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Authors

Nelson, Bryan S
Tierney, Camlin
Persaud, Deborah
et al.

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BRIEF REPORT

Infants Receiving Very Early Antiretroviral Therapy Have High CD4 Counts in the First Year of Life

Bryan S. Nelson,[1] Camlin Tierney,[1] Deborah Persaud,[2] Jennifer Jao,[3,4] Mark F. Cotton,[5] Yvonne Bryson,[6] Anne Coletti,[7] Theodore D. Ruel,[8] Stephen A. Spector,[9,10] Christina Reding,[11] Kira Bacon,[11] Diane Costello,[12] Charlotte Perlowski,[7] Maria Leticia Santos Cruz,[13] Josphat Kosgei,[14] Sai Majji,[15] Dwight E. Yin,[16] Patrick Jean-Philippe,[16] and Ellen G. Chadwick[3,4]; for the IMPAACT P1115 Team

[1]Center for Biostatistics in AIDS Research in the Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [2]Division of Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Division of Pediatric Infectious Diseases, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [4]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [5]Department of Pediatrics and Child Health, Family Center for Research with Ubuntu, Stellenbosch University, Tygerberg, South Africa; [6]Department of Pediatrics, University of California–Los Angeles David Geffen School of Medicine, Los Angeles, California, USA; [7]Science Facilitation Department, FHI 360, Durham, North Carolina, USA; [8]Department of Pediatrics, San Francisco School of Medicine, University of California, San Francisco, California, USA; [9]Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, California, USA; [10]Rady Children's Hospital, San Diego, California, USA; [11]Frontier Science and Technology Research Foundation, Amherst, New York, USA; [12]IMPAACT Laboratory Center, University of California Los Angeles, Los Angeles, California, USA; [13]Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil; [14]Kenya Medical Research Institute/Walter Reed Project, Kericho, Kenya; [15]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; and [16]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, USA

We followed 54 infants with in utero HIV after initiating very early antiretroviral treatment. At weeks 24 and 48, ≥80% had CD4 ≥1500 cells/mm^3 and CD4% ≥25%. Routine *Pneumocystis jirovecii* pneumonia prophylaxis in the first year of life may not be necessary for all very early treated infants.

Clinical Trials Registration. NCT02140255.

Keywords. *Pneumocystis jirovecii* pneumonia; cotrimoxazole; neonatal; HIV; CD4.

Treatment guidelines recommend cotrimoxazole (CTX) prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) through age 1 year for all infants diagnosed with human immunodeficiency virus (HIV) [1–4]. This practice originated early in the AIDS era [1], when early infant diagnosis and suppressive antiretroviral therapy (ART) were unavailable, and many infants were at risk of PCP due to uncontrolled HIV and low/falling CD4 counts. Universal PCP prophylaxis initiated before definitive HIV diagnosis eliminated the need to monitor CD4 counts. Currently, infants are often diagnosed with HIV and begin ART shortly after birth, preserving CD4 counts and likely reducing the risk of PCP [5, 6]. We summarize CD4 counts and percentages during the first year of life for infants with in utero HIV after initiating very early antiretroviral treatment.

METHODS

Study Design and Procedures

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1115 study (NCT02140255) is an ongoing phase I/II proof-of-concept study of very early treatment of neonates with in utero HIV who started nevirapine (NVP)-based ART within 48 hours of life, with the primary objective of observing ART-free remission [7]. We enrolled 2 cohorts. Written informed consent was obtained from the legal guardian of each study participant. Study conduct adhered to international guidelines, and the study was approved by the institutional review board and/or ethics committee responsible for oversight of the study at each site. Cohort 1 infants, born to mothers not receiving ART during pregnancy, were treated presumptively within 48 hours of life with treatment-dose NVP (6 mg/kg twice daily if ≥37 weeks' gestation or 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily thereafter if 34 to <37 weeks' gestation) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs). Cohort 2 infants enrolled after HIV diagnosis by age 10 days, having initiated NVP (at least 8 mg/day for infants weighing ≤2 kg or 12 mg/day for infants weighing >2 kg) plus 2 NRTIs within 48 hours of life. For both cohorts, NVP dosing remained at 6 mg/kg twice daily until week 4, then increased to 200 mg/m^2 twice daily or World Health Organization (WHO) weight-band dosing. Ritonavir-boosted lopinavir (LPV/r) was added after age 14 days and 42 weeks postmenstrual age. Nevirapine was discontinued after at least 12 weeks of confirmed HIV plasma viral load (VL) below the limit of detection (LOD). All participants remained in the study through week 24; those with confirmed VL of 200 or more copies/mL at or after week 24 discontinued follow-up. Cotrimoxazole was prescribed per local practices by the study clinicians. Study visits occurred at entry; weeks 1, 2, 4, 8, and 12; and then every 12 weeks. CD4 counts and percentages were measured at entry, weeks 2 and 12, and then every 12 weeks.

