Pediatric Monitoring - CD4 issues in HIV Disease

Transfer of HIV Monitoring Technologies into Resource-Poor Settings: Moving the Field Forward
HIV Forum for Collaborative Research
CROI Satellite Meeting
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Estimated percentage of adults covered among those in need of antiretroviral treatment, situation as of March 2004
Reviewing the Literature
Fig 1.—CD4 T-lymphocyte count, CD4 percent by age, and mode of transmission for Pneumocystis carinii pneumonia (PCP) cases: Los Angeles County, California, June 1982 through June 1990. Circles represent perinatally HIV-infected PCP cases; triangles, HIV infected by transfusion; and squares, HIV infected by clotting factor. Definitive cases are represented with closed symbols; presumptive cases, open symbols.
Figure 4: CD4 Count vs AGE

AGE GROUP:
1-3, 4-8, 12-23, 24-59

Least Squares Line
95% Prediction Interval
Lymphocyte Subsets in Healthy Children During the First Five Years of Life

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JAMA, March 1992 - Vol 267, #11
NJ Pediatric Reference Range (Absolute CD4)

<table>
<thead>
<tr>
<th>Age in Months</th>
<th>CD4 5^{th}</th>
<th>CD4 95^{th}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1460</td>
<td>5110</td>
</tr>
<tr>
<td>4-9</td>
<td>1690</td>
<td>4600</td>
</tr>
<tr>
<td>9-12</td>
<td>1355</td>
<td>4100</td>
</tr>
<tr>
<td>12-24</td>
<td>1020</td>
<td>3600</td>
</tr>
<tr>
<td>24-60</td>
<td>900</td>
<td>2860</td>
</tr>
<tr>
<td>60 - Adult</td>
<td>689</td>
<td>1566</td>
</tr>
</tbody>
</table>
# NJ Pediatric Reference Range (CD4%)

<table>
<thead>
<tr>
<th>Age in Months</th>
<th>CD4 % 5&lt;sup&gt;th&lt;/sup&gt;</th>
<th>CD4 % 95&lt;sup&gt;th&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>41</td>
<td>64</td>
</tr>
<tr>
<td>4-9</td>
<td>36</td>
<td>61</td>
</tr>
<tr>
<td>9-12</td>
<td>34</td>
<td>58</td>
</tr>
<tr>
<td>12-24</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>24-60</td>
<td>35</td>
<td>51</td>
</tr>
<tr>
<td>60 - Adult</td>
<td>33</td>
<td>59</td>
</tr>
</tbody>
</table>
Figure 2. Recommendations for initiation of PCP prophylaxis for children >1 month old who are a) HIV infected, b) HIV seropositive, or c) <12 months old and born to an HIV-infected mother.

A CD4+ count and CD4% should be obtained for each child. Use test results and child's age as charts for starting PCP prophylaxis.

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4+ ≥20% or unknown, with CD4+ count (cells per mm²) ≤:</th>
<th>CD4+ &lt;20% with any CD4+ count</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 mo-5 yr</td>
<td>START PCP PROPHYLAXIS</td>
<td></td>
</tr>
<tr>
<td>12-23 mo</td>
<td>START PCP PROPHYLAXIS</td>
<td></td>
</tr>
<tr>
<td>1-11 mo.</td>
<td>START PCP PROPHYLAXIS</td>
<td></td>
</tr>
</tbody>
</table>

A: No prophylaxis recommended at this time; recheck CD4+ count in 1 month.
B: No prophylaxis recommended at this time; recheck CD4+ count at least every 3-4 months.
C: No prophylaxis recommended at this time; recheck CD4+ count at least every 6 months.

Recommended regimen for PCP prophylaxis (see Table 3 for alternate regimens):

**Trimethoprim-sulfamethoxazole (TMP-SMX)** 160 mg TMP/SMX/day with 750 mg SMX given orally in divided doses twice a day, 3 times per week, on consecutive 4 days (e.g., Monday-Tuesday-Wednesday). When starting TMP-SMX prophylaxis:
- Obtain baseline CBC, differential count, platelet count.
- Monitor CBC, differential count, platelet count monthly.
- Monitor CD4+ count at least every three months.

Note: Any child who has had an episode of PCP should be started on PCP prophylaxis regardless of age or CD4+ count.
FIG. 1. Relationship between CD4 percent and age in human immunodeficiency virus-infected and control children. CD4 cell percents from 61 infected and 63 control children from 3 weeks to 13 years of age were evaluated using multiple regression methods to determine whether the slopes of fall of CD4 percents with age were different for infected and control children. The intersects and r values are shown for both controls (top line) and infected children (bottom line).
HIV Pediatric Prognostic Markers Collaborative Study Group

• Meta analysis
  – 3941 children enrolled
    • 8 cohort studies
    • 9 randomized trials in Europe / US

• Estimates of risk are derived from parametric survival models

• http://www.ctu.mrc.ac.uk/penta/hppmcs/default.htm
Probability of AIDS within 12 months

HIV Paediatric Prognostic Markers Collaborative Study – Lancet 2003
Probability of death within 12 months

