infants receiving NVP based vs PI based HAART**
- **P1032 demonstrated a 7 day regimen of IP/PP ZDV/ddI/LPV/r significantly reduced the incidence of NVP resistant mutations in Thai women exposed to sdNVP.**
- **P1041 showed that INH prophylaxis for 96 wk failed to prevent TB disease and latent TB infection compared to placebo among HIV perinatally exposed uninfected infants**

## **Accomplishments to date**

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- **From Feb 2008 to Feb 2009, 2559 women, children and adolescents were enrolled [1596 into 11 IMPAACT trials internationally (62%) and 963 into 9 trials in the US (38%)].**
- **1815 (71%) of 2559 were enrolled into interventional trials.**
- **6372 participants (3396 international and 2976 in US) were followed on study this past year.**
- **Since Feb 2008, 54 papers were published and 35 manuscripts submitted for review.**

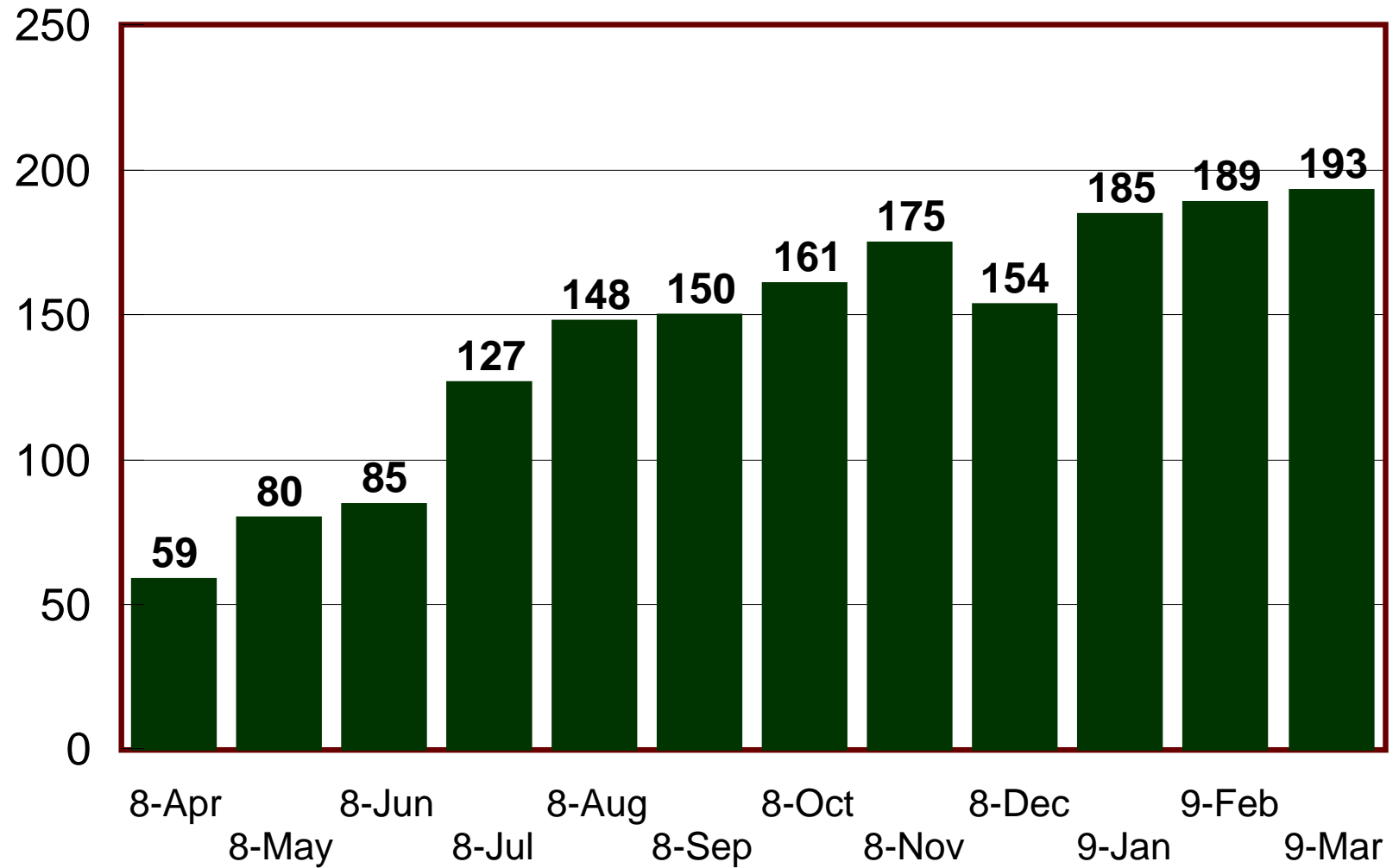
**All CRSs: Intervention Studies**  
**Number of Subjects Entered by Month**  
**1-Apr-08 Through 31-Mar-09**



