Pediatric AIDS Clinical Trials Group (PACTG) Publications
Nancy Hutton, MD

PACTG 219/219C
Hutton Roles: National Protocol Team Member, Author, and JHU Site Investigator

Member PACTG 219/219C Protocol Team: invited to join national protocol team in 2000, participated in monthly conference calls, contributed to hypothesis generation and revision for 219C (opened Sep 2000), review/recommend/contribute to generation of concept sheets for analysis of multicenter data, participate in author teams for manuscripts relevant to palliative care, review/approve lay summaries of planned team publications; 24 team publications from 2002-2010 (see below)
Author contributions: refined research question, defined variables for analysis from study database, reviewed data analysis and interpretation, wrote/reviewed/edited final manuscript for 2 of the team publications (see below)
JHU lead investigator for PACTG 219/219C: submit/renew IRB, identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse. This study enrolled and retained subjects continuously from 1993 through 2007.
Impact: This protocol enrolled over 3451 subjects at multiple centers in the US and evaluated mortality trends, medication toxicity, impact of primary therapy on HIV complications
Context: As individual clinical drug and vaccine studies were forced to utilize surrogate markers in short duration trials, this long term outcomes study provided the structure to assess the impact of antiretroviral therapy on the natural history of pediatric HIV infection, monitor for potential toxicity in infected children and in uninfected children exposed to antiretroviral therapy in utero.

PACTG 219C publications (2002-2010) - Author

1. Lyon ME, Williams P, Woods ER, **Hutton N**, Butler AM, Sibinga E, Brady MT, Oleske JM for the PACTG 219C Team. Do-not-resuscitate orders and/or hospice care, psychological health and quality of life among children/adolescents with AIDS. J Palliat Med (2008) 11(3):459-469.

   Roles: member PACTG 219/219C Study Team, author, JHU site lead investigator
   Impact: This study is the first multicenter trial to address and refute the concern that discussing end of life health care decisions increases emotional distress.
   Context: The tension between a focus on disease modifying therapy and a focus on recognition of the life-threatening nature of HIV/AIDS is active and highly relevant. This study supports the approach of integrating palliative care principles with HIV care and treatment.

2. Butler AM, Williams PL, Howland LC, Storm D, **Hutton N**, Seage GR, Pediatric AIDS Clinical Trials Groups 219C Study Team. Impact of disclosure of HIV infection on health-related quality of life among children and adolescents with HIV infection. Pediatrics (2009) 123:935-943.

   Roles: member PACTG 219/219C Study Team, author, JHU site lead investigator
   Impact: This study uses the multicenter database to confirm the findings of single site observations that disclosure to children of their HIV diagnosis does not cause harm to psychological or physical health.

Context: The need for diagnosis disclosure to children born with HIV infection is not anticipated in settings where the mortality rate is high and the expectation for survival to adolescence low. By the time of this analysis and publication, US based pediatric HIV clinical programs had already grappled with this emerging challenge. However, HIV programs in international settings with recent access to antiretroviral therapy in the context of high background childhood mortality are just beginning to encounter this "benefit" of highly active antiretroviral therapy.

PACTG 219C publications (2002-2010) – Team Member

1. Gaughan DM, Hughes MD, Seage GR 3rd, Selwyn PA, Carey VJ, Gortmaker SL, Oleske JM. The prevalence of pain in pediatric human immunodeficiency virus/acquired immunodeficiency syndrome as reported by participants in the **Pediatric Late Outcomes Study (PACTG 219)**. Pediatrics (2002) 109(6):1144-52.

2. Gaughan DM, Mofenson LM, Hughes MD, Seage GR 3rd, Ciupak GL, Oleske JM; **Pediatric AIDS Clinical Trials Group Protocol 219 Team**. Osteonecrosis of the hip (Legg-Calve-Perthes disease) in human immunodeficiency virus-infected children. Pediatrics (2002) 109(5):E74-4.

3. Gaughan DM, Hughes MD, Oleske JM, Malee K, Gore CA, Nachman S; **Pediatric AIDS Clinical Trials Group 219C Team**. Psychiatric hospitalizations among children and youths with human immunodeficiency virus infection. Pediatrics (2004) 113(6):e544-51.

