Update in HIV Medicine for the Generalist

Society of General Internal Medicine
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No Disclosures

Lawrence Linn Award 2008

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Learning Objectives

- Review the most recent data regarding HIV counseling, testing, and treatment, with a focus on cost-effectiveness

- Discuss new findings regarding survival and general management of HIV, including a brief review of new antiretroviral medications and updated treatment guidelines

- Discuss the intersection of HIV with other chronic diseases commonly encountered by generalist physicians

Methodology

- Literature review of peer-reviewed studies dealing with the management of HIV as relevant to the generalist physician, published since July 2006
  - PUBMED Medical Subject Heading (MeSH) search limited to articles published on or after July 2006
  - Review of published studies in the major peer-reviewed general medicine and HIV journals since July 2006
- Final articles were selected by group consensus of HIV experts and practicing clinicians

Agenda

- Cost-effectiveness of screening and treatment (Gifford)
- Survival and management (Chaudhry)
- HIV and other chronic diseases (Sullivan)

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- Cost-Effectiveness of Screening and Treatment (Gifford)
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Update on Issues in Cost-Effectiveness of HIV Screening and Treatment

Allen L. Gifford, M.D.

VA New England Healthcare and
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Overview

- Promises & pitfalls of economic evaluation
- Cost-effectiveness ratios in HIV care
- Recent studies

Cost-Effectiveness: *Common Misconception #1*

“Cost-Effective” = “Cheap”

“Cost-Effective” = “Saves Money”

Cost-Effectiveness is About "Value for Money"

- Very, very few health interventions save more money than they cost
- Cost-effectiveness analysis is about comparative assessment of worth
- Investments in health can be compared to evaluate competing claims on scarce resources

Cost-Effectiveness: *Common Misconception #2*

“If an intervention is cost-effective, payers should be willing to pay for it.

“If they’re <u>not</u> willing to pay for it, they’re just being irrational, or poor managers”

Cost-Effectiveness Takes a Societal Perspective

- Cost-effectiveness analyses account for all costs and benefits, regardless of payer or beneficiary
- “Cost-effective” from the societal perspective doesn’t mean “budget neutral” from the payer perspective
- Does not directly address where the money should come from

