Interaction of HIV and Malaria

Malaria Branch
Division of Parasitic Diseases
National Center for Infectious Diseases

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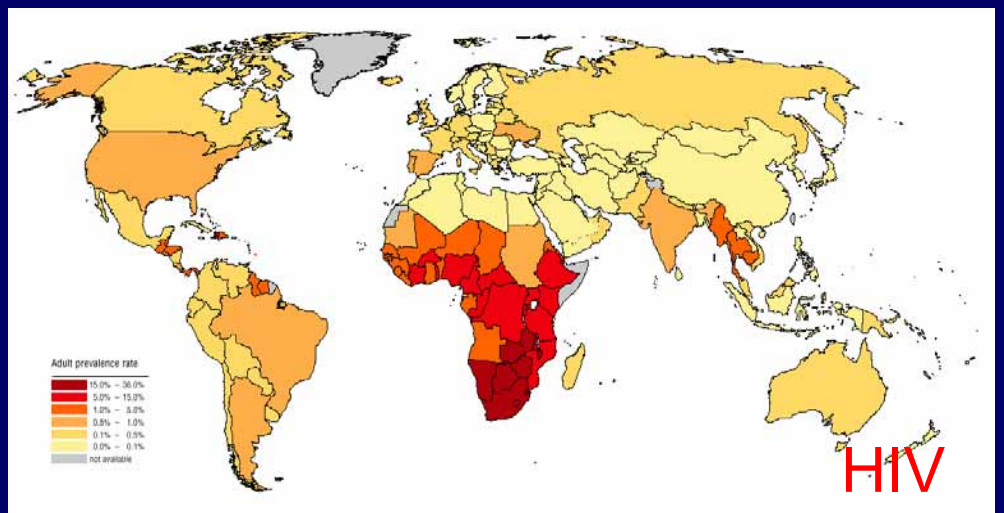
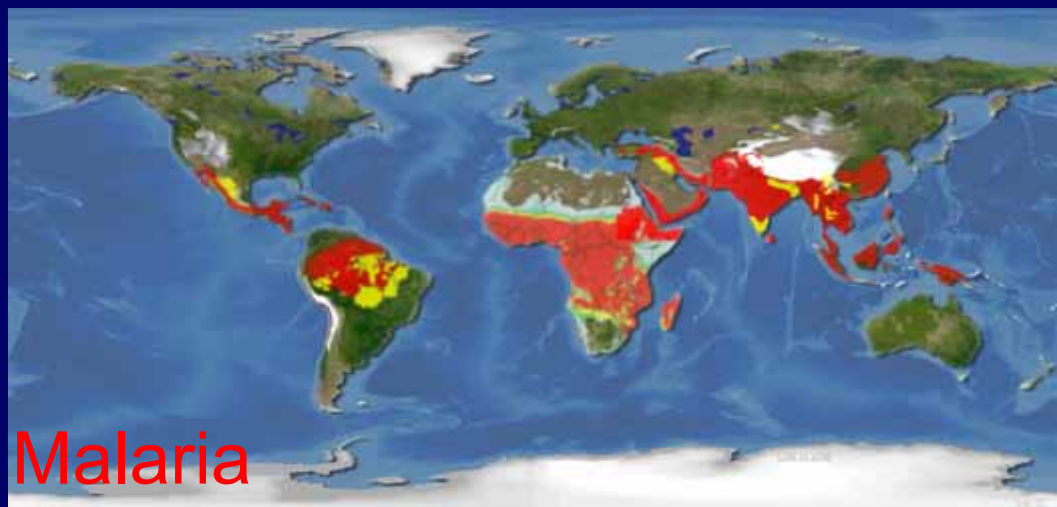
Malaria and HIV disease in sub Saharan Africa

- Malaria and HIV are leading causes of morbidity and mortality, particularly in sub Saharan Africa
- Both diseases are highly endemic and have a wide geographic overlap
  - A small effect of malaria on HIV or vice-versa could have substantial population-level implications



HIV


Malaria

Malaria and HIV disease in sub Saharan Africa

- Background on malaria
- What we do and don't know:
  - Malaria <-> HIV interaction
  - Science & program

Scope of the Malaria Problem:

- Malaria is the most common life-threatening infection
  - 1 million deaths/yr
  - 300-500 million infections/yr
- ~90% of these deaths occur in sub-Saharan Africa
- most victims are children <5 yrs
- Pregnant women are also especially vulnerable.