4. Brogly S, Williams P, Seage GR 3rd, Oleske JM, Van Dyke R, McIntosh K; **PACTG 219C Team**. Antiretroviral treatment in pediatric HIV infection in the United States: from clinical trials to clinical practice. JAMA (2005) 293(18):2213-20.

5. Farley J, Gona P, Crain M, Cervia J, Oleske J, Seage G, Lindsey J; **Pediatric AIDS Clinical Trials Group Study 219C Team**. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4-19 years old) in Pediatric AIDS Clinical trials Group 219C. J Acquir Immune Defic Syndr (2005) 38(4):480-7.

6. Kest H, Brogly S, McSherry G, Dashefsky B, Oleske J, Seage GR 3rd. Malignancy in perinatally human immunodeficiency virus-infected children in the United States. Pediatr Infect Dis J (2005) 24(3):237-42. (PACTG 219/219C Team)

7. Williams PL, Storm D, Montepiedra G, Nichols S, Kammerer B, Sirois PA, Farley J, Malee K; **PACTG 219C Team**. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics (2006) 118(6):e1745-57. Epub 2006 Nov 13

8. Seage GR 3rd, Buchacz K, Weinberg GA, Patel K, McIntosh K, Dankner WM, for the **Pediatric AIDS Clinical Trials Group 219 Study Team**. The Pediatric AIDS Severity Score (PASS): a multidimensional AIDS-severity adjustment for pediatric HIV infection. J Acquir Immune Defic Syndr (2006) 43(5):603-10.

9. Patel K, Weinberg GA, Buchacz K, McIntosh K, Dankner WM, Seage GR 3rd, for the **Pediatric AIDS Clinical Trials Group 219 Study Team**. Simple Pediatric AIDS Severity Score (PASS): a pediatric severity score for resource-limited settings. J Acquir Immune Defic Syndr (2006) 43(5):611-7.

10. Gona P, Van Dyke RB, Williams PL, Dankner WM, Chernoff MC, Nachman SA, Seage GR 3rd. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA (2006) 296(3):292-300. (PACTG 219/219C Team)

11. Lindsey JC, Malee KM, Brouwers P, Hughes MD; **PACTG 219C Study Team**. Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy. Pediatrics (2007) 119(3):e681-93. Epub 2007 Feb 12.

12. Van Dyke RB, Wang L, Williams PL; **Pediatric AIDS Clinical Trials Group 219C** Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. J Infect Dis (2008) 198(11):1599-1608.

13. Patel K, Hernán MA, Williams PL, Seeger JD, McIntosh K, Dyke RB, Seage GR 3rd; **Pediatric AIDS Clinical Trials Group 219/219C** Study Team. Long-term effects of highly active antiretroviral therapy on CD4+ cell evolution among children and adolescents infected with HIV: 5 years and counting. Clin Infect Dis (2008) 46(11):1751-1760.

14. Williams PL, Van Dyke R, Eagle M, Smith D, Vincent C, Ciupak G, Oleske J, Seage GR 3rd; **PACTG 219C** Team. Association of site-specific and participant-specific factors with retention of children in a long-term pediatric HIV cohort study. Am J Epidemiol (2008) 167(11):1375-1386. Epub 2008 Apr 15.

15. Tassiopoulos K, Williams PL, Seage GR 3rd, Crain M, Oleske J, Farley J; **International Maternal Pediatric Adolescent AIDS Clinical Trials 219C** Team. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. J Acquir Immune Defic Syndr (2008) 47(5):607-614.

16. Malee K, Williams PL, Montepiedra G, Nichols S, Sirois PA, Storm D, Farley J, Kammerer B; **PACTG 219C** Team. The role of cognitive functioning in medication adherence of children and adolescents with HIV infection. J Pediatr Psychol (2009) 34(2):164-175. Epub 2008 Jul 22.

17. Nachman SA, Chernoff M, Gona P, Van Dyke RB, Dankner WM, Seage GR 3rd, Oleske J, Williams PL; **PACTG 219C** Team. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. Arch Pediatr Adolesc Med (2009) 163(2):164-171.

