

Clinical Manifestations of AIDS in Different Parts of the World

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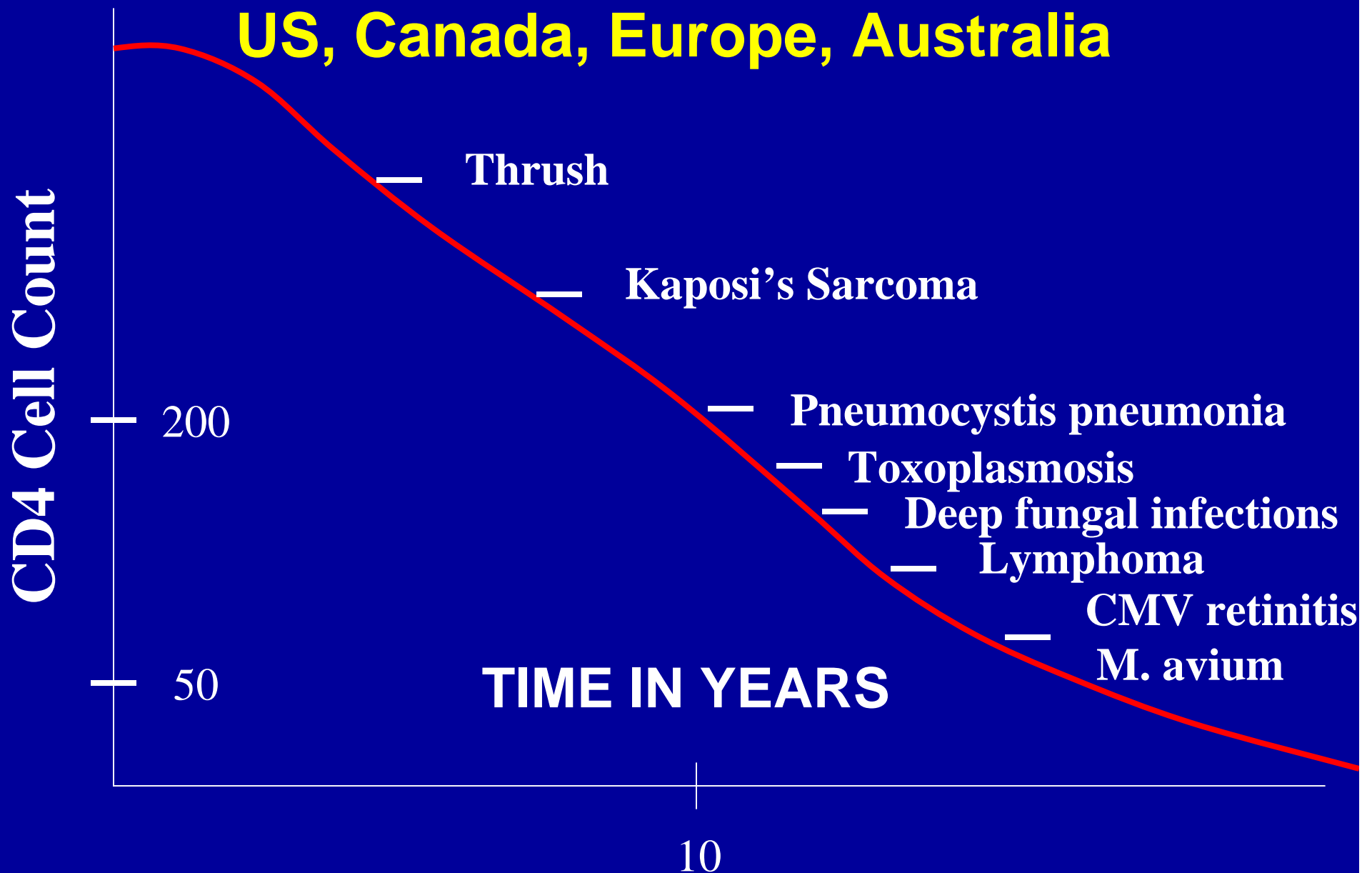
San Francisco, CA, USA

