CD4 Assays Are No Longer Needed for Care of Children in Low-Resource Countries

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My Challenges

- My opponent
- CD4 monitoring is deeply entrenched in our practice and thinking about HIV

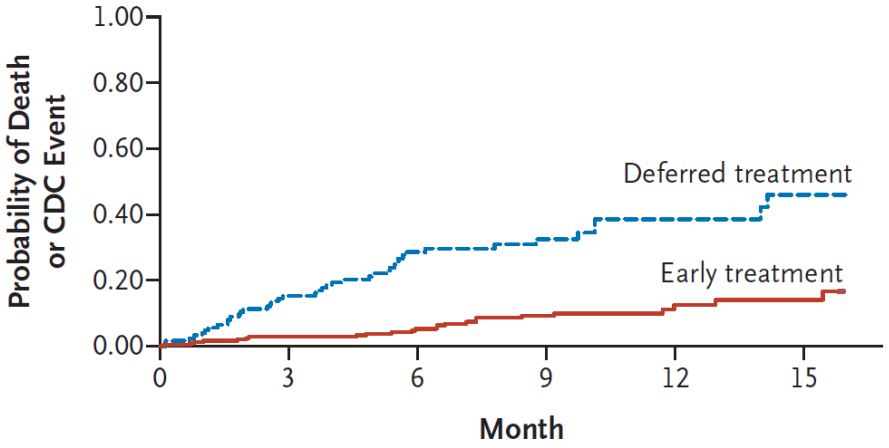
CD4 monitoring is history

- Recognition of low CD4 levels was an early breakthrough in understanding HIV, but …
- CD4 levels are only a limited measure of HIV-related pathology
  - B-cell abnormalities such as poor responses to vaccines and hyper-gammaglobulinemia, neutropenia, inflammation
  - Non-immunologic morbidities such as neurocognitive impairment

Huson et al, LID 2015.

If you wait for low CD4 counts before starting therapy … patients get sick

- CHER
  - Infants randomized to start ART @ CD4%<25 or immediately
  - 16% vs 4% mortality



- START (Strategic Timing of Antiretroviral Treatment)
  - adults randomized to ART at > 500 or wait until < 350
  - DSMB stopped trial this year, because risk of AIDS, other illnesses or death was reduced by 53% with early ART.

Violari et al. NEJM. 2008. ; http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx (released 5/27/15)

*Even just the **waiting** for a CD4 test result can have consequences…*

- Among 223 HIV-infected children eligible for ART at clinic in Gambia
  - 73 (32.7%) started treatment
  - 15 (6.7%) requested transfer to other facility
  - **105 (47.1%) were lost to follow-up**
  - **30 (13.5%) died!**

>50% of children that should have started ART didn't get the chance!

Okomo, ART, 2012.

Guidelines are steadily moving away from using CD4 counts to guide ART initiation

- 2006 – CD4 and clinical stage driven for all ..
- 2010 – universal treatment for < 24 months
- 2013 – universal treatment for < 5 years
- *2015 - ? Treat all ?*

World Health Organization

Is CD4 monitoring a good way to decide when to switch ART? NO

- 457 Cambodian children with ART managed per 2010 WHO guidelines using CD4 levels
  - 33% falsely considered treatment failure
    - (had suppressed virus, but low CD4)
  - 11% as falsely considered treatment success
    - (had viremia, but no CD4 decline, yet!)
- *If you use CD4 to guide treatment changes, you could switch ART **too early** AND **too late**!!*

Westley ,CID ,2012.