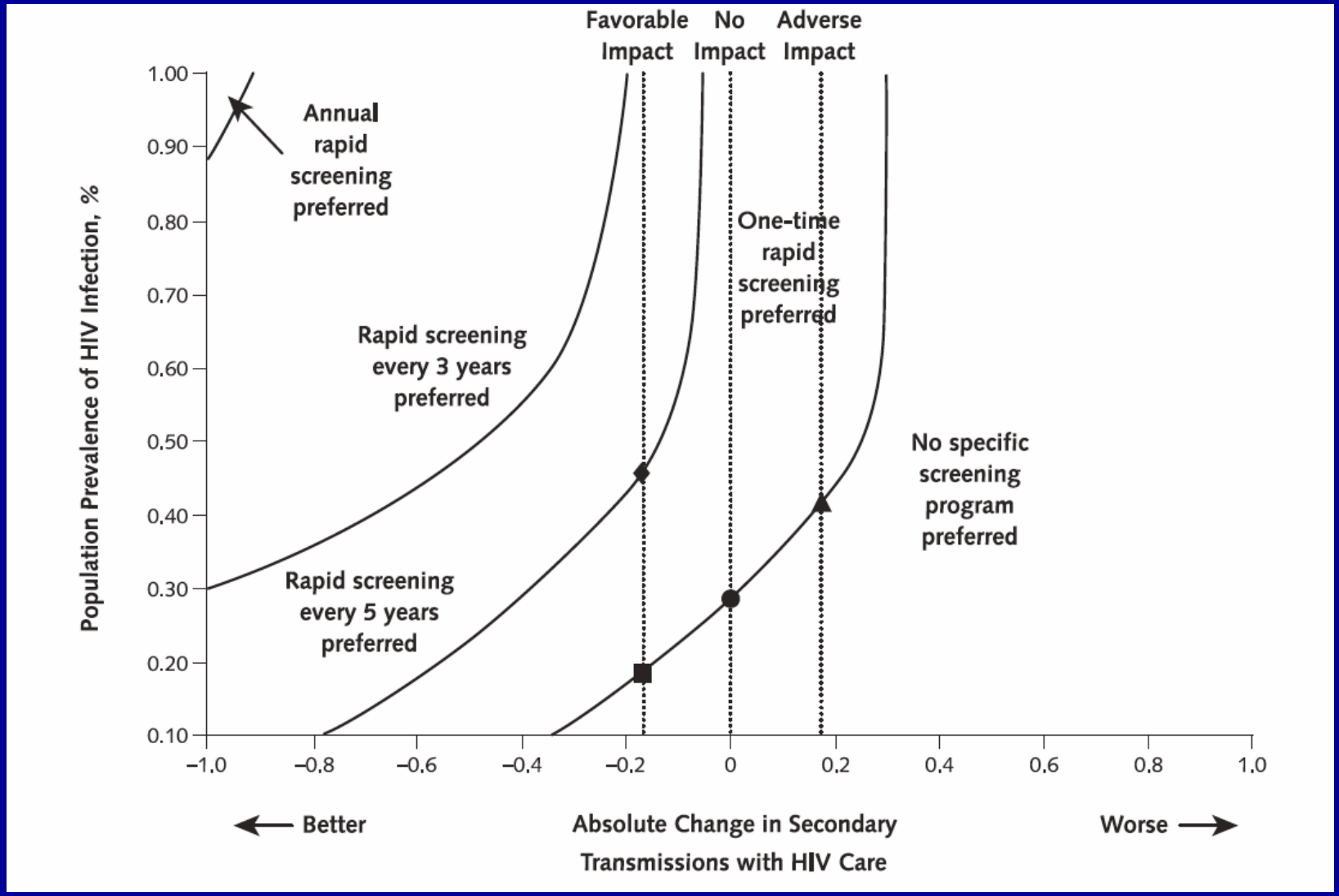
Cost-Effectiveness Ratios for HIV Care

Intervention	Agent	C-E Ratio ($/QALY)*	Reference
ART	AZT/3TC/EFV	$11,700	Freedberg NEJM 2001
Resistance Testing	---	$20,200	Weinstein Annals 2001
Inpatient HIV screening	---	$38,600	Walensky AJM 2005
MAC proph.	Azithromycin	$43,300	Freedberg JAMA 1998
One-time routine HIV screening	---	$38,000	Paltiel NEJM 2005