HIV INFECTIONS AND MALIGNANCIES



HIV DISEASE PROGRESSION

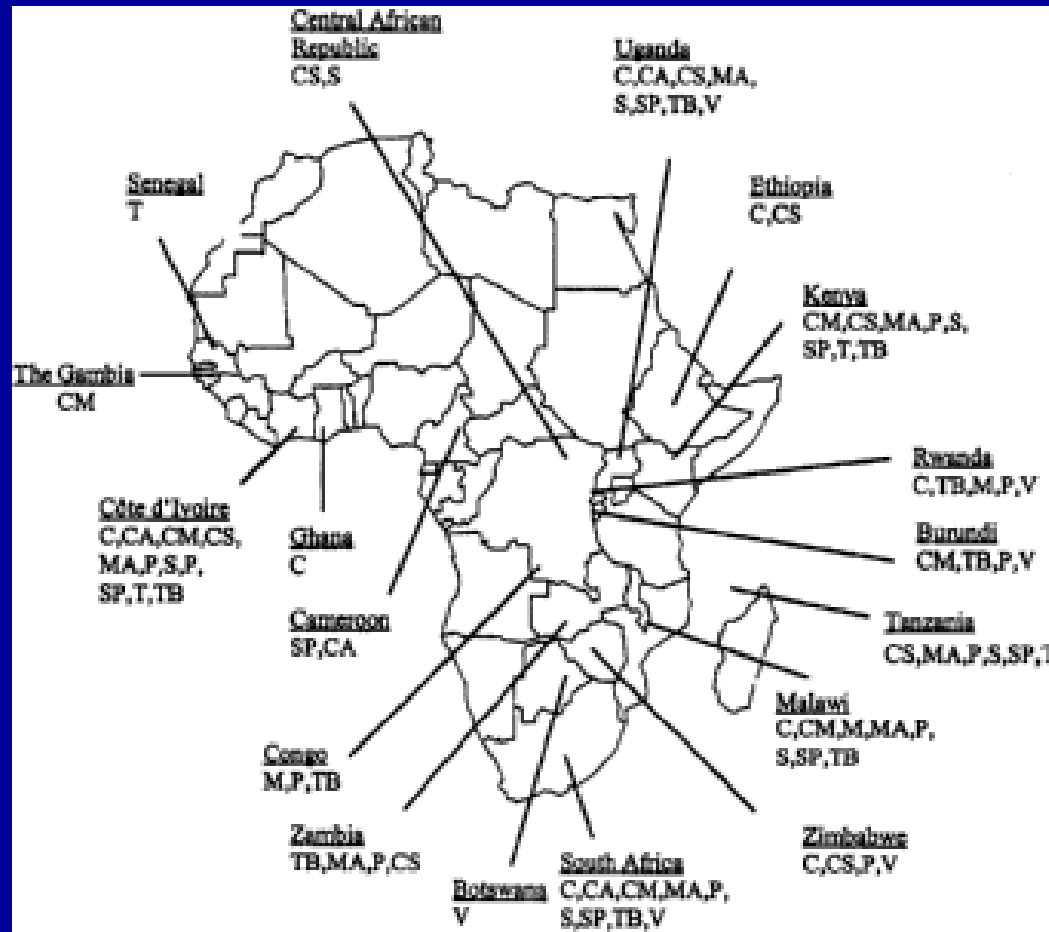
US, Canada, Europe, Australia



OBSERVATIONS: US, Canada, Europe, Australia

- **Opportunistic infections produced enormous suffering and stigma**
- **Diagnostic tests were often invasive and expensive**
- **Treatments were complex, toxic and more difficult than current antiretroviral therapy**
- **Some complications were untreatable**
- **Prophylaxis was only partially effective**

OPPORTUNISTIC INFECTIONS REPORTED IN AFRICA



Cryptococcus
C. albicans
CMV
Cryptosporidium
Isospora
Malaria
M. avium
Microsporidium
Pneumocystis
Salmonella
Pneumococcus
Toxoplasmosis
M. tuberculosis
Varicella

HIV COMPLICATIONS IN AFRICA

- Non-typhoidal salmonella, pneumococcus, E. coli bacteremia are associated with high mortality^{1,2}
- Pneumocystis occurs in adults and children ³
- Cryptococcal meningitis is common
- Squamous cell carcinoma of the conjunctiva is 10-fold more frequent in HIV disease ⁴
- Kaposi's sarcoma occurs in males and females⁵
- Leprosy is not more frequent or severe⁶



¹Grant, AIDS, 1997

²Gordon, AIDS, 2002

³Fisk, CID, 2003

⁴Newton, Br J Cancer, 2003

⁵Dedicoat, Br J Cancer, 2003

⁶Gebre, Lepr Rev, 2000

MALARIA AS IN OPPORTUNISTIC INFECTION

- Increased frequency in HIV infection¹
- Increased severity in HIV infection²

¹Whitworth, Lancet 2000

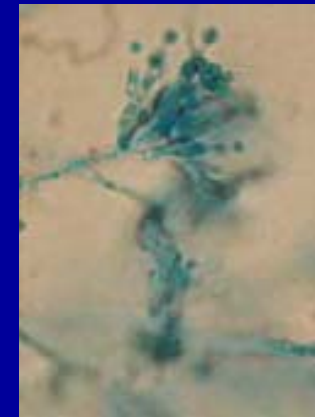
²Grimade, AIDS, 2004

MALARIA AND HIV ARE ASSOCIATED WITH LOW BIRTH WEIGHT

	<u>PRIMA</u>		<u>MULTI</u>	
	N	%	N	%
No Infection	676	4.1	809	2.7
Malaria +	226	9.3	129	2.3
HIV+	160	7.5	256	3.8
HIV+, Malaria+	91	14.3	84	4.8

PERCENT OF PATIENTS WITH HIV COMPLICATIONS IN ASIA

	<u>India</u> ¹	<u>Thailand</u> ²
Tuberculosis	60.4	28.9
Candidiasis	54.5	nr
Herpes Zoster	8.6	nr
Pneumocystis	6.1	19.8
Herpes Simplex	5.7	0.8
Cryptosporidiosis	4.7	1.2
Cryptococcal meningitis	4.7	18.5
CMV retinitis	3.2	0.6
Penicillium marneffeii	nr	3.0
Wasting	nr	28.2