18. Levin MJ, Anderson JP, Seage GR 3rd, Williams PL; **PACTG/IMPAACT 219C Team**. Short-term and long-term effects of highly active antiretroviral therapy on the incidence of herpes zoster in HIV-infected children. J Acquir Immune Defic Syndr (2009) 50(2):182-91.

19. Kapetanovic S, Aaron L, Montepiedra G, Sirois PA, Oleske JM, Malee K, Pearson DA, Nichols SL, Garvie PA, Farley J, Nozyce ML, Mintz M, Williams PL; **Pediatric AIDS Clinical Trials**. The use of second-generation antipsychotics and the changes in physical growth in children and adolescents with perinatally acquired HIV. AIDS Patient Care STDS (2009) 23(11):939-947.

20. Sirois PA, Montepiedra G, Kapetanovic S, Williams PL, Pearson DA, Malee K, Garvie PA, Kammerer BL, Nichols SL, Nozyce ML, Mintz M, Mitchell WG, Oleske JM; **IMPAACT/PACTG 219C Team**. Impact of medications prescribed for treatment of attention-deficit hyperactivity disorder on physical growth in children and adolescents with HIV. J Dev Behav Pediatr (2009) 30(5):403-412.

21. Patel K, Ming X, Williams PL, Robertson KR, Oleske JM, Seage GR 3rd; **International Maternal Pediatric Adolescent AIDS Clinical Trials 219/219C Study Team**. Impact of HAART and CNS-

penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS (2009) 23(14):1893-1901.

22. Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM; **PACTG 219C Team**. Neurodevelopment and in utero antiretroviral exposure of HIV-exposed uninfected infants. Pediatrics. 2010 Feb;125(2):e250-60. Epub 2010 Jan 18.

ACTG 128 – Author & JHU site lead investigator

Brady M, McGrath N, Brouwors P, Gelber R, Fowler MG, Yogev R, **Hutton N**, Bryson YJ, Mitchell CD, Fikrig S, Borkowsky W, Jimenez E, McSherry G, Rubenstein A, Wilfert CM, McIntosh K, Elkins M, Weintrub PS. Randomized study of the tolerance and efficacy of high- versus low-dose zidovudine in human immunodeficiency virus-infected children with mild to moderate symptoms (AIDS Clinical Trials Group 128). Pediatric AIDS Clinical Trials Group. J Infect Dis (1996) 173(5):1097-1106.

Author: One of top enrolling sites nationally, reviewed/approved manuscript
JHU lead investigator for PACTG 128: submit/renew IRB, identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: This study opened for enrollment in 1989, providing the first clinical access to antiretroviral treatment for children with HIV infection whose disease did not yet meet AIDS case definition. It proved that lower dose zidovudine (AZT) was equally efficacious and much less toxic than the original dose tested in children with AIDS.
Context: 1986 AZT approved for use in adults with AIDS; DSMB interrupted placebo controlled clinical trial at 7 months due to significantly improvied survival in AZT group. AZT not yet studied in children, no dosing guidelines, no pediatric formulation, not approved for use.

PACTG 076 – JHU site investigator

Connor E, Sperling R, Gelber R, Kiselev P, Scott G, O'Sullivan M, VanDyke R, Bey M, Shearer W, Jacobson R, Jimenez E, O'Neill E, Bazin B, Delfraissy J-F, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, and Balsley J, for the **Pediatric AIDS Clinical Trials Group Protocol 076** Study Group. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med (1994) 331: 1173-1180.

JHU co- investigator for PACTG 076: identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: This randomized placebo-controlled trial was unblinded following the first DSMB review due to the dramatic 66% reduction of mother to infant HIV transmission observed in the treatment arm.
Context: PACTG 076 changed the world! It proved that antiretroviral medication could prevent HIV transmission. National and international efforts followed to implement and improve upon these findings. Its impact on HIV science, health policy, health services research, bioethics, and public health is incalculable.

ACTG 152 – JHU site investigator

Englund J, Baker C, Raskino C, McKinney R, Petrie B, Fowler M, Pearson D, Gershon A, McSherry G, Abrams E, Schliozberg J, Sullivan J, for the **AIDS Clinical Trials Group (ACTG) Study 152** Team. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. N Engl J Med (1997) 336:1704-1712.