higher risk patients	---	$42,000	Sanders NEJM 2005

How Will HIV Testing Effect Subsequent HIV Transmission?

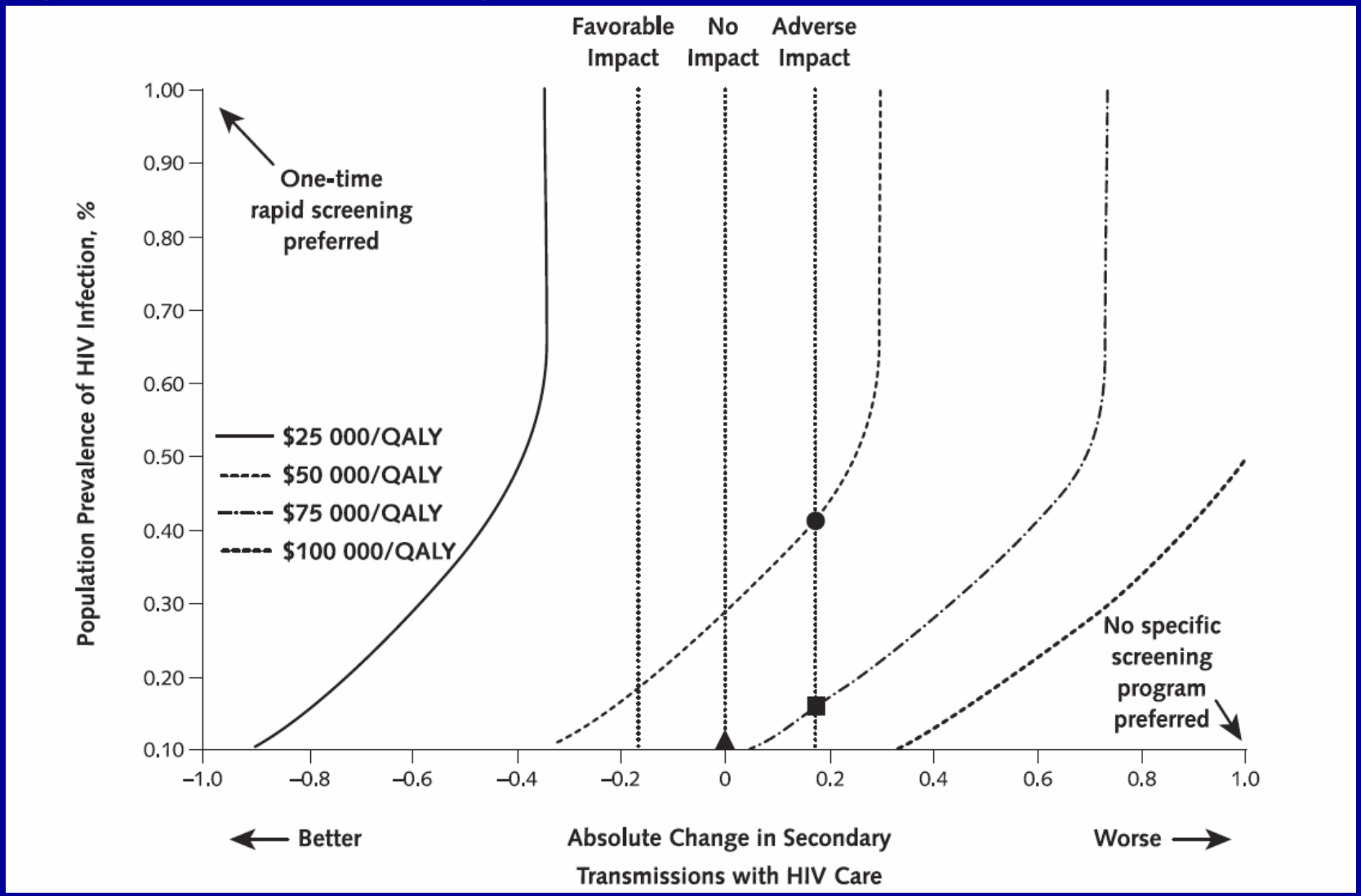
- Number of lifetime infections depends on:
  - HIV transmission efficiency
  - Number of risky contacts
  - Duration of infectiousness
- HIV testing might *reduce* subsequent infections
- HIV testing might *increase* subsequent infections