Penicillium

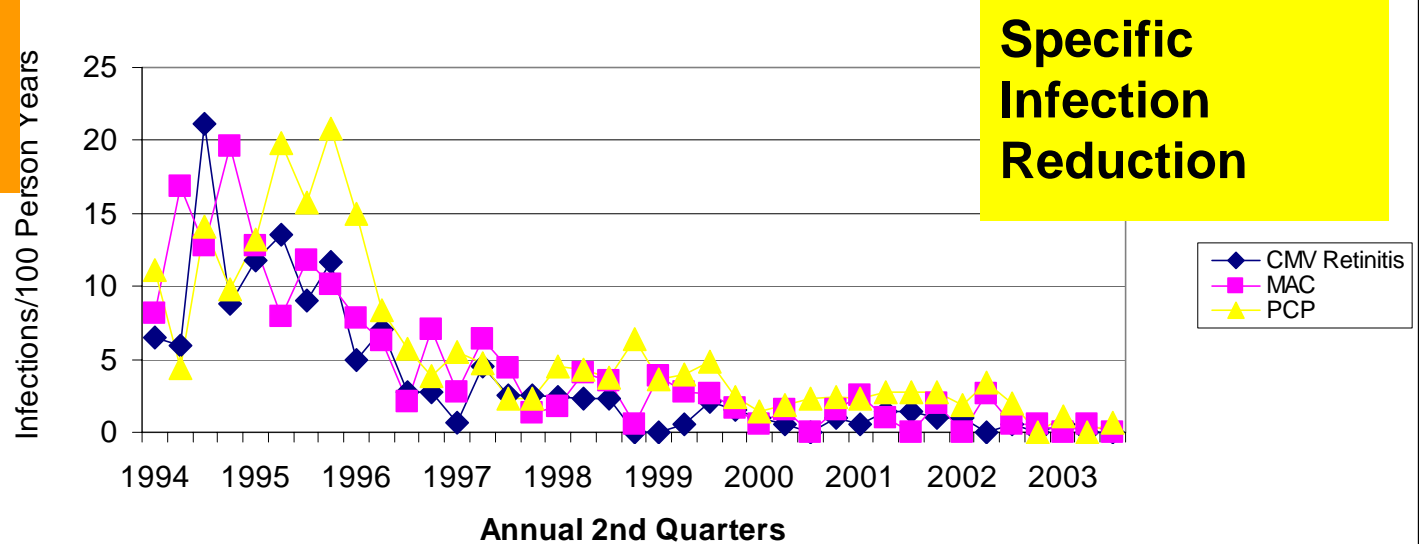
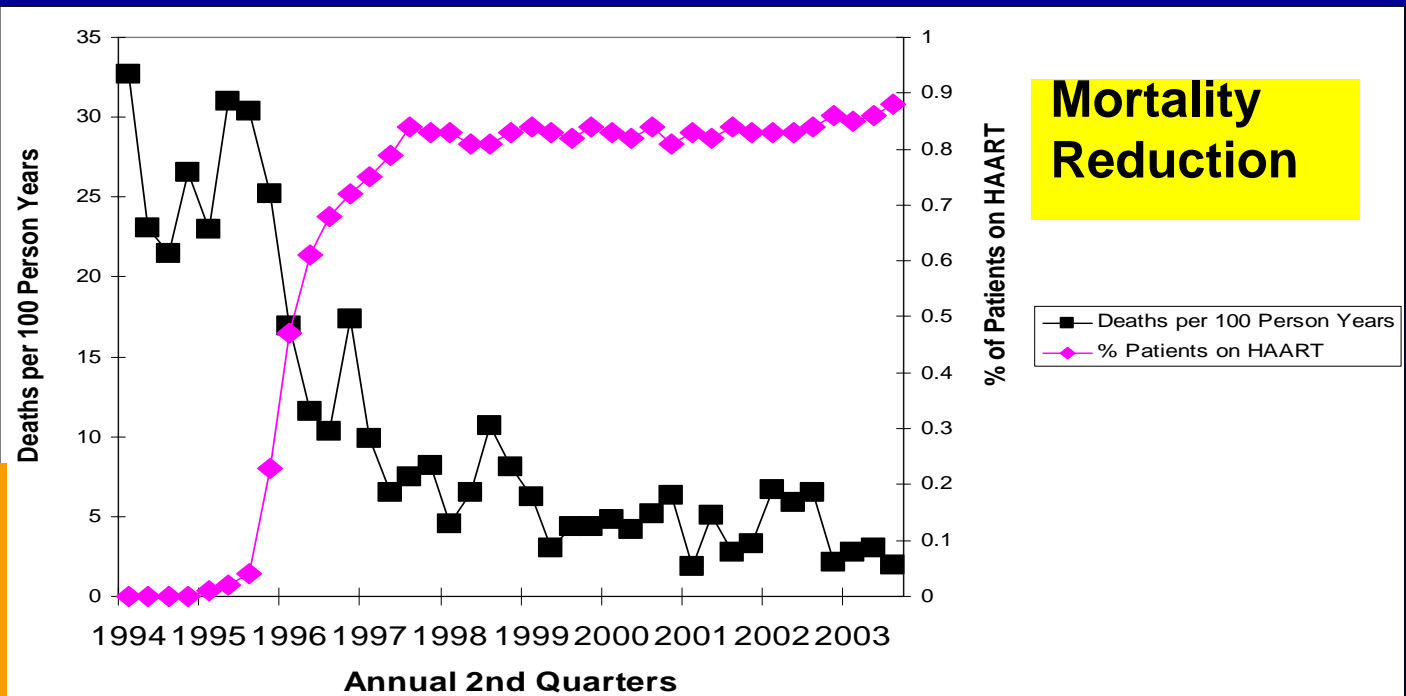
nr= not reported

