2008 National Summit
ON HIV DIAGNOSIS, PREVENTION AND ACCESS TO CARE

Forum for Collaborative HIV Research

When Do We Start Treatment How do find out? What Evidence will Guidelines be Based On?

November 21, 2008

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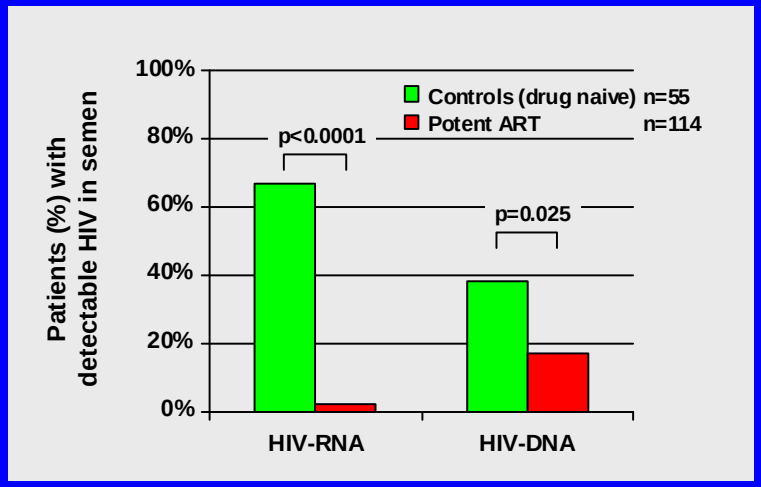
Forum for Collaborative HIV Research

Antiretroviral Treatment of HIV Infection

- Suppresses viral replication
  - Leads to decreases in viral load
    - Less virus in plasma and in genital secretions

Semen HIV in patients with suppressed viral load



Antiretroviral Treatment of HIV Infection

- Clinical benefit to patient being treated

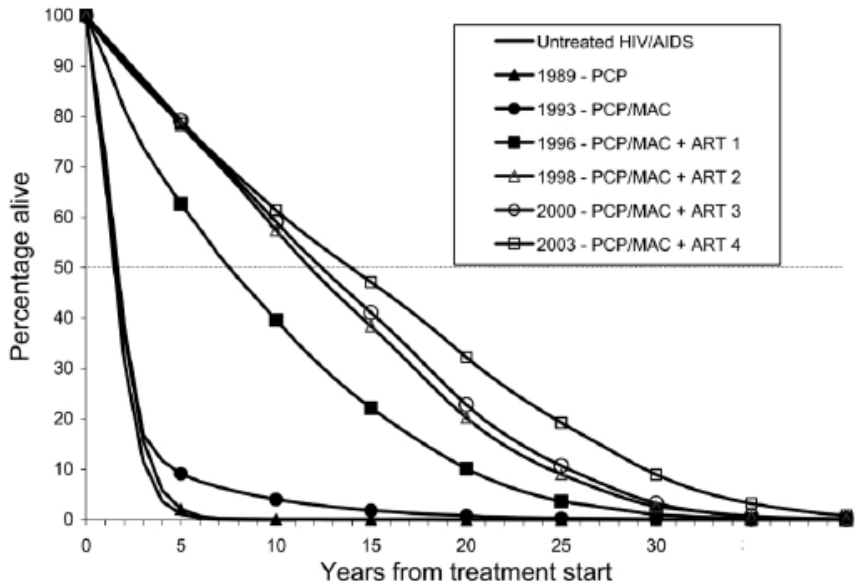


Figure 2. Survival curve produced by model simulations of the cohort that received diagnoses in the first year of each treatment era, with a mean age at treatment start of 39 years (SD, 9 years). ART, antiretroviral therapy; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jiroveci* pneumonia.

Antiretroviral Treatment of HIV Infection

- Does it contribute to reduced HIV transmission?
- Will it contribute to "controlling the epidemic"?