MALARIA 101

Human Malaria is caused by one of 4 protozoan parasites:

Plasmodium falciparum

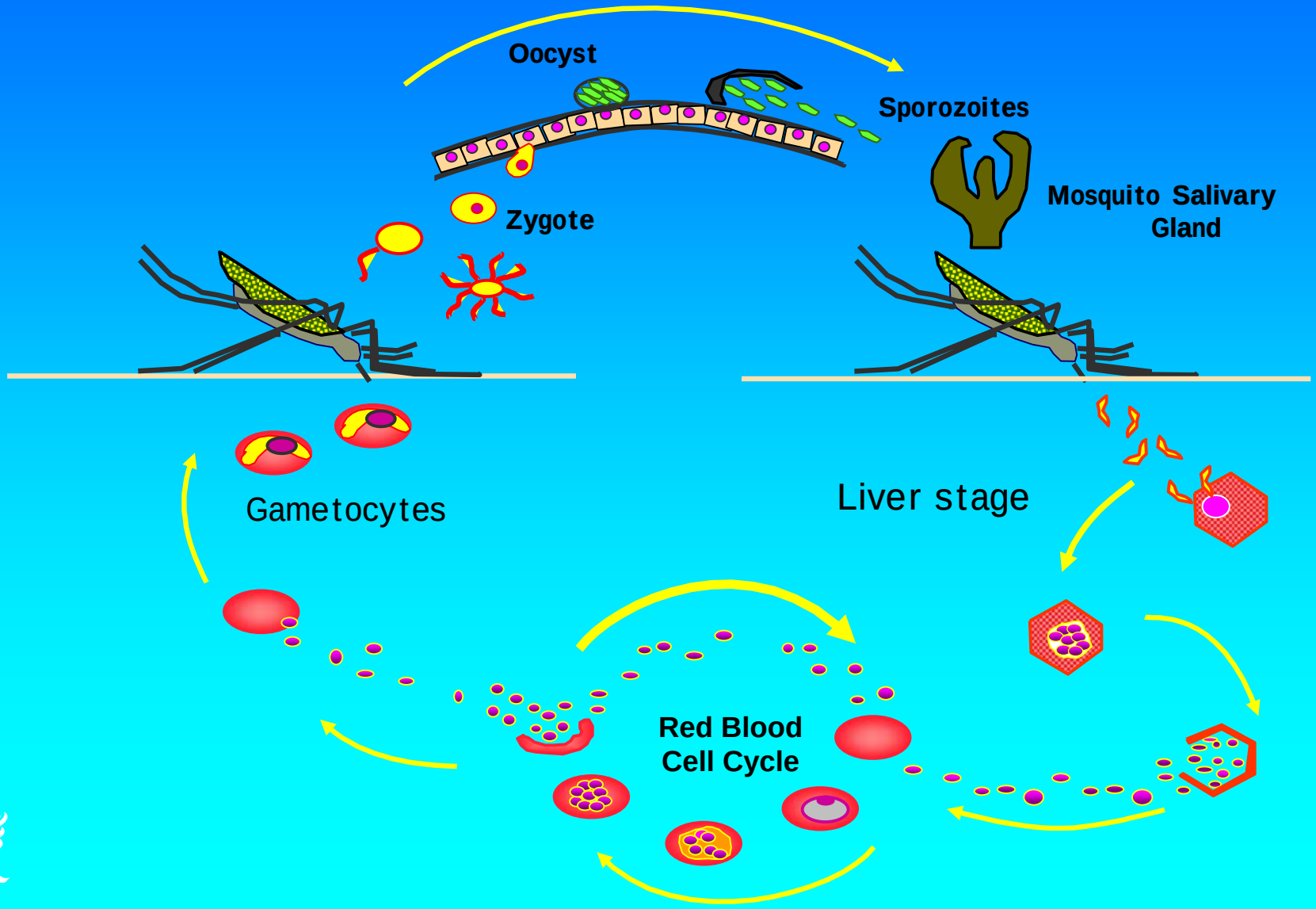
Plasmodium vivax