¹Kumarsamy, CID, 2003

²Chariyalertsak, CID, 2001

EFFECT OF ANTIRETROVIRAL THERAPY ON COMPLICATIONS OF HIV DISEASE

INTRODUCTION OF ANTIRETROVIRAL THERAPY IN USA



HOPS Study, Courtesy of Holmberg and Palella

OBSERVATIONS: US, Canada, Europe, Australia

Antiretroviral therapy (ART)

- **Was the best prophylaxis for opportunistic infections**
- **Treated some “untreatable” infections and malignancies**
- **Treated hepatitis directly**
- **Reduced need for prophylaxis**

CLINICAL LANDSCAPE: 2004

US, Canada, Europe, Australia

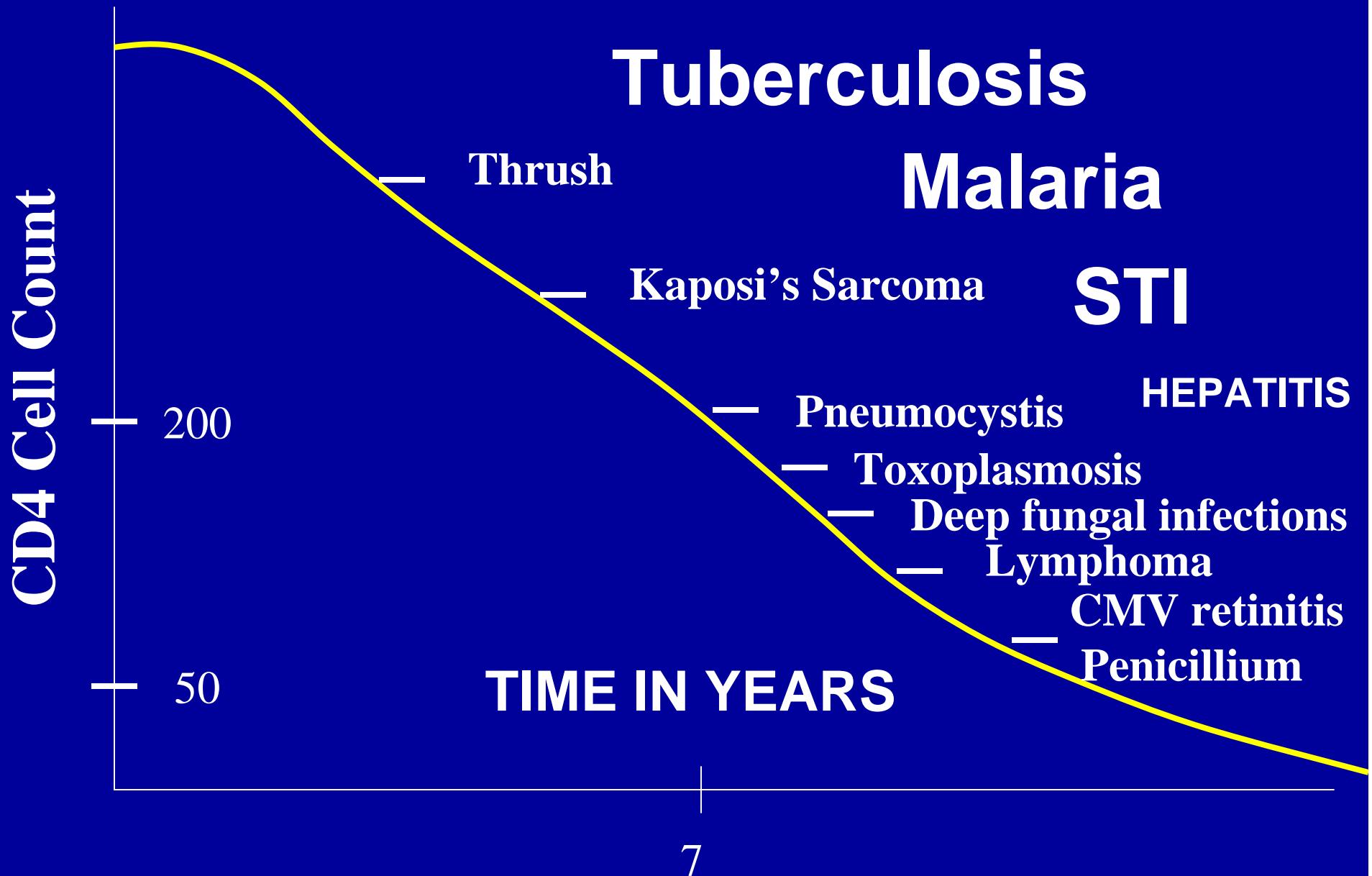
- **HIV is a chronic, clinic based disease**
- **Hepatitis has emerged as important cause of morbidity and mortality**
- **Complications of antiretroviral therapy (metabolic, vascular disease) are a major focus of HIV care**
- **Selection of ART regimens are made to avoid complications of therapy**