# International CRSs: Intervention Studies

## Number of Subjects Entered by Month

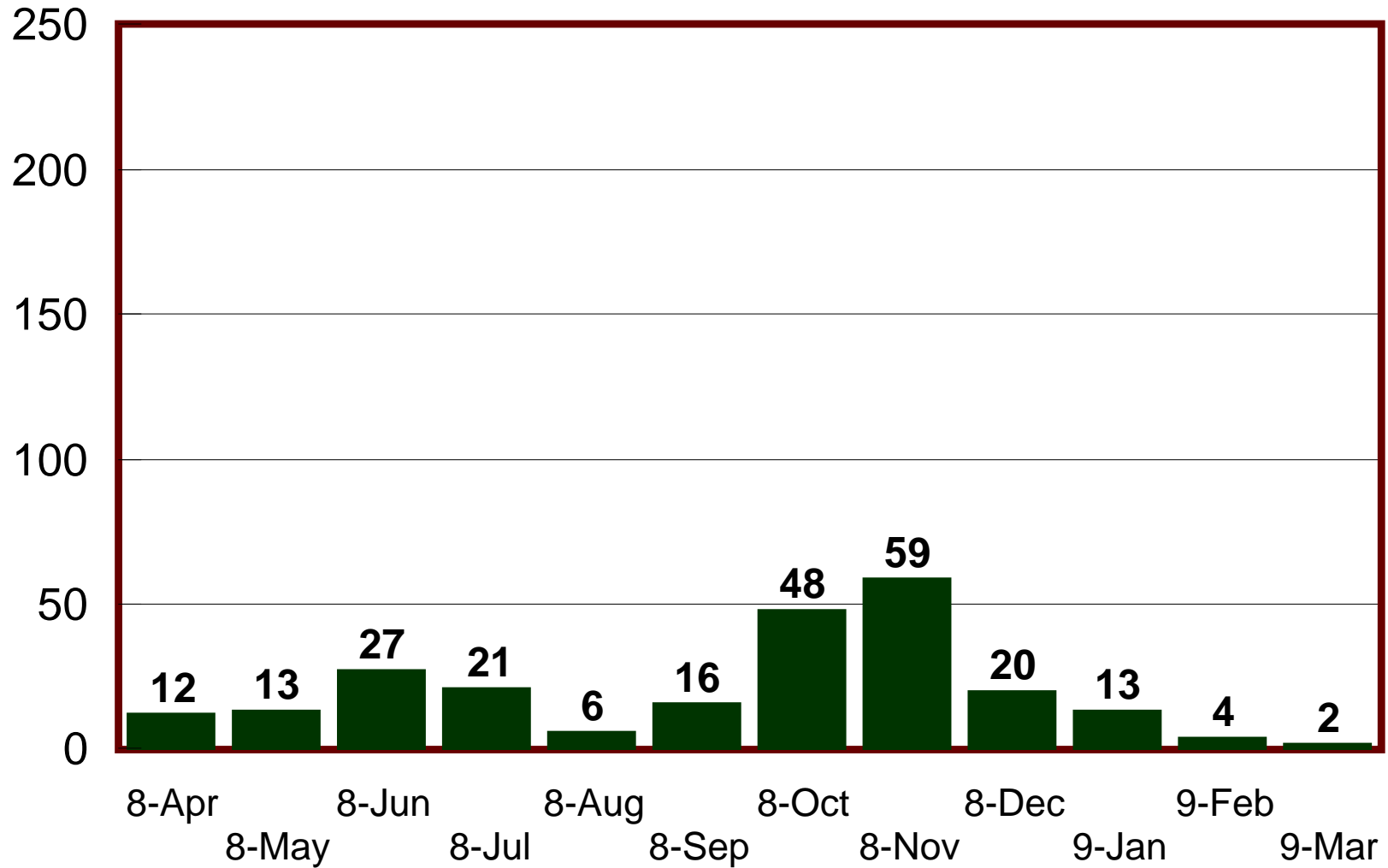
1-Apr-08 Through 31-Mar-09



# Domestic CRSs: Intervention Studies

## Number of Subjects Entered by Month

1-Apr-08 Through 31-Mar-09



# Present and future protocol plans

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- **The network has 14 open protocols, with 15 protocols in development.**
- **Thirteen new interventional protocols are planned to open by December 31, 2009 (P1063, P1070, P1071, P1073, P1076, P1077, P1078, P1079, P1080, P1081, P1083, A5240) requiring a total of 10,775 participants to be enrolled (9225 at international sites and 1550 at domestic sites).**