Plasmodium ovale

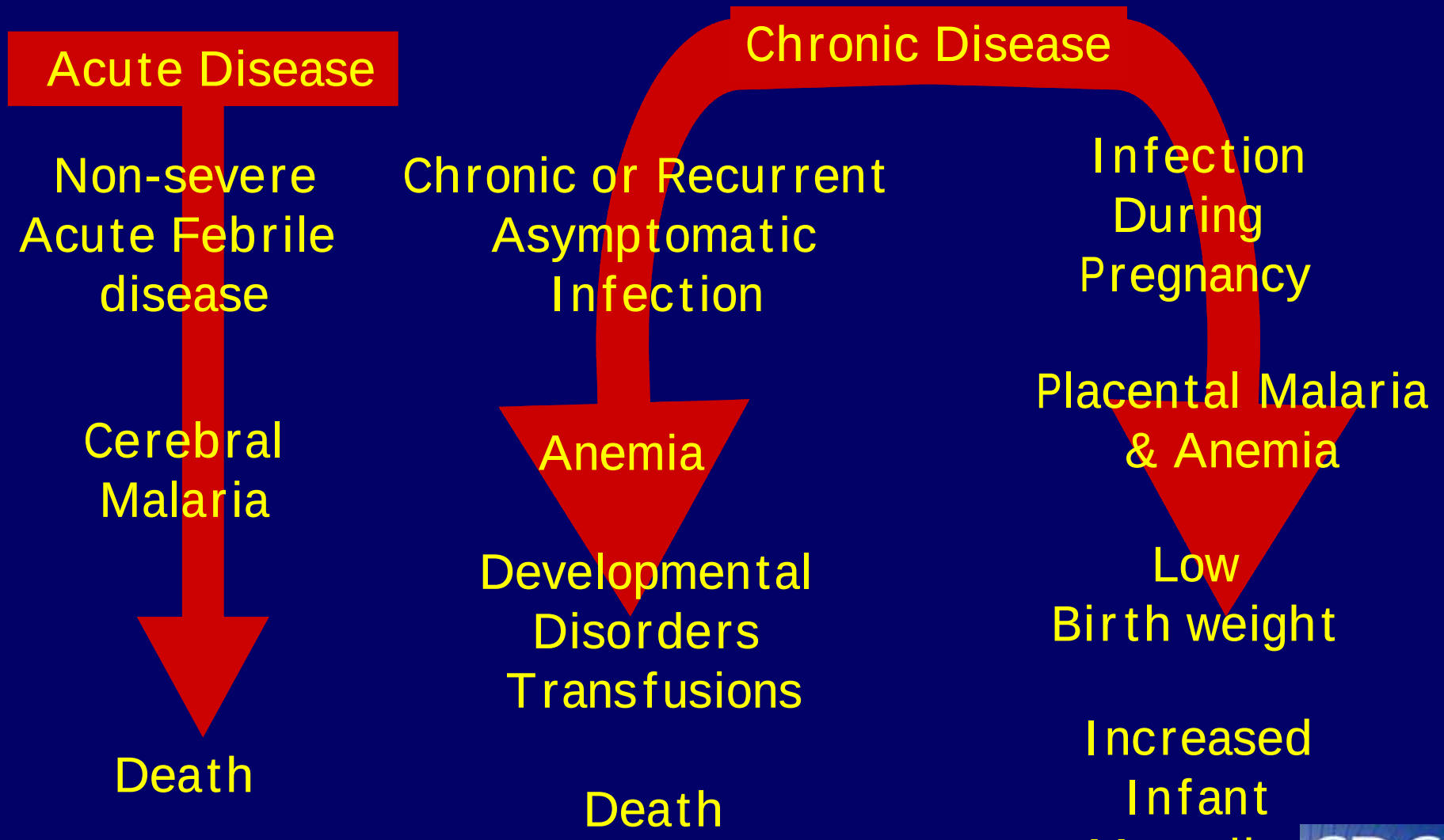
Plasmodium malariae

Malaria is transmitted through the bite of an infected female *Anopheles* mosquito