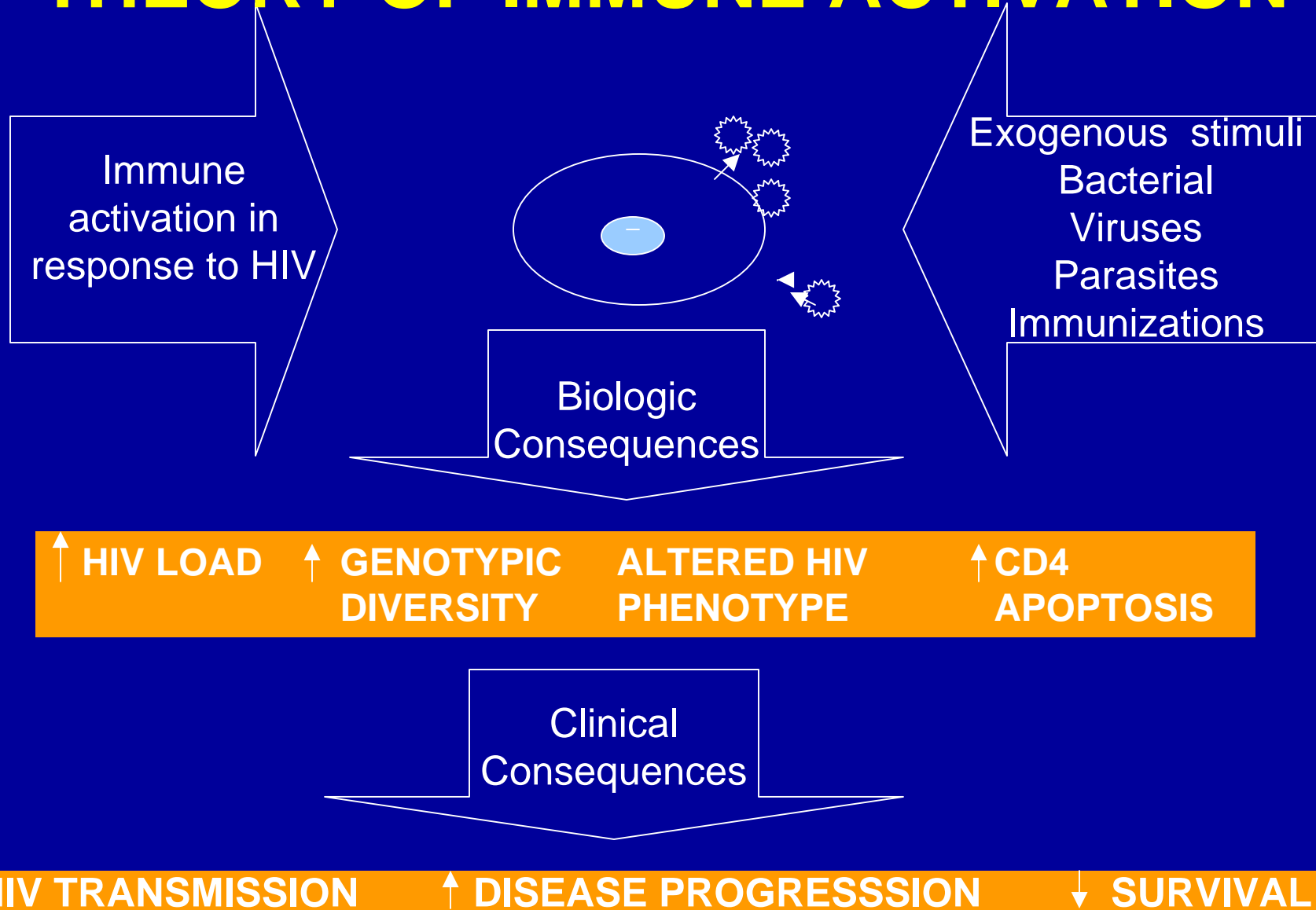
Facial Lipoatrophy

The biggest challenge of the HIV epidemic is that it is superimposed on pre-existing epidemics of TB, malaria and sexually transmitted infections, all fueled by inadequate health care infrastructure.