Statistical Methods

Cross-sectional descriptive summary statistics were generated with point estimates and 95% exact confidence intervals (CIs)

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Correspondence: B. S. Nelson, SM, 651 Huntington Avenue, Boston, MA 02115, USA (bnelson@sdac.harvard.edu).

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for parameters of interest. Participants with CD4 count less than 1500 cells/mm^3 or CD4% less than 25% were considered at risk of PCP [1]. Analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics and Study Follow-up

Fifty-four infants with HIV (34 in cohort 1, 20 in cohort 2) enrolled, primarily in Africa (Supplementary Table 1) and received ART for the duration of follow-up. Seventy-two percent (39/54) initiated CTX, with the earliest initiations at 2.43 (cohort 2) and 3.71 (cohort 1) weeks of age; the remaining initiations occurred after 5 weeks of age. Thirty-seven percent (20/54) discontinued study follow-up before 12 months of age, mostly (15/20) due to VL of 200 copies/mL or greater (Supplementary Figure 1). One infant from cohort 1 not receiving CTX died at age 19 weeks due to probable bacterial pneumonia. The infant's last CD4 count (CD4%) was 3621 cells/mm^3 (40%) at age 15 weeks and last VL was less than 40 copies/mL with no virus detected at age 18 weeks.

CD4 Cell Count and Percentage

The median earliest CD4 count (CD4%) was 2416.5 cells/mm^3 (52.1%). At weeks 24 and 48, 84% (42/50; 95% CI: 71–93%) and 80% (28/35; 95% CI: 63–92%) of infants had both CD4 counts of 1500 cells/mm^3 or greater and CD4% of 25% or greater (Figure 1), including 6 of 9 participants at week 24 with a VL of 200 copies/mL or greater. Sixty percent (32/53) remained above both CD4 thresholds at all study visits. Of 21 infants with at least 1 visit with a CD4 count of less than 1500 cells/mm^3 and/or CD4% less than 25%, 11 had only a single drop below these thresholds, 2 each had 2 single-visit drops below these thresholds with normal values in between, and 8 had at least 2 consecutive measurements below these thresholds: 4 had ongoing VL greater than 200 copies/mL, 1 fell below CD4 thresholds with VL less than the LOD and no virus detected and remained below the threshold after viral rebound to more than 1000 copies/mL (minimum CD4 count: 1780 cells/mm^3; minimum CD4%: 19.8%), 1 had low-level viremia (145 copies/mL) or detectable VL less than the LOD (minimum CD4 count: 1119 cells/mm^3; minimum CD4%: 35%), and 2 had sustained undetectable VL (minimum CD4 count: 1079 cells/mm^3; minimum CD4%: 24%) (Supplementary Figure 2).