Alternative Programs for HIV Screening: Comparisons with $50,000/QALY Threshold



Paltiel et al., *Ann Intern Med* 2006

One-time HIV Screening vs. No Specific Screening Program: Sensitivity to Cost-Effectiveness Threshold

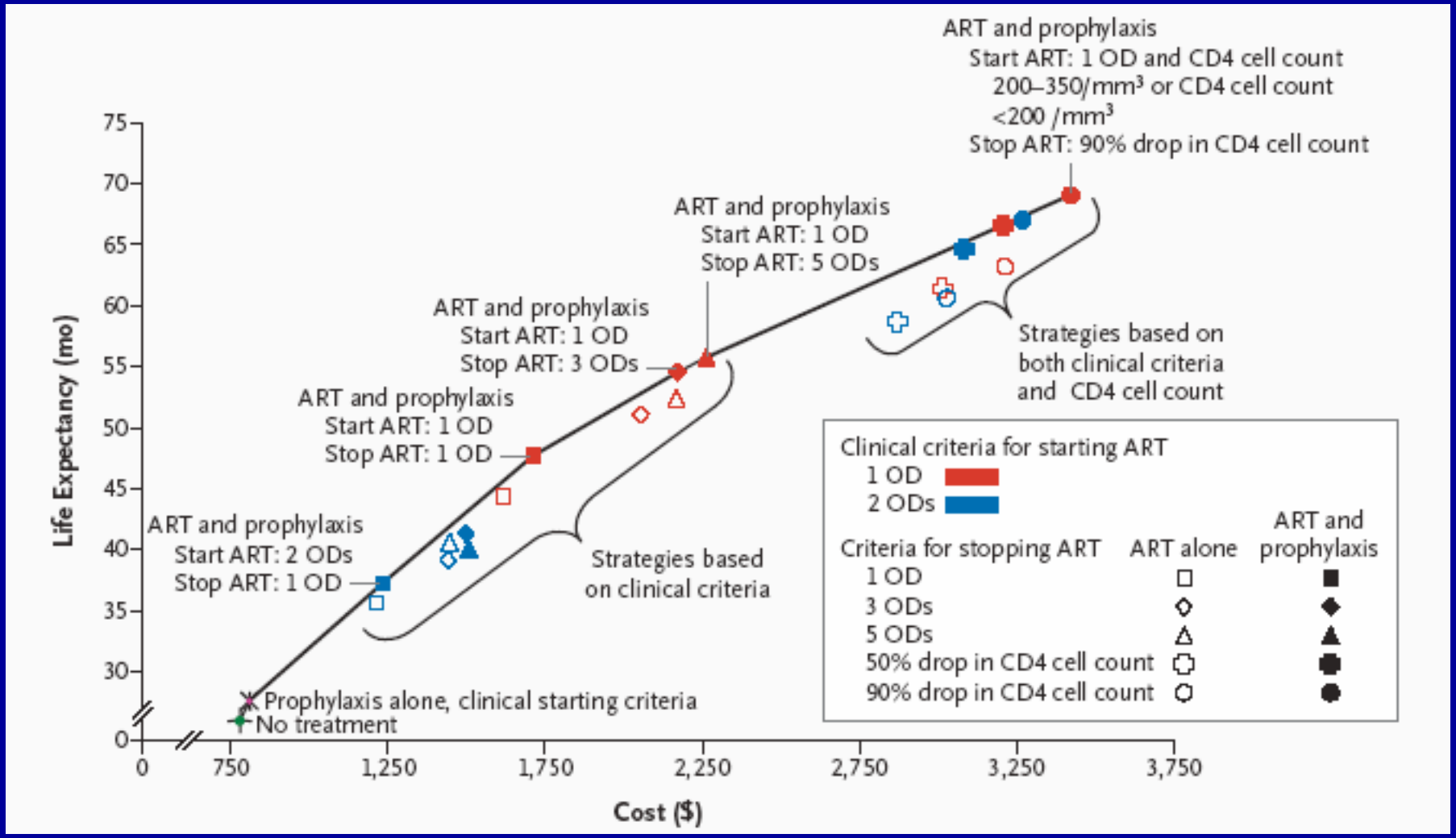


Paltiel et al., *Ann Intern Med* 2006

Cost-effectiveness of Treatment in Resource-Poor Settings

- Limited resources mean selecting between treatment strategies that are not considered in developed countries
- Questions about timing of prophylaxis and ARV drugs, and of diagnostic tests
- C-E ratio:
  - less than the per capita GDP = very cost-effective
    less than 3x the per capita GDP = cost-effective