Bunnell et a. AIDS 20: 85-92, 2006

- **ART offered May, 2004 in Uganda**
- **454 subjects and co-habiting partners available for 24 month follow-up**
- **Baseline viral load (122,500 copies) "suppressed"**
- **Increased sex, but reduced risky behavior**
- **HIV Seroconversions reduced from 45.7/1000 py to 1/1000 py**
- **Only one seroconversion in 2 years**

Substantial loss to follow-up noted

HPTN HIV Prevention Trials Network

March 2007, Slide 33

The Question

- Should treatment be initiated sooner?
  - Greater clinical benefit?
  - Potential public health impact?
- What evidence will the decision/policy be based on?

Historical Considerations

- Recommendations on when to start treatment – changes over time depending on:
  - Confidence in understanding of the role of HIV replication in disease progression and confidence in ability to suppress viral replication
  - Appreciation for treatment associated side effects
    - need to balance risk:benefit
  - Appreciation of the 'side effects' of viral infection
    - Chronic infection, inflammation
    - CVD, non-AIDS malagnancies and other complications
    - Accelerating aging?

Guidelines for Initiating ART in Asymptomatic Patients: 1998-2005

Panel	CD4+ Cell Count, cells/mm^3
US DHHS	
June 1998	< 500
February 2001	< 350
April 2005	< 200
International AIDS Society-USA Panel	
July 1998	Any
January 2000	< 500
July 2004	≤ 200
British HIV Association (BHIVA)	
June 1998	> 350
July 2003	201-350
July 2005	< 200

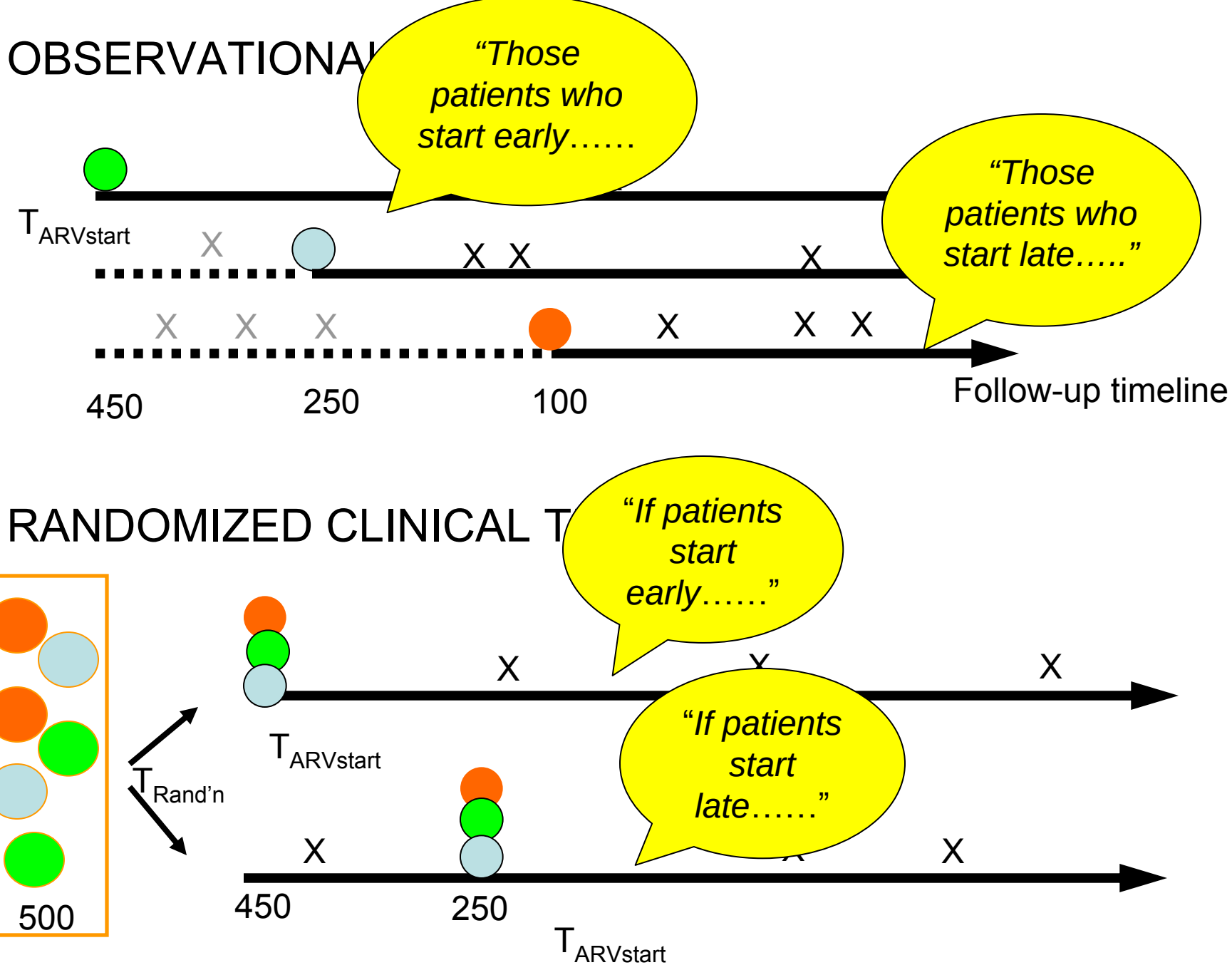
- Observational studies - allow study of many exposure-disease associations, but:
  - specificity?
  - Reliability?
  - comprehensiveness?
- Intermediate outcome RCTs - useful, but:
- rather typical limited set of outcomes
- Full-scale RCTs - reliable for a limited set of hypotheses, but:
  - cost, logistics, adequacy of follow-up durations?