HIV DISEASE PROGRESSION



THEORY OF IMMUNE ACTIVATION

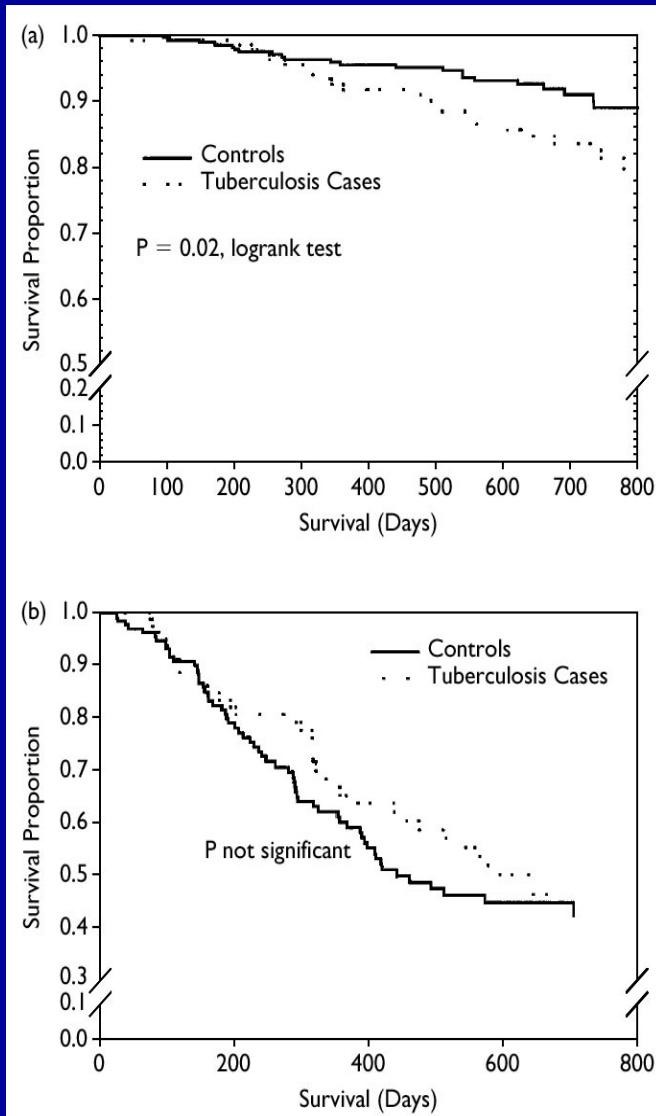


HSV-2 INCREASES HIV ACQUISITION AND TRANSMISSION

- HSV-2 increases risk of HIV acquisition
 - 2-fold overall increased risk in metaanalysis¹
- HSV-2 increases risk of HIV transmission
 - 5-fold increase in per-contact risk due to genital ulcer disease

