A Historical Analysis of the Cost-Effectiveness of CD4 Cell Count Versus Immediate Treatment for ART Initiation

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Abstract #: 1112

BACKGROUND

- Since 2002, WHO ART eligibility guidelines have been based on CD4 count.
- Although low CD4 counts predict illness, most HIV-associated outcomes – HIV transmission, morbidity, mortality, and response to medication – are generally better predicted by other surrogate markers.[1,2]
- CD4 counts can be a barrier to ART initiation and are inferior to viral load tests for monitoring ART response
- Despite the considerable variability in CD4 measurements, the opportunity costs of using CD4 count staging as a criteria to initiate antiretroviral therapy (ART) have not been previously assessed.

→OBJECTIVES:

1. Assess the ART coverage among highly infectious persons in the past, and the impact on HIV-associated outcomes of using CD4 counts to stage HIV-positive persons and initiate ART compared to offering ART to persons who tested positive in KwaZulu-Natal, South Africa.
2. Estimate the cost-effectiveness of strategies for ART provision from 2004 to present relative to no ART.

METHODS: Model Structure and Assumptions

MODEL EPIDEMIOLOGY AND ASSUMPTIONS

- We used a previously developed model parameterized to KwaZulu-Natal, South Africa.[3]
- Over 1.5 million people were living with HIV and less than one-third were on ART in 2011 in KwaZulu-Natal.[4]
- The transmission probability of HIV is based on plasma viral load of the infectious partner.[2] (Table 1)
- Rates of CD4 count and viral load progression estimated from studies in east and southern Africa.[5,6]
- ART reduces infectiousness by 96%[7] with 6% annual drop out from ART programs.[8]
- HIV-positive persons progress dependently through HIV stages by CD4 count and viral load. (Figure 1)
- Costs assumed for CD4 and viral load tests, ART, and hospitalization pre- and post-ART initiation. (Table 2)

Table 1. HIV transmission probability by viral load stage.

Viral Load	Transmission Probability (Baseline=0.0006)
Acute	26 * Baseline
VL≤1000	1 * Baseline
VL 1,000-10,000	5.8 * Baseline
VL 10,000-50,000	6.9 * Baseline
VL>50,000	11.9 * Baseline

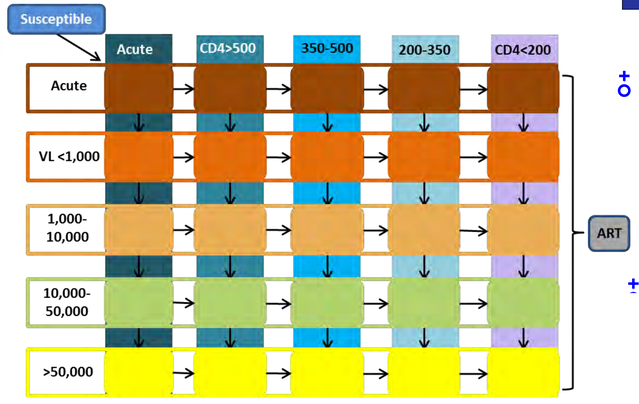


Figure 1. Flow diagram of population compartments simulated in the model. Susceptible individuals acquire HIV and face risks of decreasing CD4 count and increasing viral load over time.

METHODS: Modeled Scenarios

- Assess whether CD4-based ART-initiation criteria (Table 3) sufficiently captured people with high viral load.
- Assess the impact of ART initiation strategies on infections and deaths averted, and QALYs gained. (Table 4)

Table 2. Assumed costs used in the cost-effectiveness analysis. All costs are discounted by 3% annually.

Item	Cost
CD4 Count[9]	$83 per test and only applicable in CD4-based scenario

Item	Cost
Annual ART[10]	$682 per person
Hospitalization[11]	Pre- and post-ART

Table 3. Historical CD4-based ART guidelines by the WHO and South Africa, including their year of implementation.

	2002	2004	2006	2010	2011	2013	2014
WHO	CD4≤200 cells/μL		Consider for 200-350 cells/μL	CD4≤350 cells/μL		CD4≤500 cells/μL	
South Africa		CD4≤200 cells/μL			CD4≤350 cells/μL		CD4≤500 cells/μL

Table 4. Simulated scenarios for ART scale-up. ART coverage is assumed to increase linearly between years. ART for persons with high CD4 count is assumed to be for clinical indications such as TB and Hepatitis.