Are people on suppressive therapy at risk for significant CD4 decline? NO

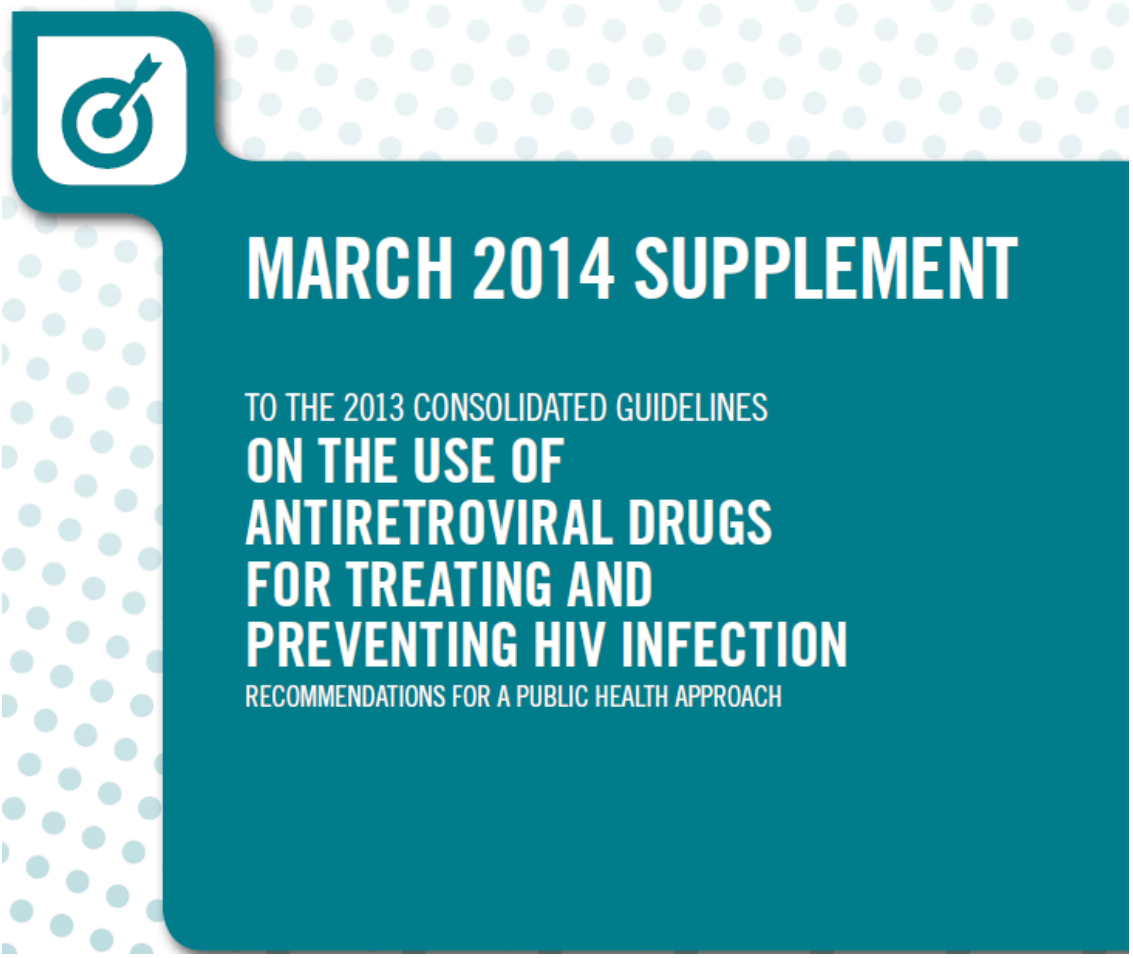
- Study of 1,820 patients, 25,463 CD4 counts, 13 years ; if > 300c/ul and maintained suppressed:
  - **Less than 1% had CD4 decline to below 200**
  - Of those who did have CD4 decline
    - Transient, with spontaneous resolution
    - **No adverse clinical events**

Gale, CID,2013.

Let go of CD4 thinking!

- It is a poor test and just doesn't make sense

- To monitor ***HIV*** we should measure ***HIV***, *not the damage we are trying to prevent!*



World Health Organization

- "HIV viral load, when available, is a more reliable tool for monitoring adherence to treatment and efficacy of ART than CD4 cell counts."