Probability of death (%)
6 months
1 year
2 years
5 years
10 years

CD4 percent
LYMPHOCYTE SUBSETS IN HEALTHY CHILDREN FROM BIRTH THROUGH 18 YEARS OF AGE:
THE PACTG P1009 STUDY


Supported by AAAAI, NIAID, NICHD
PEDIATRIC IMMUNOLOGY
CORE LABORATORIES (PICLs)

- Baylor College of Medicine / Texas Children’s Hospital (TCH)
- Children’s Hospital of Philadelphia (CHOP)
- University of California, Los Angeles (UCLA)
- University of California, San Diego (UCSD)
- University of California, San Francisco (UCSF)
- University of Colorado
METHODS: STUDY DESIGN, ELIGIBILITY, SAMPLE SIZE

- Observational, Cross-Section of HIV-Noninfected/HIV-Nonexposed Children
- Well Children: No Rx Meds, Pregnancy, Acute Infections
- 7 Age Strata: 0-3 mos, 3-6 mos, 6-12 mos; 1-2 yrs; 2-6 yrs, 6-12 yrs, 12-18 yrs (non-overlapping)
- Up to 120 Children Per Age Stratum: 851 Total Enrollment
P1009: CD4 Count

Counts

Age Categories

0-3 mos 3-6 mos 6-12 mos 1-2 yrs 2-6 yrs 6-12 yrs 9 yrs
P1009: CD3⁺ CD4⁺ CD45RO⁺ PERCENT

Age Categories
- 0-3 mos
- 3-6 mos
- 6-12 mos
- 1-2 yrs
- 2-6 yrs
- 6-12 yrs
- yrs

Percent
RESULTS: REGRESSION ANALYSIS/SIGNIFICANT VARIABLES

- Age: Highly Significant
- PICL: Highly Significant
- Race/Ethnicity: Much Less So
- Gender: Much Less So
Pediatric CD4 Technology Issues

- Dual Platform
- Single Platform
- Suitable for different settings
- Technology Transfer
- Cost / test
- Sustainability
Burkina Faso
PointCARE System

Hematology/Flow Cytometry for HIV/AIDS Patient Care in Decentralized Settings
Closed-Tube Operation – Loading/Cap Piercing

1. Patient Whole Blood Sample Tube
2. CD4 Reagent Tube
3. Rinse Tube
4. Lysing Reagent Tube or Cleaning Solution Tube

Patient sample and reagents bar-code are tracked in the instrument.
Automated Patient Results – No operator data interpretation

HIV/AIDS Care Test Menu - Patient Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
<th>Units</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 T Cell Counts</td>
<td>785</td>
<td>/ CU MM</td>
<td>500 - 2000</td>
</tr>
<tr>
<td>CD4 %</td>
<td>14.0</td>
<td>%</td>
<td>12.5 - 50.0</td>
</tr>
<tr>
<td>WBC Counts</td>
<td>6.1</td>
<td>10^3 / CU MM</td>
<td>4.3 - 10.0</td>
</tr>
<tr>
<td>Lymphocyte Counts</td>
<td>5.3</td>
<td>10^3 / CU MM</td>
<td>1.5 - 4.0</td>
</tr>
<tr>
<td>Lymphocyte %</td>
<td>47.0</td>
<td>%</td>
<td>19.6 - 52.7</td>
</tr>
</tbody>
</table>
Quality Control
Fig. 1. Variability of the differential leukocyte (and lymphocyte) count as a function of the number of cells counted. Note that the CV increases markedly as the proportion of the minor cell population decreases (modified for Rümke).
### 31 Replicates Same Tech

![Graph showing counts for CD4 and CD8](image)

<table>
<thead>
<tr>
<th></th>
<th>CD4%</th>
<th>CD4 Absolute</th>
<th>CD8%</th>
<th>CD8 Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>1.122943</td>
<td>22</td>
<td>1.988587</td>
<td>31</td>
</tr>
<tr>
<td>Mean</td>
<td>22.52</td>
<td>350.34</td>
<td>58.49</td>
<td>918.31</td>
</tr>
<tr>
<td>Median</td>
<td>22.65</td>
<td>355.29</td>
<td>58.83</td>
<td>923.63</td>
</tr>
<tr>
<td>Max</td>
<td>24.60</td>
<td>386.22</td>
<td>60.77</td>
<td>954.09</td>
</tr>
<tr>
<td>Min</td>
<td>17.63</td>
<td>276.79</td>
<td>49.25</td>
<td>773.23</td>
</tr>
</tbody>
</table>
CD4 Absolute
Samples Acquired on Day 1 and Day 2 (Same stained sample)

<table>
<thead>
<tr>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>286</td>
<td>255</td>
</tr>
<tr>
<td>166</td>
<td>269</td>
<td>254</td>
</tr>
</tbody>
</table>
Samples Acquired on Machine 1 and Machine 2

(Different stained sample)

Tech 1

CD4 Count

Tech 2

CD4 Count
Guyana – FACSCCount
10 Samples in Triplicate
(CV’s are displayed above replicates)

Mean CV = 6.81%

October 2004
That's All, Folks!