Diagnoses and Hospitalizations

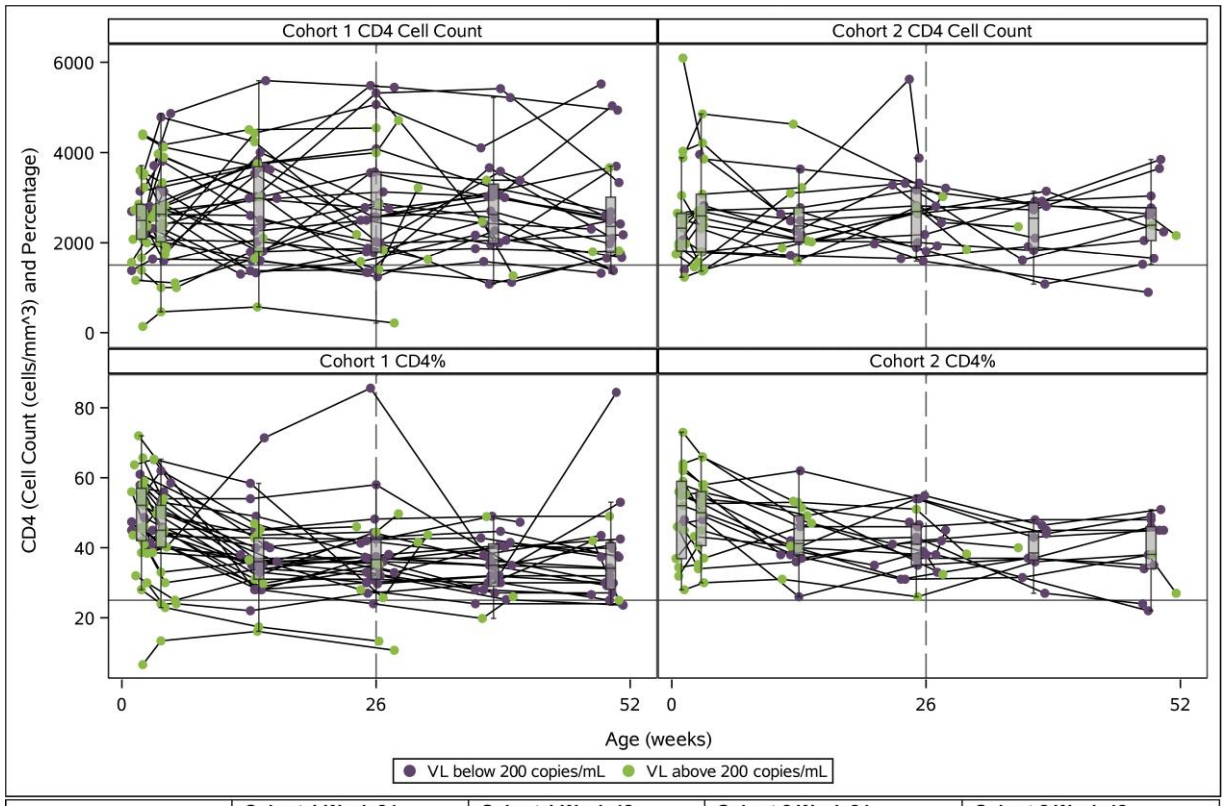
No opportunistic infections (OIs) or PCP were reported over 2275 infant-weeks of follow-up (1175 infant-weeks of CTX). Other diagnoses were reported in 87% (47/54) of infants, and were mostly infections or hematologic disorders (Supplementary Table 2). Thirty percent (16/54) were hospitalized, including 9 infants with infections (bronchiolitis [1 infant taking CTX, 1 not], otitis media [1 infant not taking CTX], bacterial pneumonia [3 infants taking CTX], neonatal sepsis [3 infants not taking CTX]) and 1 infant with anemia (not taking CTX).

DISCUSSION

In the first year of life, most infants with in utero HIV and very early ART maintained CD4 counts and percentages above historical infant thresholds for PCP prophylaxis (CD4 count ≥1500 cells/mm^3 and CD4% ≥25%) [1]. Other cohorts of treatment-naive children ages 0.3–17 years have also shown marked recovery of CD4 profiles upon achieving viral suppression with ART, especially when below 3 years of age [8, 9]. Interestingly, most infants in this study without virologic control (≧200 copies/mL) by the first 24 weeks of life maintained high CD4 counts/percentages, raising the notion that early ongoing ART may, in fact, be the critical factor.

In 1995, when few antiretrovirals were available and significant improvement in immune function among these children was unlikely, the US Centers for Disease Control and Prevention recommended PCP prophylaxis for all infants with HIV aged 6 weeks to 1 year [1]. When these guidelines were adopted, infants generally exhibited uncontrolled viremia, and CD4 counts could drop precipitously, increasing the risk of PCP and other OIs. National surveillance data from 1991–1993 showed that, among 129 children younger than 12 months of age, the estimated mean decline in CD4 count during the 3 months before PCP diagnosis was 967 cells/mm^3 (95% CI: 724–1210 cells/mm^3) [10]. However, the introduction of protease-inhibitor–based combination ART in 1996 resulted in substantial increases in CD4 counts, especially among children younger than 5 years [11]. The Perinatal AIDS Collaborative Transmission Study reported a 95% decline in PCP cases per 100 child-years from 5.8 (during 1986–1996) to 0.3 (during 1997–2004) [5]. In a prospective US-based observational cohort of 2767 children with HIV, the incidence of PCP cases per 100 child-years declined from 1.3 during the precombination ART era (1981–1988) to less than 0.5 during the combination ART era (2001–2004) [6]. We observed no OIs or PCP in our study, albeit most participants received CTX prophylaxis. There was 1 death due to presumed bacterial pneumonia, but PCP seemed unlikely in this case, considering the infant's high CD4 count and percentage and undetectable VL.