Cost-Effectiveness of ART in Côte d'Ivoire



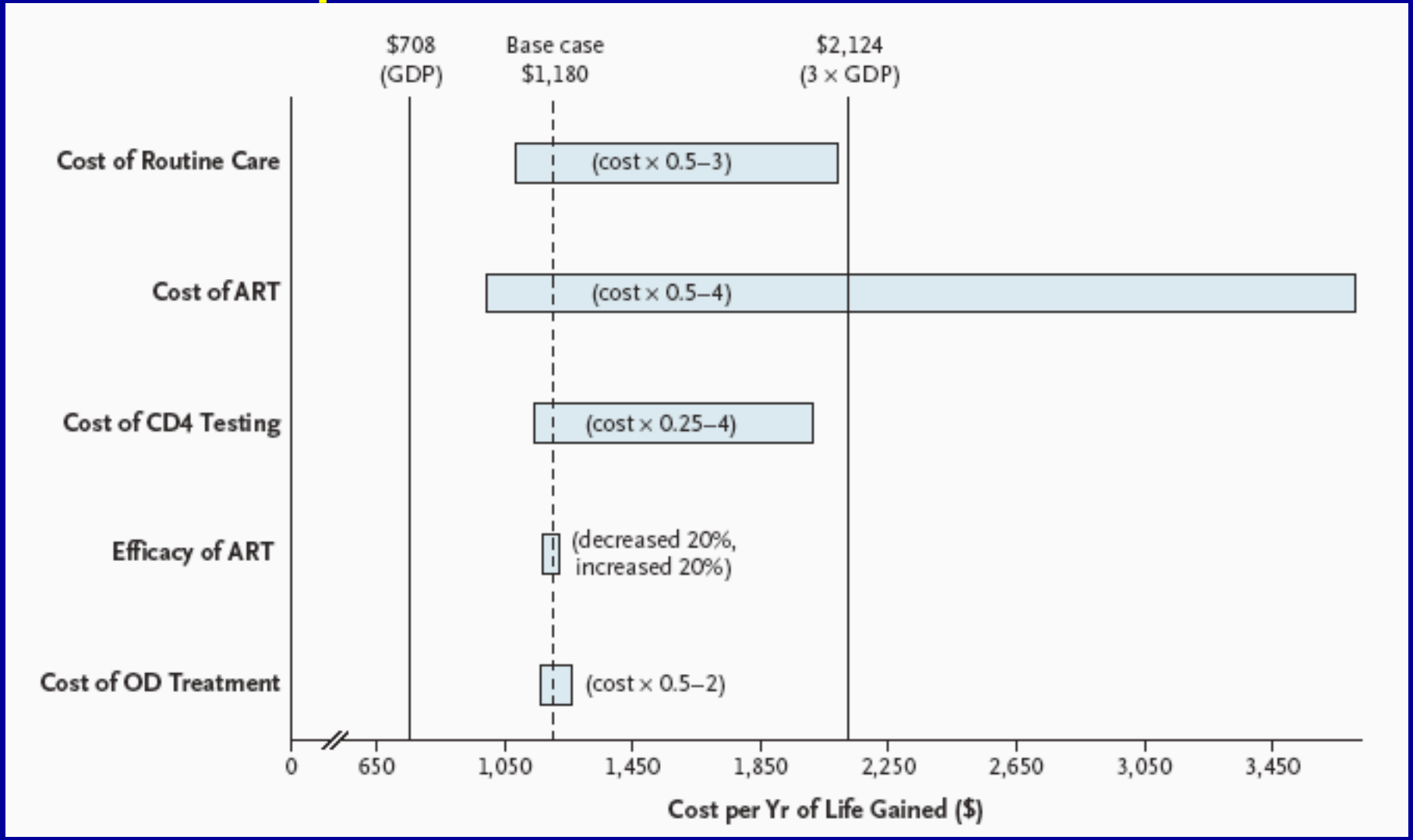
Goldie et al., *NEJM* 2006

Cost-Effectiveness Ratios for Strategies

Strategy	CD4 Testing	ART Starting Criteria	ART Stopping Criteria	Incremental C-E Ratio
No treatment	--	--	--	--
TMP-SMX alone	No	--	--	$240/yr
TMP-SMX & ART	No	2 OD	1 OD	$590/yr
TMP-SMX & ART	No	1 OD	1 OD	$620/yr
TMP-SMX & ART	No	1 OD	3 OD	$890/yr
TMP-SMX & ART	No	1 OD	5 OD	$1060/yr
TMP-SMX & ART	Yes	<200/mm^3 or <350/mm^3 & 1 OD	90% CD4 drop	$1180/yr

Goldie et al., *NEJM* 2006

Sensitivity Analysis of Potentially Important Model Variables



Goldie et al., *NEJM* 2006

Agenda

- Cost-Effectiveness of Screening and Treatment (Gifford)
- Survival and Management (Chaudhry)
- HIV and Other Chronic Diseases (Sullivan)

Survival and Management

Amina A. Chaudhry, M.D., M.P.H
Johns Hopkins University School of Medicine

Survival of Persons With and Without HIV Infection in Denmark, 1995-2005

Lohse, N, A Hansen, G Petersen, G Kronborg, J Gerstoft, HT Serensen, M Vaeth, and N Obel

Ann Intern Med 2007; 146:87-95

BACKGROUND/PURPOSE

- Mortality among persons with HIV/AIDS has decreased considerably in the HAART era
- Still, studies comparing mortality rates have shown increases of 3- to 10-fold among those being successfully treated for HIV compared to the general population
- Comparing rates of mortality does not specifically provide information about survival
- The **purpose** of the current study: to examine survival and age-specific mortality among the entire HIV-infected population in Denmark

METHODS

- Population-based cohort study
- All HIV-infected persons receiving care in Denmark from 1995-2005, matched by sex, age, and residence with ~95 persons from the general population
- Causes of death were available for HIV-infected patients and were categorized as:
  - HIV-related
  - Non-HIV-related
  - Unknown
- HIV patients were observed from date of diagnosis or first visit to the HIV clinic, and matched controls were observed from the same starting date
- Mortality and median survival times from age 25 years were estimated

STUDY SAMPLE

- 3990 HIV-infected; median observation 5.8 person-yrs
- 379,872 general population: median obs. 8.4 person-yrs
- 3.0% loss to follow up in both groups

RESULTS (1)

Median survival from age 25 years

Population	Survival from age 25 (all) (years)	Survival from age 25 (women) (years)	Survival from age 25 (men) (years)
HIV-infected (overall)	19.9	24.2	17.5
HIV-infected (2000-2005)	32.5	32.3	32.1
HIV *without* HCV (2000-2005)	38.9	40.1	37.8
General population	51.1	54.8	50.8