What have been the barriers?

- "…when available…"
- Old PCR-based viral load assays have:
  - been costly
  - been labor intensive
  - long turn around times
- New assays must be tested, approved (CE marked or FDA) and be distributed in countries.

A new era of viral load testing is here!

- Rapid turn-around
- Low blood volumes
- Can be operated in local clinics, requiring no formal laboratory training
- Cost low with minimal reagents
- *Many assays in race to dominate the market …*

A new era of viral load testing is here!

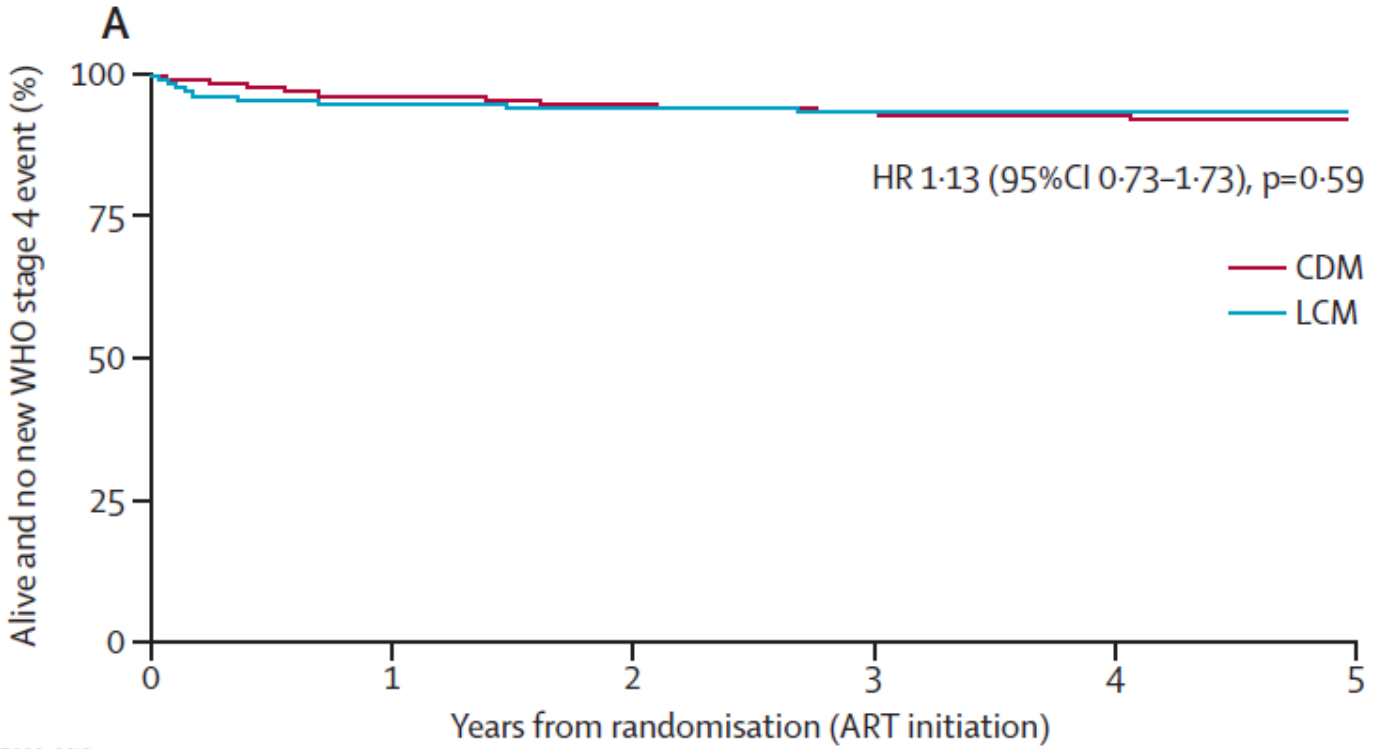
- **X-pert HIV (CEPHEID)**
  - CE mark April 2015, platform already in use in South Africa
- **Simple Amplification-Based Assay (SAMBA I and II)**
  - Results from within two hours, fingerprick volumes
  - 97-99% accurate vs Roche
  - Available in Malawi and Uganda; approved in Kenya
- **Alere-Q**
  - 25 ul of blood
  - high sensitivity and specificity (98% and 99%)
  - Use for early infant diagnosis and monitoring
- ***And others …***

(Ritchie, JCM, 2014; Jani , JAIDS, 2014.)