Because zidovudine and CTX may have overlapping hematologic toxicity, it can be difficult to determine which drug should be interrupted for severe anemia or neutropenia. Importantly, CTX prophylaxis also reduces mortality and prevents bacterial infections, malaria, and possibly tuberculosis in high incidence settings in addition to providing PCP prophylaxis [2, 12]. However, in settings where malaria and tuberculosis are rare, prophylactic CTX may not provide additional benefit during ART when VL remains under control and CD4 counts and percentages remain high. In these settings, a more tailored



	Cohort 1 Week 24	Cohort 1 Week 48	Cohort 2 Week 24	Cohort 2 Week 48
CD4 Cell Count ≥1500 cells/mm^3	26/32 (81%, 95% CI* 64%-93%)	20/23 (87%, 95% CI* 66%-97%)	18/18 (100%, 95% CI* 81%-100%)	11/12 (92%, 95% CI* 62%-100%)
CD4 Percentage ≥25%	29/32 (91%, 95% CI* 75%-98%)	21/23 (91%, 95% CI* 72%-99%)	18/18 (100%, 95% CI* 81%-100%)	10/12 (83%, 95% CI* 52%-98%)
CD4 Cell Count ≥1500 cells/mm^3 and CD4 Percentage ≥25%	24/32 (75%, 95% CI* 57%-89%)	18/23 (78%, 95% CI* 56%-93%)	18/18 (100%, 95% CI* 81%-100%)	10/12 (83%, 95% CI* 52%-98%)

Figure 1. Infant profile plots of CD4 cell counts and CD4 percentages by concurrent VL status. The dashed vertical line corresponds to the week 24 visit, after which only infants with HIV plasma viral load <200 copies/mL continue to be followed. Horizontal lines are shown at 1500 cells/mm^3 and 25%. *Clopper-Pearson exact CI. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; VL, viral load.

approach to PCP prophylaxis in the first year of life may be feasible. This would minimize cost and potential drug-related toxicity and, by reducing the number of daily medication administrations, improve adherence to ART.

This analysis was limited by its observational nature and generalizability given the tightly monitored research setting with very early treatment initiation and high ART adherence. Of note, we could not address the role of PCP prophylaxis after 6 months of age for infants with a VL of 200 copies/mL or greater due to our study design. Our ART regimen included up to 4 drugs (NVP + 2 NRTIs [adding LPV/r at 2 weeks of life]), and CD4 and VL profiles may be different with other regimens. Further, these are findings from a study that enrolled primarily from sub-Saharan Africa, and generalizations to other populations should be made cautiously. Although a clinical trial evaluating CTX prophylaxis would be ideal, it is likely infeasible in nonmalarial settings due to the limited number of infants born with HIV and low PCP incidence.

In conclusion, most infants receiving very early ART in our study maintained high CD4 counts and percentages during the first year of life. These findings may inform management of early-treated infants in settings with a low prevalence of malaria and bacterial infections. In these cases, PCP prophylaxis may only be necessary when suboptimal ART adherence results in poor virologic control or CD4 count and percentage cannot be adequately monitored.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Authors' contributions. B. S. N., C. T., and E. G. C. led the writing of the manuscript. B. S. N. and C. T. led data analysis. All authors contributed to the protocol development, data collection, drafting of the manuscript, and approved of the final version submitted.

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Data sharing. The data cannot be made publicly available because of the restrictions in the study's informed consent documents and in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human participants protection plan; public availability might compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Center's data access committee (sdac.data@fstrf.org) with the agreement of the IMPAACT Network.

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Potential conflicts of interest. D. P. received a one-time consultation fee from Merck to serve on their scientific advisory board, received an honorarium from the American Society of Pathology, provided expert testimony on behalf of the Children's Hospital of Philadelphia, and serves (unpaid) on the IAS Industry Collaborative Group. D. E. Y. was previously an unpaid technical advisor to the nonprofits Cover the Globe and Maipelo Trust and reports support from Astellas, Chimerix, and Viracor-Eurofins provided to his previous institution, prior to his current work at the National Institutes of Health. E. G. C.'s partner retired from and holds stock in AbbVie; she also received consulting fees from the National Clinicians Consultation Center and was paid for expert testimony by Brown & James P.C. A. C., B. S. N., C. P., C. T., D. P., E. G. C., J. J., M. F. C., S. A. S., and Y. B. report grants from the National Institutes of Health (NIH). All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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