Pearson DA, McGrath NM, Nozyce M, Nichols SL, Raskino C, Brouwers P, Lifschitz MC, Baker CJ, Englund JA, **Pediatric AIDS Clinical Trials 152 Study** Team. Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning. Pediatrics (2000) 106(6):E76.

Chantry CJ, Byrd RS, Englund JA, Baker CJ, McKinney RE Jr; **Pediatric AIDS Clinical Trials Group Protocol 152** Study Team. Growth, survival and viral load in symptomatic childhood human immunodeficiency virus infection. Pediatr Infect Dis J (2003) 22(12):1033-9.

JHU co-investigator for PACTG 152: identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: This three-armed, randomized, placebo-controlled study proved that dual NRTI combination therapy was more efficacious than mono-therapy with either zidovudine or didanosine.
Context: This protocol was the first to test the use of two HIV drugs together in children.

Multiple protocols - JHU site investigator

Dankner WM, Lindsey JC, Levin MJ; **Pediatric AIDS Clinical Trials Group** Protocol Teams **051, 128, 138, 144, 152, 179, 190, 220, 240, 245, 254, 300 and 327**. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. Pediatr Infect Dis J (2001) 20(1):40-8.

JHU lead and co-investigator for PACTG (multiple protocols): submit/renew IRB, identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: combined data from multiple protocols, including data collected prior to the opening of PACTG 219, to describe the epidemiology of opportunistic infections in children
Context: Highly active antiretroviral therapy (HAART) was just being implemented on a wide scale in children; this analysis provided baseline for comparison of potential benefits of HAART

PACTG 1042S - JHU site lead investigator

Farley JJ, Montepiedra G, Storm D, Sirois PA, Malee K, Garvie P, Kammerer B, Naar-King S, Nichols S; **PACTG P1042S** Team. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count. J Dev Behav Pediatr (2008) 29(5):377-384

Naar-King S, Montepiedra G, Nichols S, Farley J, Garvie PA, Kammerer B, Malee K, Sirois PA, Storm D; **PACTG P1042S** Team. Allocation of family responsibility for illness management in pediatric HIV. J Pediatr Psychol (2009) 34(2):187-194. Epub 2008 Jun 27.

JHU lead investigator for PACTG : submit/renew IRB, identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: evaluated methods for assessing medication adherence and identified correlates of successful adherence
Context: with the availability of HAART and new laboratory tests that measured quantitative plasma HIV viremia, it became clear that suboptimal medication adherence played a significant role in the failure of HIV medications to suppress viremia and control disease progression, and in the

development of drug resistant viral strains. This was more complex for children who depended on adult caregivers to administer medication with strict adherence.

PACTG 1038 - JHU site investigator

Robbins BL, Capparelli EV, Chadwick EG, Yogev R, Serchuck L, Worrell C, Smith ME, Alvero C, Fenton T, Heckman B, Pelton SI, Aldrovandi G, Borkowsky W, Rodman J, Havens PL; **PACTG 1038 Team**. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. Antimicrob Agents Chemother (2008) 52(9):3276-3283. Epub 2008 Jul 14.

JHU co-investigator for PACTG : identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: one of the first trials targeting novel approaches to combination therapy in children with prior antiretroviral exposure and resistance; incorporated pharmacokinetic study of drug interactions with primary virologic and clinical endpoints.
Context: offered "salvage" therapy for children with multi-drug resistant virus in the context of a safely structured and closely monitored protocol

PACTG 1057 – JHU site investigator

Weinberg A, Song LY, Walker R, Allende M, Fenton T, Patterson-Bartlett J, Nachman S, Kemble G, Yi TT, Defechereux P, Wara D, Read JS, Levin M; IMPAACT P1057 Team. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. J Acquir Immune Defic Syndr (2010) 55(2):189-196.

JHU co-investigator for PACTG : identify eligible subjects, recruit, enroll, and retain subjects, conduct study visits, review study data for completeness and accuracy, supervise research nurse
Impact: initial findings on immunogenicity of live attenuated influenza vaccine compared with inactivated vaccine (standard of care)
Context: influenza vaccine is now routinely recommended for children older than age six months annually; inactivated injectable vaccine is recommended for use in immunocompromised children; intra-nasal live-attenuated vaccine is licensed for use in healthy children and avoids a painful injection.