Malaria Life Cycle



MALARIA 101 – clinical syndromes



Effective Malaria Interventions Include:

- Providing prompt access to curative treatment
- Preventing and controlling malaria during pregnancy
- Promoting the use of insecticide-treated mosquito nets
  shown to reduce all-cause child mortality by 20%-25%

Malaria Interventions - Costs

- Insecticide-treated mosquito nets: $2.50 -- 5.00
- Malaria treatment:
  - CQ, SP, AQ, Lap-Dap: $0.10 – 0.50
  - Artemisinin-combinations: $2.00 or more
- Intermittent Preventive Tx in preg: $0.35

HIV and Malaria Interaction

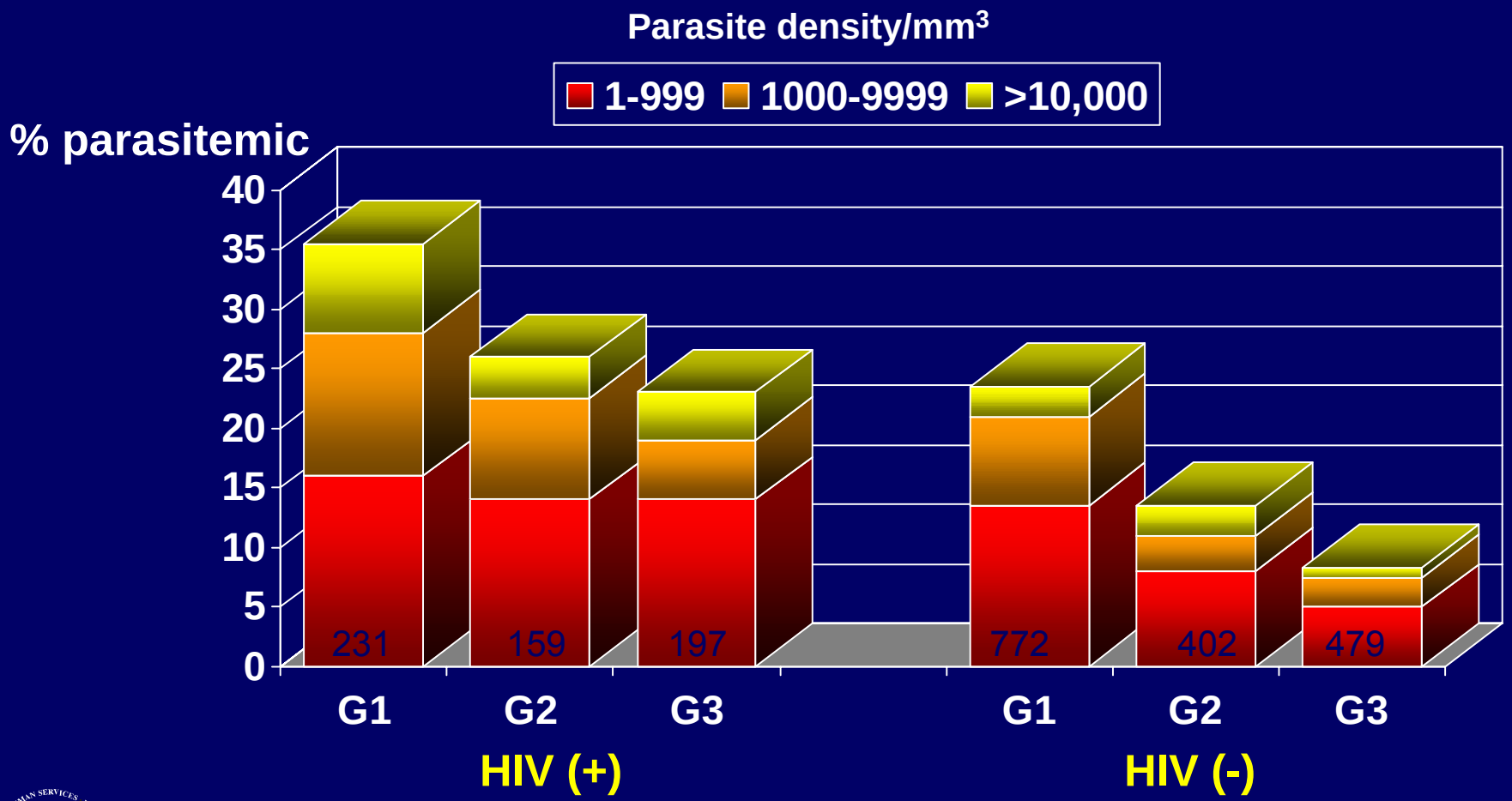
Early studies – mid/late 1980s

- HIV transmission modes: mosquitoes? No
- Does HIV make malaria worse?
- Does malaria make HIV worse? "probably No"
  - Malaria is not an "opportunistic infection"
  - Curious because CD4-dependant immune response is thought to be important for malaria
- Malarial anemia → blood transfusion → HIV infection

Recognition of the effect of HIV on malaria in pregnant women

- Malawi study (1987-1991):
  - During pregnancy, malaria was more common and of higher density in HIV(+) vs. HIV(-) women
  - These findings were repeated in other studies and countries -Malawi (2 sites), Kenya (3), Rwanda (1)

Placental parasitemia by HIV status and pregnancy number, Kenya



Total n = 2263

Summary RR = 1.63 (1.41-1.89), p<0.001

Current knowledge
Malaria and HIV interactions

- Does HIV make malaria worse?
- Does malaria make HIV worse?

- Anemia and Blood safety
- Pregnant women and their fetus/newborn
- Non-pregnant adults
- Children
- Program overlap