New VL assays aren't in my country, and I am setting up a clinic tomorrow … what should I do?

- *DON'T buy a CD4 machine*
- *Start children on ART, and skip monitoring …*

Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial



Number alive at follow-up (deaths or WHO stage 4 events in following interval)											
CDM	606	(24)	577	(8)	567	(9)	556	(5)	280	(1)	0
LCM	600	(33)	563	(2)	559	(3)	555	(1)	273	(0)	0

***Lancet* 2013; 381: 1391–403**

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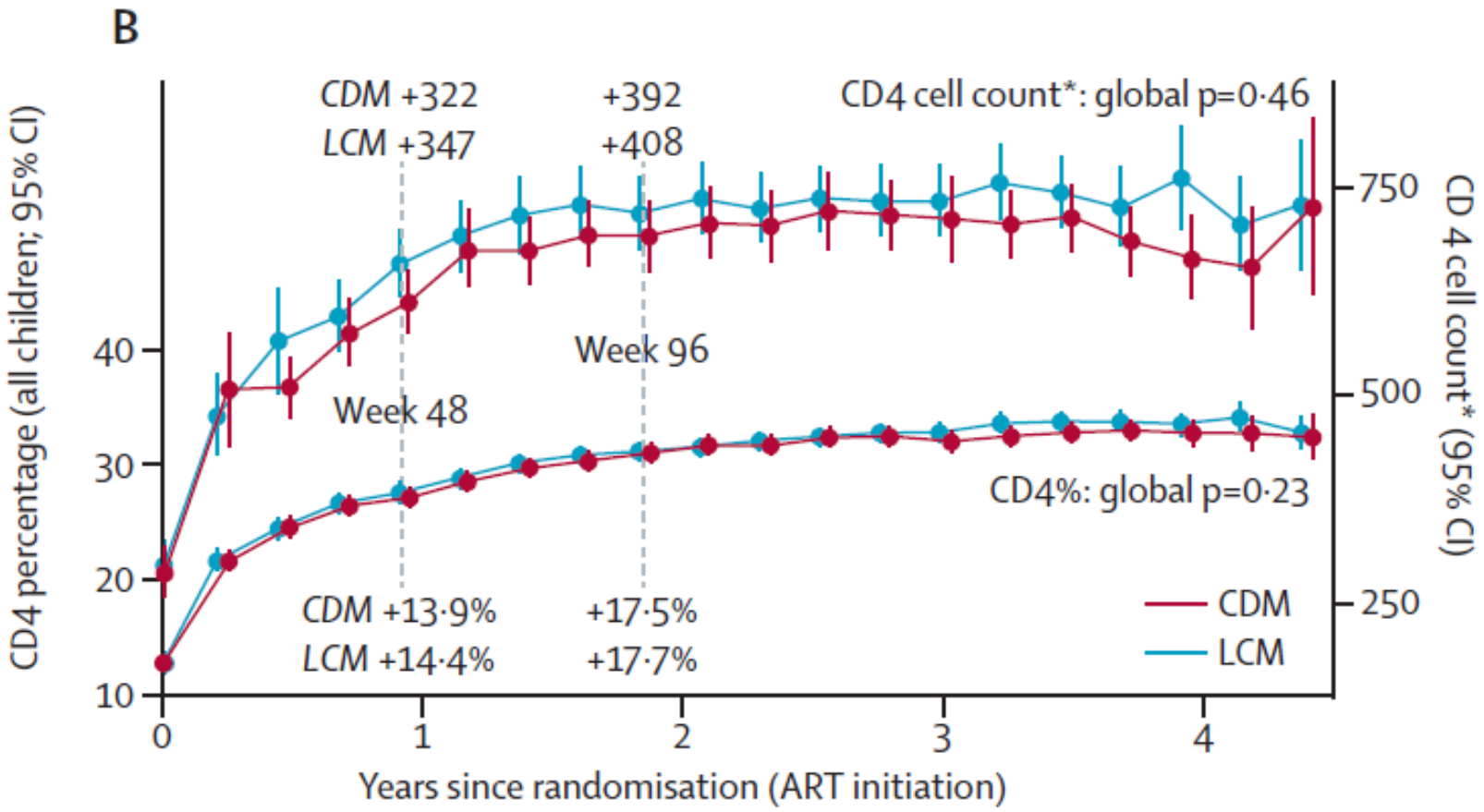