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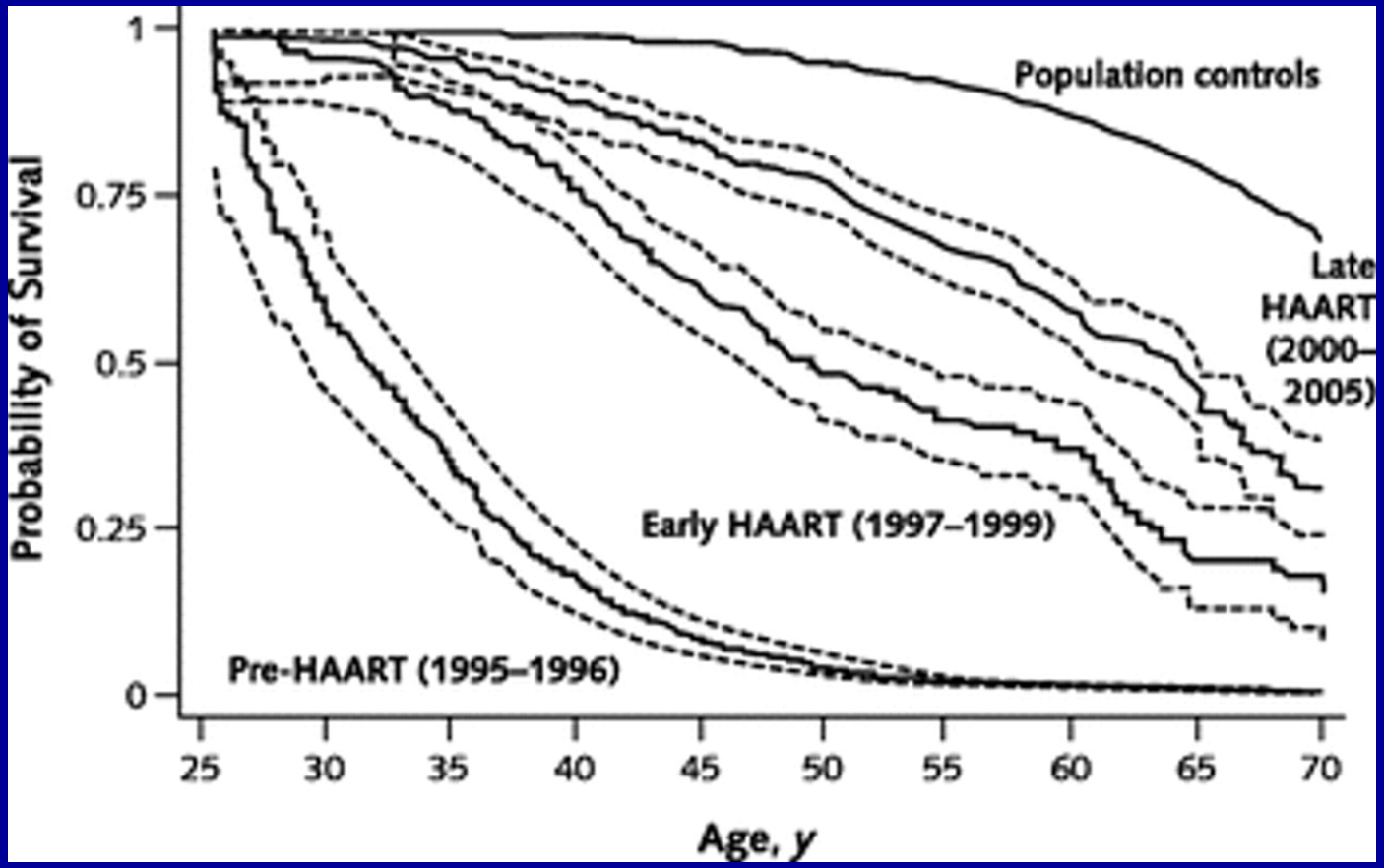
Survival from age 25 years



Lohse, N. et al. Ann Intern Med 2007;146:87-95

Annals of Internal Medicine

RESULTS (2)

Mortality Rates and Causes of Death

Overall crude mortality rate

- HIV-infected: 43 per 1000 p-y (95%CI: 40-45)
- General population: 4.7 per 1000 p-y (95% CI: 4.6-4.8)

Observation period	Mortality rate per 1000 p-y All Causes (95% CI)	Mortality rate per 1000 p-y HIV-related (95% CI)	Mortality rate per 1000 p-y Non-HIV-related (95% CI)
1995-1996	124 (112-137)	71.2 (62.6-81.0)	23.1 (18.4-29.0)
1997-1999	37.9 (33.2-43.2)	17.8 (14.7-21.5)	13.7 (11.0-17.0)
2000-2005	25.4 (22.8-28.2)	7.0 (5.8-8.6)	9.4 (7.9-11.2)

RESULTS (3)

Age-Specific Mortality Rates (95% CI)

	25-30 y	**>30-35 y**	**>35-40 y**	**>40-45 y**
HIV	30.5 (23.4-39.9)	28.5 (23.7-34.3)	35.8 (30.8-41.4)	45.7 (39.7-52.7)
general	0.7 (0.6-0.8)	0.9 (0.8-1.0)	1.3 (1.3-1.4)	2.6 (2.4-2.7)
Mortality rate ratio	44.5 (32.0-61.9)	32.0 (25.9-39.7)	27.4 (23.1-32.4)	18.0 (15.4-21.1)

	>45-50 y	**>50-55y**	**>55-60y**	**>60-65 y**
HIV	50.5 (43.1-59.1)	49.2 (40.8-59.2)	45.2 (35.7-57.3)	73.4 (55.4-97.1)
general	4.7 (4.4-4.9)	7.3 (7.0-7.6)	11.0 (10.5-11.4)	18.0 (17.1-18.9)
Mortality rate ratio	10.8 (9.1-12.8)	7.2 (6.0-8.8)	4.1 (3.2-5.2)	4.2 (3.2-5.6)