¹Wald, JID, 2002

TB INCREASES RISK OF AIDS PROGRESSION AND DEATH

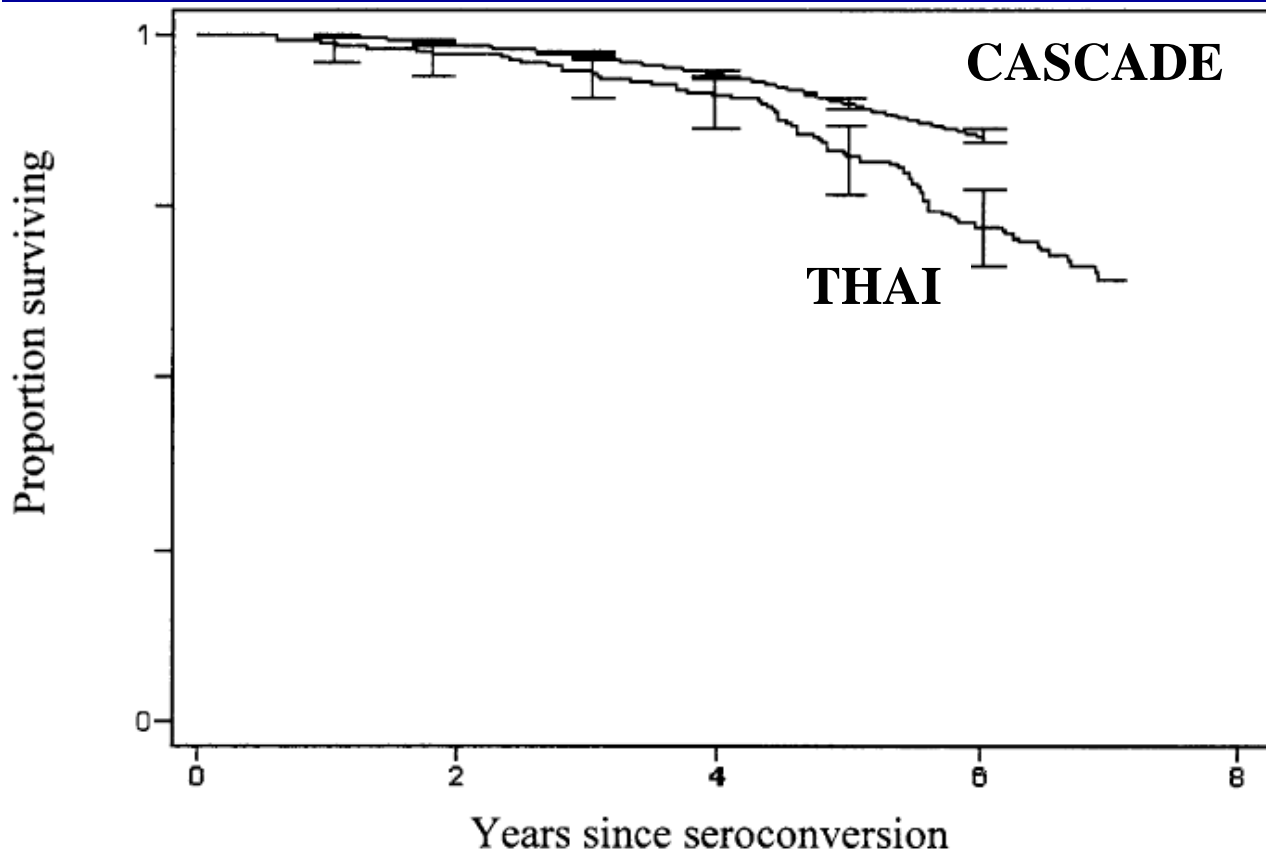


- Prospective cohort study in Kampala, Uganda

- 230 patients with TB/HIV 442 controls with HIV only

- 2 fold increase in mortality with TB/HIV

HIV DISEASE PROGRESSES FASTER IN A THAI SEROCONVERSION COHORT



- Prospective cohort study in Royal Thai Army
- 235 seroconversions
- Median time to AIDS 7.4 years

INTERVENTIONS

INTERVENTION: TREAT STI TO REDUCE HIV TRANSMISSION

EFFECTIVE

NOT EFFECTIVE

Site	¹ Mwanza Tanzania	² Rakai Uganda
Participants	12,500	14,000
Intervention	Syndromic Treatment	Treatment q10 months
Results	Decrease HIV by 38%	HIV unchanged

¹Grosskurth, Lancet, 1995

²Wawer, Lancet, 1999

NEW STUDY: WILL HSV TREATMENT REDUCE HIV TRANSMISSION?

3646 HIV- discordant couples



HSV-2/HIV co-infected persons



Randomize HIV/HSV-2 + persons w/ CD4 >250



Acyclovir 400 mg bid

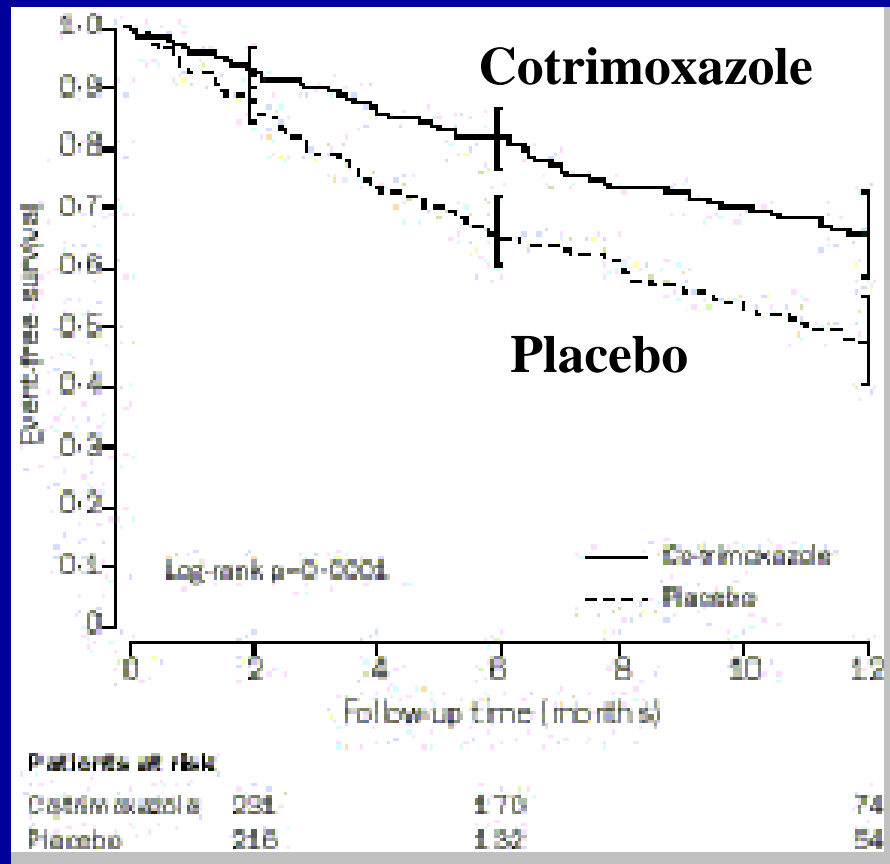


Placebo bid

1° endpoint: HIV infection in HIV-negative partners at 1 yr

Courtesy of C. Celum

INTERVENTION: COTRIMOXAZOLE TO REDUCE MORBIDITY AND MORTALITY



- 545 subjects in Abidjan
- Reduced risk for death or hospitalization in-cotrimoxazole arm
- Benefit over all CD4

Anglaret, Lancet, 1999

**INTERVENTION:
START ANTIRETROVIRAL
THERAPY EARLY**

ANTIRETROVIRAL THERAPY REDUCES TB INCIDENCE IN SOUTH AFRICA AT CD4 <350

ANTIRETROVIRAL THERAPY

<u>CD4</u>	<u>YES</u>	<u>NO</u>
• ALL	2.4*	9.7
• <200	3.4	17.5
• 200-350	1.7	12.0
• >350	2.0	3.6

*TB incidence per
100 person years

Badri, Lancet, 2002

PRACTICAL CONSIDERATIONS

Intermittent Preventive (IPT) Therapy for Malaria: Pregnant Women and Children

- “IPT –P” recommended for for pregnant women to prevent malaria, with emphasis on the first pregnancy
- “IPT-I” recommended for infants in “Expanded programs of immunization” (EPI) where a treatment dose of malaria is administered at the time of routine vaccination

CONFLICTING OR COMPLIMENTARY GUIDELINES?