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Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial

Authors conclude …

"… CD4 monitoring provided clinical benefit after the first year on ART, but event rates were very low and long-term survival high, suggesting ART rollout should take priority."

***Lancet* 2013; 381: 1391–403**

What about need for prophylaxis and a CD4 test at baseline? NO

- Trimethoprim-sulfamethoxazole (TS, Cotrim) beneficial for children of all CD4 counts …
- ARROW showed that stopping TS after 96 weeks of ART was associated increased hospitalizations for malaria and non-malarial infections (Bwakura-Dangarembizi, NEJM, 2014)
- *So children in LRC should be on TS, and stay on it, regardless of CD4 status*

Should we use CD4 assays to …

- Decide when to start ART? NO
- Monitor ART response? NO
- Decide about prophylaxis? NO
- *Prop the door open while you let more children in to start ART? YES !*

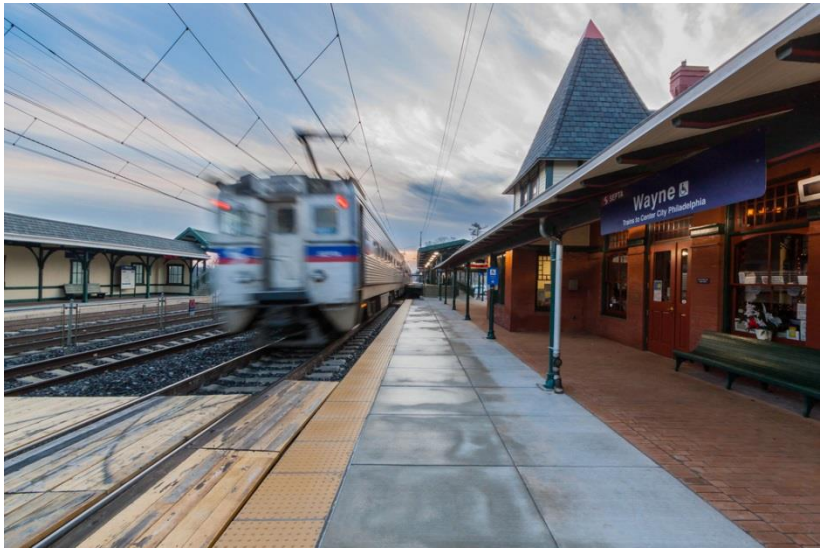
Time to let CD4 assays go …

- It is 2015, not 1990
- CD4 levels are poor measures of HIV disease
- We should provide children with modern HIV care and spend our “CD4 money” on:
  - new affordable/low-tech viral load assays
  - more ART and start more children now

This is not a radical idea … it is common sense.

- Viral load testing is the gold standard , the standard of care, and affordable assays have arrived!
- WHO already recommends viral load over CD4 for monitoring …

The train is leaving the station … don't lollygag on the platform!



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Thank you for your attention …