YEAR	SCENARIO 1: No ART	SCENARIO 1: CD4-based	SCENARIO 3: Immediate Treatment following a positive HIV test
2004	0% coverage	0% coverage	0% coverage
2008	0% coverage	35% for CD4<200 5% for CD4>200	15.1% for males and 22% for females (interpolated from 2004 and 2014)
2014	0% coverage	60% for CD4<200 40% for CD4 200-350 10% for CD4>350	37.8% for males and 55.0% for females[12] (assuming 100% testing and linkage to care)

RESULTS: Model Validation

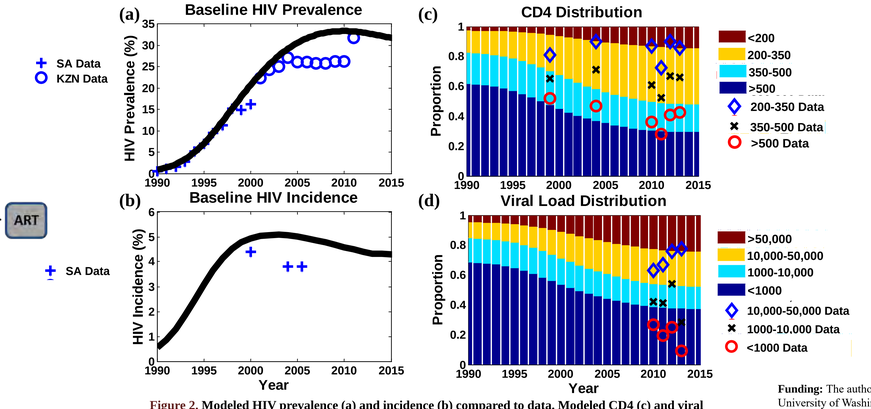


Figure 2. Modeled HIV prevalence (a) and incidence (b) compared to data. Modeled CD4 (c) and viral load (d) distributions over time compared to data.

RESULTS: Impact of ART Initiation Strategies

- Using a CD4 criterion captured many patients with high viral load (Figure 3a), but over 50% of those with CD4>200 cells/μL had viral load greater than 1,000 copies/mL. (Figure 3b)

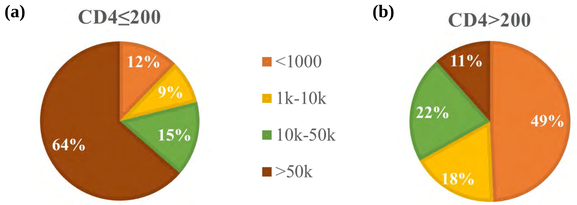


Figure 3. Distribution of viral load for persons eligible (a) and ineligible (b) for ART in 2004 when ART scale-up began in South Africa.

- From 2004 to 2014, Immediate Treatment would have cost $1.5 billion compared to $550 million with a CD4-based ART initiation policy.
- Relative to providing ART by CD4 count, immediate treatment for those who test HIV-positive would have prevented 195% more HIV infections and 113% more HIV-associated deaths. (Table 4)
- The Immediate Treatment scenario is cost-effective for averting HIV infections, deaths and QALYS.
- The CD4-based scenarios are most cost-effective for averting deaths and increasing QALYs, but have limited impact due to low ART coverage.
- Immediate Treatment remains very cost-effective relative to South Africa's per capita GDP ($6,618).[13]

Table 4. The incremental cost-effectiveness ratios for each strategy relative to the Baseline scenario of current ART coverage.

Outcome	Scenario	Effectiveness	Cost (millions USD)	ICER
	No Intervention	0	0	Baseline
HIV Infections Averted	CD4-based	136,000 (5%)	550	Dominated
	Immediate Treatment	401,000 (15%)	1,490	$3,712
HIV Deaths Averted	CD4-based	236,000 (10%)	550	$2,333
	Immediate Treatment	500,000 (21%)	1,490	$3,553
QALYs Gained	CD4-based	928,000	550	$592
	Immediate Treatment	2,054,000	1,490	$835

DISCUSSION

- Using a CD4-based ART initiation criterion may have resulted in many HIV-positive persons delaying ART initiation and experiencing excess morbidity.
- Immediate treatment compared with CD4 based criteria would have prevented 401,000 HIV infections and 500,000 deaths between 2004 and 2014 through increased access to earlier ART coverage
- CD4-based ART initiation is dominated by immediate treatment for averting HIV infections.
- Limitations include the uncertainty inherent in retrospective analyses and not including factors such as ART monitoring and immune recovery for early versus late ART initiation.
- We currently have robust evidence to phase out CD4 count for ART staging and delays will result in lost public health opportunities to prevent illness, HIV transmission, death, and costs.

Funding: The authors acknowledge funding from the University of Washington Center for AIDS Research (NIH P30 AI027757), and the Whitaker Foundation.

References: [1]Mellors, et al. JAMA (2007); [2]Quinn, et al. N Engl J Med (2000); [3]Barnabas, et al. Cell-Lancet (2013); [4]KZN NASA (2013); [5]Celum, et al. N Engl J Med (2010); [6]Baeten, et al. N Engl J Med (2012); [7]Cohen et al. N Engl J Med (2011); [8]KAIS (2012); [9]Freedberg, et al. NEJM (2001); [10]CHAI Facilities-Base Costing (2013); [11]Meyer-Rath, et al. JAIDS (2013); [12]Shisana, et al. HSRC (2014); [13]World Bank 2012