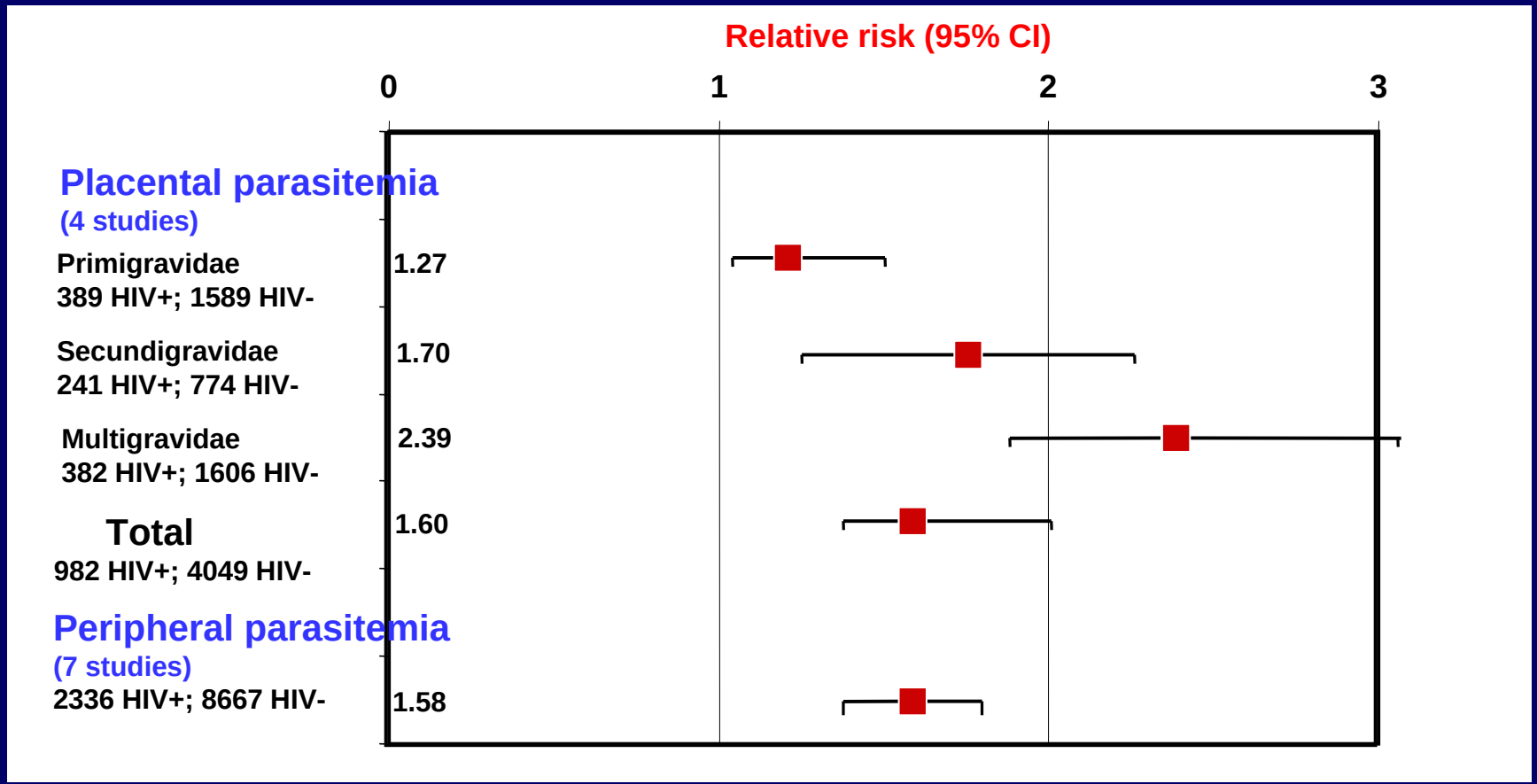
Anemia and Blood Safety

- Not much new to report
  - Remains a serious problem
  - Despite available technology, universal blood screening is not yet achieved, especially in some high HIV prevalence settings
  - Important unmet needs include:
    - anemia prevention
    - clarity on best criteria to limit transfusions except when truly needed