Data from Clinical Trials

- Ideal clinical conditions
  - Frequent monitoring
  - Highly motivated patients and providers
  - Screening at baseline for ability to participate in clinical trials

Data from Observational Cohort Studies

- "Real life" scenario
- Cohorts from various settings
  - Different patient groups
  - Different type of clinics
  - Longer term follow up possible
- Observe trends over time
- Compare different 'eras' of highly active antiretroviral therapy


OBSERVATIONAL
"Those patients who start early……
"Those patients who start late….."
T ARVstart
X
X X
X
X X X
X
X X
450
250
100
Follow-up timeline
RANDOMIZED CLINICAL T
"If patients start early……"
"If patients start late……"
500
T Rand'n
T ARVstart
X
X
X
X
X
450
250
T ARVstart

Evidence & Policy

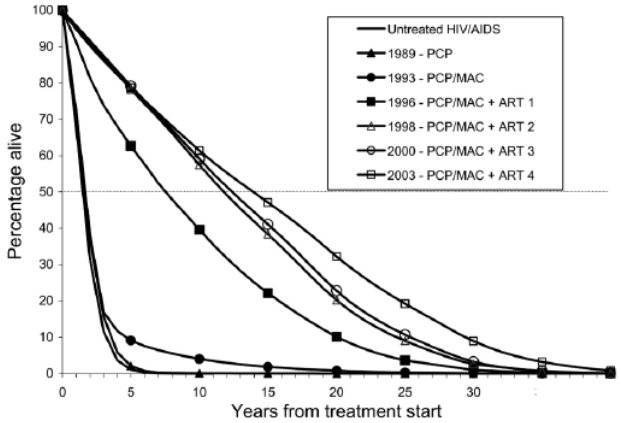
- Regulatory:
  - Randomized clinical trials
- Treatment Guidelines
  - Randomized clinical trials
  - Observational cohort data

Treatment Guidelines
(Nov 3, 2008 update)