CONCLUSIONS--IMPLICATIONS

- Survival has improved over the years, primarily due to a decrease in HIV-related mortality
- Despite gains in survival in the HAART era, life expectancy is still markedly decreased compared to the general population
- Although mortality increased across the board with increasing age, relative mortality rates decreased with increasing age
- Limitations
  - Denmark has free HIV and antiretroviral care dispensed at 8 specialized centers
  - Care models may not be generalizable to US
  - Certain populations may not have been adequately represented

New Antiretrovirals and Treatment Guidelines

Antiretrovirals Newly FDA Approved Since 2006

NAME	TRADE NAME	CLASS	APPROVAL DATE	REFERENCE
efavirenz, emtricitabine, and tenofovir disoproxil fumarate	Atripla	Multi-class combination	12 July 2006	___
etravirine	Intelence	Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI)	18 January 2008	Lazzarin et al. 2007 Madruga et al. 2007
darunavir	Prezista	Protease Inhibitor (PI)	23 June 2006	Clotet et al. 2007 Madruga et al. 2007
maraviroc	Selzentry	Entry Inhibitor (CCR5-co-receptor antagonist)	06 August 2007	*Lalezari et al. 2007 *Nelson et al. 2007
raltegravir	Isentress	HIV Integrase strand transfer inhibitors	12 October 2007	Grinsztejn et al. 2007

*Reference in abstract form. Presented at the 14th Conference on Retroviruses and Opportunistic Infections; 2007

Updated DHHS Guidelines:

When to Treat

Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
▪History of AIDS-defining illness ▪CD4 <350 cells/mm³ ▪Pregnant women ▪HIV-associated nephropathy ▪Hepatitis B coinfection, when HBV treatment is indicated*	Initiate ART

*Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
▪CD4 >350 cells/mm³, asymptomatic, without conditions listed above	Optimal time to initiate ART is not well defined. Consider individual patient characteristics and comorbidities.

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Mallal, S, E Phillips, G Carosi, J Molina, C Workman, J Tomažič, E Jägel-Guedes, S Rugina, O Kozyrev, JF Cid, P Hay, D Nolan, S Hughes, A Hughes, S Ryan, N Fitch, D Thorborn, and A Benbow, for the PREDICT-1 Study Team

N Engl J Med 2008;358:568-79

BACKGROUND/PURPOSE

- Abacavir hypersensitivity, a potentially life-threatening condition, may affect 5-8% of patients during the first 6 weeks of therapy
- Symptoms of abacavir hypersensitivity are nonspecific, which may lead to false positive diagnoses
- An association has been recognized between the MHC Class I allele HLA-B*5701 and a *diagnosis* of hypersensitivity
- The **purpose** of the current study: Can screening for HLA-B*5701 reduce the incidence of abacavir hypersensitivity reaction?

METHODS

- Prospective, multicenter, randomized, double-blind study
- 265 centers, 19 countries
- Eligibility: HIV-1 infection, need for treatment with an abacavir containing regimen, HLA-B*5701 status unknown, no previous abacavir
- 2 arms:
  - Prospective screening (test first, if negative, then treatment with abacavir-containing regimen)
  - Control (treat, then test retrospectively)
- Epicutaneous patch testing
- Primary outcomes:
  - Rate of clinically diagnosed hypersensitivity reactions
  - Rate of immunologically confirmed hypersensitivity reaction

RESULTS

- N=1956 (980 prospective screening, 847 control)
- 55 excluded from the prospective screening group after testing positive for HLA-B*5701
- 109 patients out of 1956 (5.6%) were HLA-B*5701
- Incidence of both clinical (OR 0.03; 95% CI,0.00-0.18) and immunologically confirmed (0.40; 95% CI, 0.25-0.62) hypersensitivity reaction were lower in the prospective screening group
- In multivariate analysis, *only* prospective screening was a significant negative predictor of hypersensitivity reaction

RESULTS

Positive and Negative Predictive Value of HLA-B*5701 testing

Type of hypersensitivity reaction	Positive Predictive Value	Negative Predictive Value
Immunologically confirmed	47.9%	100%
Clinically diagnosed	62.1%	95.5%

CONCLUSIONS--IMPLICATIONS

- Prospective HLA-B*5701 testing can reduce the risk of abacavir hypersensitivity reaction
- In a similar population, screening of 100 patients could prevent 4 diagnoses of abacavir hypersensitivity
- Although this population was 83% white, other studies suggest that the association between hypersensitivity and HLA-B*5701 occurs across racial/ethnic groups
- Cost-effectiveness may vary across different groups and settings and further work is needed in this area