    - universal and quality-controlled HIV testing

Pregnant women and their fetus/newborn

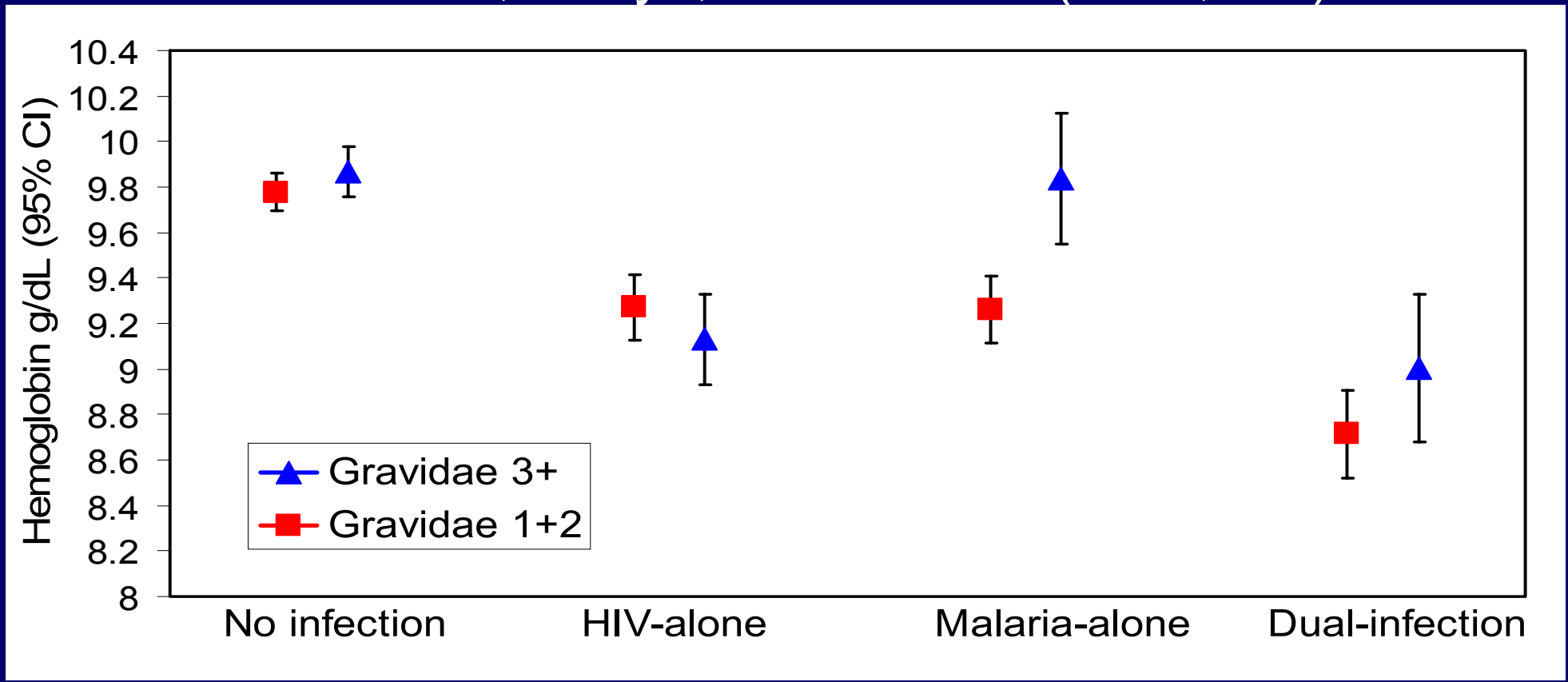
- HIV does make malaria in pregnancy worse
  - More and higher density malaria, more illness, more anemia, more low birth weight
- Malaria may make HIV worse
  - Higher HIV viral load
  - ? impact on Mother-to-Child Transmission (MTCT)