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

- Recent update (November 3 2008)
- "Abacavir + lamivudine has been moved from a preferred to an alternative dual-NRTI component because of concerns regarding an increased risk of myocardal infarction in patients with high cardiac risk factors, as suggested by large observational cohort studies…"

Observational Data



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NA ACCORD Study

M M Kitahata IDSA/ICAAC2008

- North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
  - 22 research cohorts from the US and Canada (IeDEA Network)
- Outcome: All cause mortality
  - Patients who started treatment within 1.5 years of CD4 reaching 351-500 cells/ml (8,358 patients)
  - Patients who do not initiate within this time frame (16,636 patients)

Main Findings

- Deferral of starting treatment
  - Relative Hazard for death 1.7 (1.4 - 2.1) p<0.001
- Older age:
  - Relative Hazard for death 1.6 (1.5 - 1.8) p<0.00
- Findings not changed when accounting for IDU, HepC, etc
- Both a history of IDU and HCV infection were significantly associated with increased risk of mortality

- "As with any observational study, even after adjustment for known prognostic factors, residual confounding may occur because of unmeasured factors associated with both deferral and death"

Chronic HIV Infection - Complications

research

- Immune activation
- Chronic inflammation

Table 4. Risk of Death Associated with Biomarker Levels at Study Entry for the Drug Conservation (DC) and Viral Suppression (VS) Treatment Groups

Biomarker	Type of Analysis	DC		VS		*p*-Value for Interaction[b]
		OR[a] (95% CI)	*p*-Value	OR[a] (95% CI)	*p*-Value	
hsCRP (μg/ml)	Univariate	2.0 (1.2–3.4)	0.01	1.8 (0.7–4.6)	0.18	0.41
	Adjusted[c]	2.3 (1.2–4.4)	0.01	2.7 (0.9–7.9)	0.08	0.44
Amyloid A (mg/l)	Univariate	1.6 (1.0–2.5)	0.06	1.2 (0.6–2.3)	0.67	0.08
	Adjusted[c]	1.6 (0.9–2.8)	0.11	1.5 (0.6–3.8)	0.40	0.11
Amyloid P (μg/ml)	Univariate	0.7 (0.5–1.1)	0.14	0.8 (0.4–1.4)	0.43	0.22
	Adjusted[c]	0.8 (0.5–1.3)	0.40	0.7 (0.3–1.6)	0.46	0.31
IL-6 (pg/ml)	Univariate	3.7 (2.1–6.4)	<0.0001	2.8 (1.3–6.1)	0.008	0.56
	Adjusted[c]	3.8 (2.1–7.2)	0.0002	2.4 (1.1–5.2)	0.03	0.33
D-dimer (μg/ml)	Univariate	3.6 (1.7–7.3)	0.0005	2.6 (0.7–9.1)	0.14	0.38
	Adjusted[c]	5.9 (1.9–18.7)	0.002	7.1 (0.8–63.2)	0.08	0.30
F1.2 (pmol/l)	Univariate	1.0 (0.6–1.6)	0.98	0.8 (0.3–2.2)	0.71	0.34
	Adjusted[c]	0.8 (0.4–1.5)	0.47	0.7 (0.2–2.2)	0.55	0.16