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HIV and Other Chronic Diseases: Results from 2 “DAD” Studies

Lynn E. Sullivan, M.D.
Yale University School of Medicine

Class Of Antiretroviral Drugs and the Risk of Myocardial Infarction

The DAD Study Group

N Engl J Med 356;17, 1723-1735; 2007

BACKGROUND/PURPOSE

- There is a demonstrated association between combination antiretroviral therapy and the risk of myocardial infarction (MI)

- It is unclear whether this association varies based on class of antiretroviral drugs

- The **purpose** of the current study: to investigate the association of exposure to protease inhibitors (PIs) and non-nucleoside reverse-transcriptatse inhibitors (NNRTIs) and risk of MI

METHODS

- Analysis of data collected through February 2005 from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study: 23,437 HIV-positive patients

- Calculated incidence rates of MI during follow-up period

- Determined associations between MI and PI and NNRTI exposure

RESULTS

- 345 patients had an MI during 94,469 person-years of observation

- Incidence of MI increased from 1.53/1,000 person years in non-PI-exposed to 6.01/1,000 person-years in PI-exposed for > 6 years

- After adjusting for exposure to the other drug class and to other cardiovascular risk, the relative rate of MI/year:
  - of PI exposure: 1.16; 95% CI, 1.10-1.23 [Adjusting for lipid levels: 1.10; 95% CI, 1.04-1.18]
  - of NNRTI exposure: 1.05; 95% CI, .98-1.13 [Adjusting for lipid levels: 1.00; 95% CI, 0.93-1.09]

CONCLUSIONS--IMPLICATIONS

- Increased exposure to PIs is associated with increased risk for MI—in part due to dyslipidemia

- No evidence of this association for NNRTIs

- However,the number of person-years of exposure to PIs was greater (72,846 person-years) than that of person-years exposure to NNRTIs (52,457 person-years)

Liver-Related Deaths in Persons Infected With the Human Immunodeficiency Virus The D:A:D Study

The Data Collection on Adverse Events of Anti-HIV Drugs Study Group

Arch Intern Med/Vol 166, Aug 14/28, 1632-1641; 2006

BACKGROUND/PURPOSE

- Mortality in HIV-infected patients in developed countries has dramatically decreased with the use of combined antiretroviral therapy (cART)

- >50% of deaths in HIV-infected patients are from causes other than AIDS

- Increasing deaths related to hepatitis C and B and alcohol and intravenous drug use

- The effect of cART-induced hepatoxicity on liver-related deaths is not known

- The **purpose** of the current study: to assess the relationships between liver-related deaths and HIV-associated immunodeficiency, HBV and HCV coinfections, and cART

METHODS

- To investigate the frequency and risk factors associated with liver-related deaths:
  - –Used the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study: international collaboration of 11 cohorts of investigators at 188 clinics in 21 countries in Europe, the U.S. and Australia
    - Prospectively evaluated 76,893 person-years of follow-up in 23,441 HIV-infected persons (December 1999-February 2004)

- Conducted multivariable Poisson regression analyses to identify factors associate with liver-related, AIDS-related, and other causes of death

RESULTS

- 1246 deaths: 14.4% from liver-related causes:
  - 16.9% had active HBV, 66.1% had HCV, 7.1% had HBV/HCV coinfection

- Predictors of liver-related deaths:
  - Latest CD4 count: RR, 16.1; 95% CI, 8.1-31.7 for <50 vs. ≥ 500/ul
  - Age: RR, 1.3; 95% CI, 1.2-1.4 per 5 years older
  - IV drug use: RR, 2.0; 95% CI, 1.2-3.4
  - HCV infection: RR, 3.7; 95% CI, 4.0-11.2
  - Active HBV infection: RR, 3.7; 95% CI, 2.4-5.9

- No relationship between cumulative years of cART and liver-related deaths

- Adjusting for most recent CD4 and patient characteristics-> -> increased risk of liver-related mortality/year of mono or dual therapy before cART (RR, 1.09; 95% CI, 1.02-1.16, P=.008) and per year of cART (RR, 1.11; 95% CI, 1.02-1.21; P=.02)

CONCLUSIONS--IMPLICATIONS

- Liver-related death was most frequent cause of non-AIDS-related death

- Treatment/prevention of illicit drug and alcohol use is critical in patients with HCV coinfection because of the association of these risks with progression to cirrhosis

- A longer follow-up period is needed to evaluate the relationship between cART and liver-related mortality

- Strong association between immunodeficiency and risk of liver-related death underlines the importance of HIV treatment strategies that prevent immunodeficiency

- The question of if and when to treat hepatitis coinfection must consider status of liver disease and immune status