HIV-associated Risk of Placental and Peripheral Parasitemia in Pregnant Women



Hemoglobin Level by HIV Status Malaria and Gravidity

Kisumu, Kenya, 1996 –1999 (N= 4,608)



HIV and Malaria:

Associated Reductions in Mean Birth Weight (grams)

Kisumu, Kenya, 1996-99 (N=2,466)

	Primi-gravidae	Multi-gravidae
HIV alone	44 (-32-112)	138 (78-199)
Malaria alone	145 (82-209)*	8 (-71-88)
Dual infection	206 (115-298)*	161 (63-259)

*In Primigravidae, both malaria (RR 2.24, p=0.003) and dual infection (3.45, p<0.001) associated with significant increased relative risk of LBW (< 2,500 grams) compared with uninfected women

Effect of HIV on Malaria illness in pregnancy

Kisumu, Kenya, 1996-1999

N=2539	Prevalence		RR (95% CI)
HIV (24.9%)	HIV+	HIV-	
Clinical malaria	9.4%	3.1%	3.01 (2.36-3.85)
Hospitalization (all causes)	4.3%	2.7%	1.59 (1.16-2.20)

van Eijk et al, AIDS, 2003

Does HIV make Malaria worse? Pregnant women, fetus, and newborn

- In western Kenya, where HIV prevalence in pregnant women exceeds 25%
  - HIV accounts for one-quarter of all malaria infections in pregnancy
  - HIV contributes to anemia, low birth weight, and poor infant survival (in both HIV+ and HIV- infants)

Nearly one-half of all malarious sub-Saharan African countries have HIV seroprevalence in pregnant women in excess of 10%

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Pregnant women and their fetus/newborn

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Malaria's impact on HIV Replication

- Malaria antigens induce HIV-1 replication in-vitro
  (Xiao et al, JID, 1998)

- HIV transgenic mouse model -- Murine malaria triggered increased P24 antigen production
  (Freitag, JID 2001)

Malaria and HIV viral load in pregnancy

Dar es Salaam, Tanzania (Kapiga et al, JAIDS, 2002):
Peripheral viral load >2-fold higher in parasitemic pregnant women

Kisumu, Kenya (Ayisi, in press)
Peripheral viral load 1.4-fold higher in parasitemic women (p=0.096);
↑ viral load with ↑ parasite density

Blantyre, Malawi (Victor Mwapasa, 10th CROI, Boston, 2003)
Placental viral load 2.4-fold higher in HIV+ women with placental malaria than in those without malaria

Mangochi, Malawi (Tkachuk et al. JID 2001)
Significant 3-fold higher CCR5 mRNA expression in placentas of malaria-infected women

Malaria contribution to HIV-MTCT?

Malawian pregnant women (Bloland, AJTMH 1995)

- Malaria and HIV co-infection
  - Infants born to dually infected mothers had increased post-neonatal mortality, beyond independent risk associated with exposure to either maternal HIV or placental malaria
  - Increased viral load or altered placental architecture ⟶ increased MTCT?

Malaria contribution to HIV-MTCT?