Lewis Kuller et al PLoS 2008

Recovery Of CD4 cells/ml

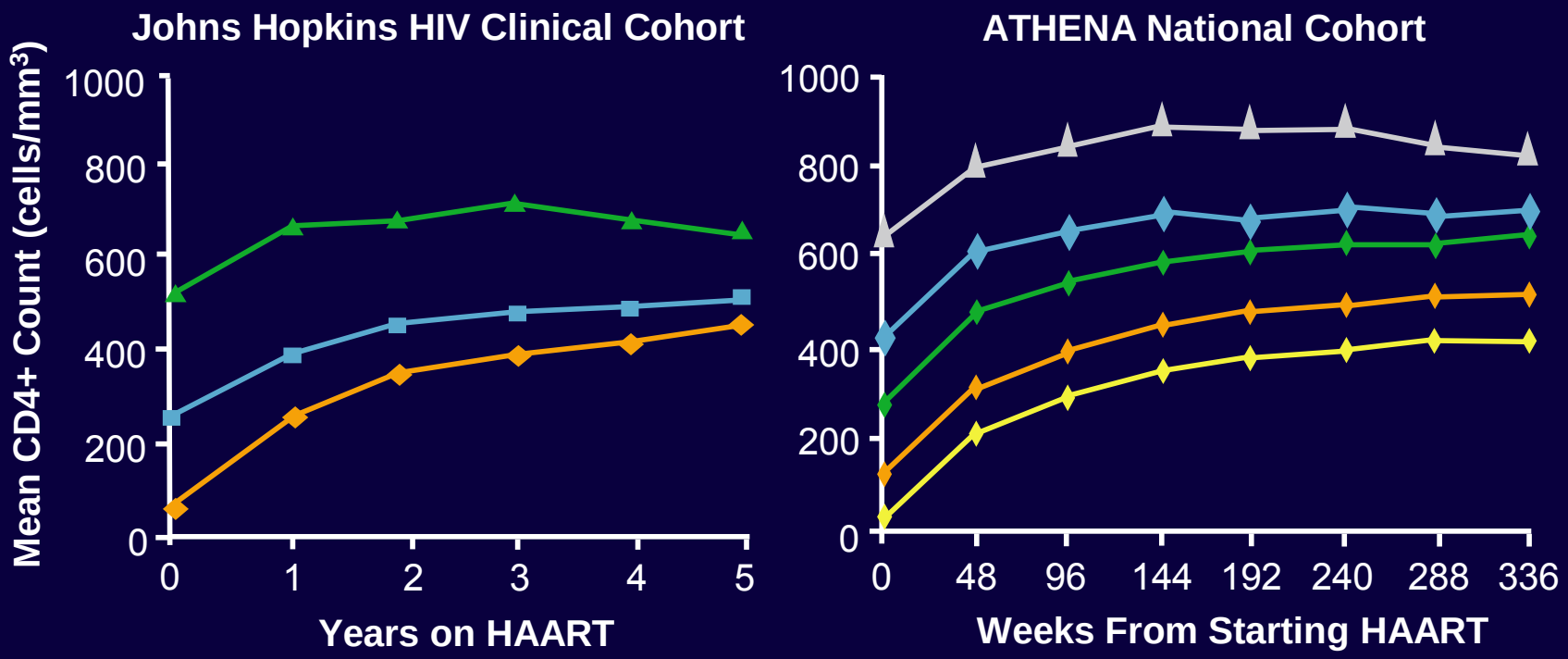
Numerous studies (observational data) demonstrate better CD4 recovery in patients who start treatment earlier

- **Among patients with > 350 cells/mm3 at baseline, the mean CD4 cell count reached a plateau, with complete immunological recovery by year 4 of suppressive HAART.**

- **Among patients with < 200 cells/mm3 at baseline, however, CD4 counts continued to increase even after 8 years without reaching full immunological recovery**

E Malincarne, A Sgrelli, G Camanni, and others. Immune restoration during HAART: 8-year follow-up in HIV-positive patients with sustained virologic suppression. 9th International Congress on Drug Therapy in HIV Infection. Glasgow, Scotland. November 9-13, 2008. *Journal of the International AIDS Society* 11(Suppl 1):P10. November 10, 2008.

CD4+ Count Response Based on Baseline CD4+ Count



- Magnitude of CD4+ increase greatest if therapy started at low CD4+ counts, but greater likelihood of CD4+ count normalization with earlier therapy

Keruly J, et al. CROI 2006. Abstract 529. Gras L, et al. CROI 2006. Abstract 530.

Where do we go from here?

- Do we need more research?
  - START (Fred Gordin)
  - HPTN 052 (Mike Cohen)