For Malaria

For HIV

Policy

Intermittent Preventive Treatment (IPT)

Opportunistic infection prophylaxis

Drugs

Two doses of sulfadoxine-pyramethamine after quickening

Cotrimoxazole for all pregnant women after the first trimester

Issues

?

Cotrimoxazole +IPT?
Two doses IPT sufficient?
Cotrimoxazole only?
Adverse drug reactions?

?

RESISTANCE AND CROSS RESISTANCE

In Vitro

P. Falciparum exhibits cross resistance to trimethoprim and pyramethamine

In Vivo

Increasing drug resistance mutations in P. Falciparum isolates

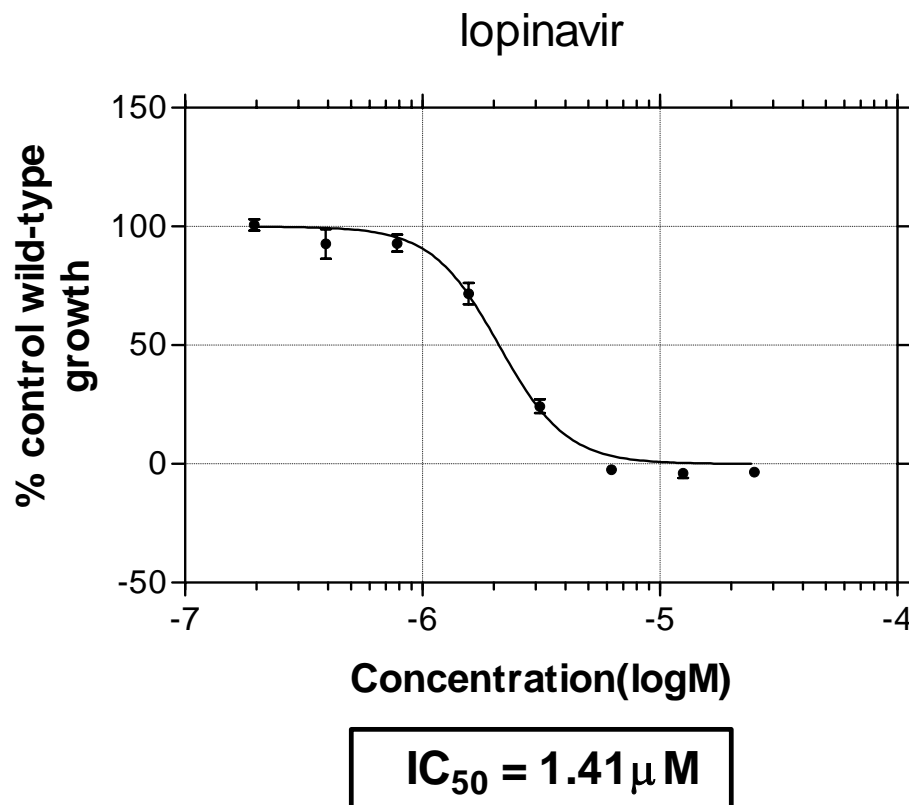
Clinical Response

10 fold higher failure rates to SP treatment with select (DHFR ARG 59 and DHPS Glu-540) resistance mutations

INTERACTIONS BETWEEN ANTIRETROVIRAL THERAPY AND MALARIA: WOULD PROTEASE INHIBITORS BE HARMFUL

- Protease inhibitors down regulate CD36 expression**
- CD36 binding of parasitized erythrocytes may protect against cerebral malaria**
- Macrophages are less effective in phagocytosing parasites in presence of protease inhibitor**

... OR POTENTIALLY HELPFUL?



- HIV-1 and *P. falciparum* contain aspartic proteases
- HIV-1 protease inhibitors inhibit *in vitro* growth at levels achievable in humans
- Serum levels of boosted lopinavir remain 5-10 fold above the IC₅₀ for *P. falciparum*

Courtesy of PARIKH AND ROSENTHAL

Take advantage of the high prevalence of infections as a point of entry into HIV care

“If HIV testing and counseling were available for all TB patients with appropriate linkages to care, TB control could recruit up to a half million persons with HIV per year which would go a long way to meet current therapy goals”

Implement cotrimoxazole prophylaxis and support for TB, malaria and sexually transmitted disease programs

**Cotrimoxazole could reduce bacterial infections,
PCP and malaria, HIV mortality and disease
progression**

**Aggressive STI programs could reduce HIV
transmission and disease progression**

**Stronger TB control programs will improve HIV
outcome**

IMPLEMENT ANTIRETROVIRAL THERAPY: IT IS THE BEST PROPHYLAXIS

Advocate for the least toxic, most affordable, reliable, co-formulated therapies for adults and children

Earlier treatment of HIV (ie CD4 >200) should be evaluated

Identify regimens that treat HIV and hepatitis