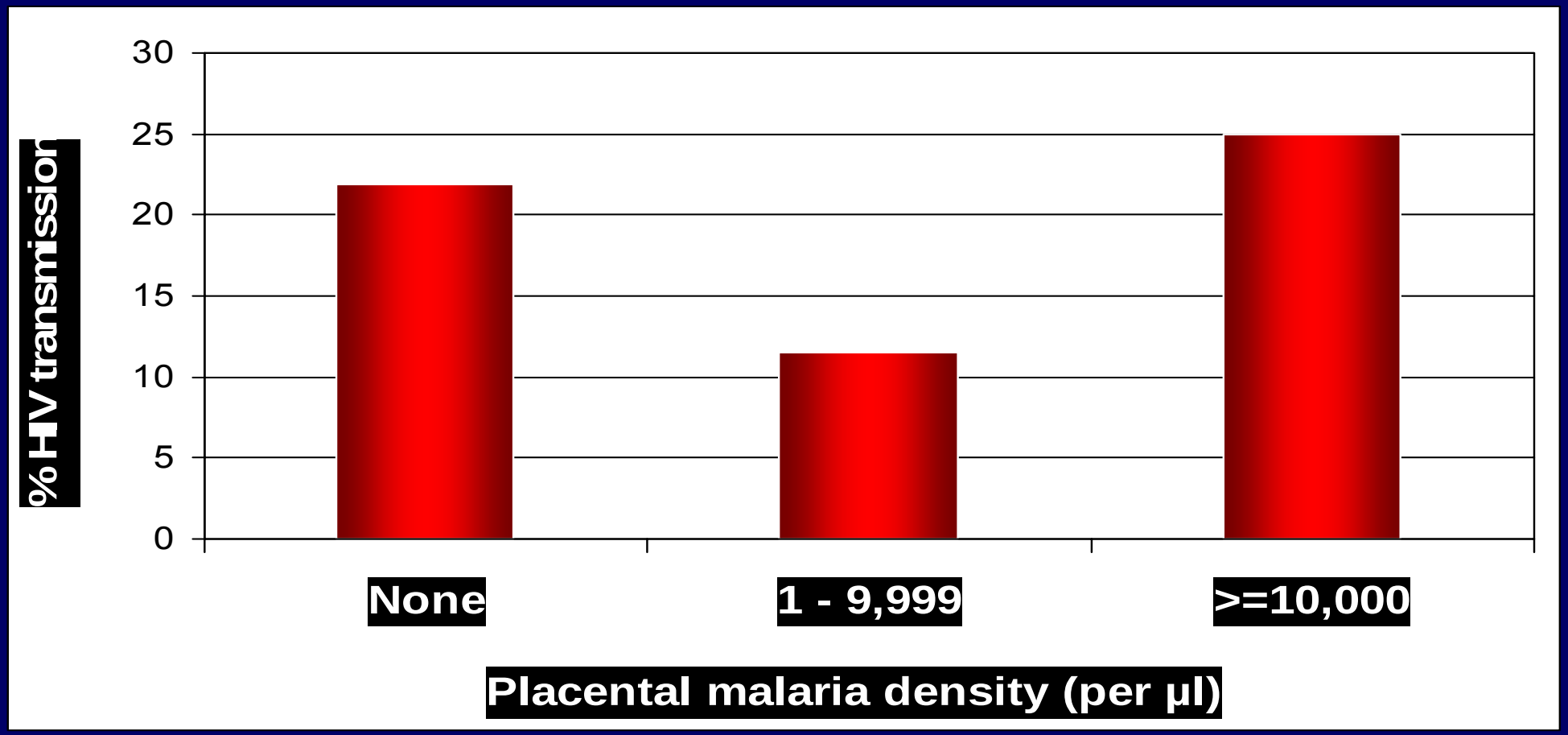
Bloland et al.	>> Infant mortality
Verhoeff et al.	<< Infant mortality
St Louis et al.	No association
Brahmbhatt et al.	RR 2.9 (1.1 -7.5)
Inion et al.	RR 0.6 (0.2-1.7)
Mwapasa et al.	RR 1.2 (0.7-2.3)
Ayisi et al.	RR 0.4 (0.3-0.7)

Placental Malaria & HIV-MTCT

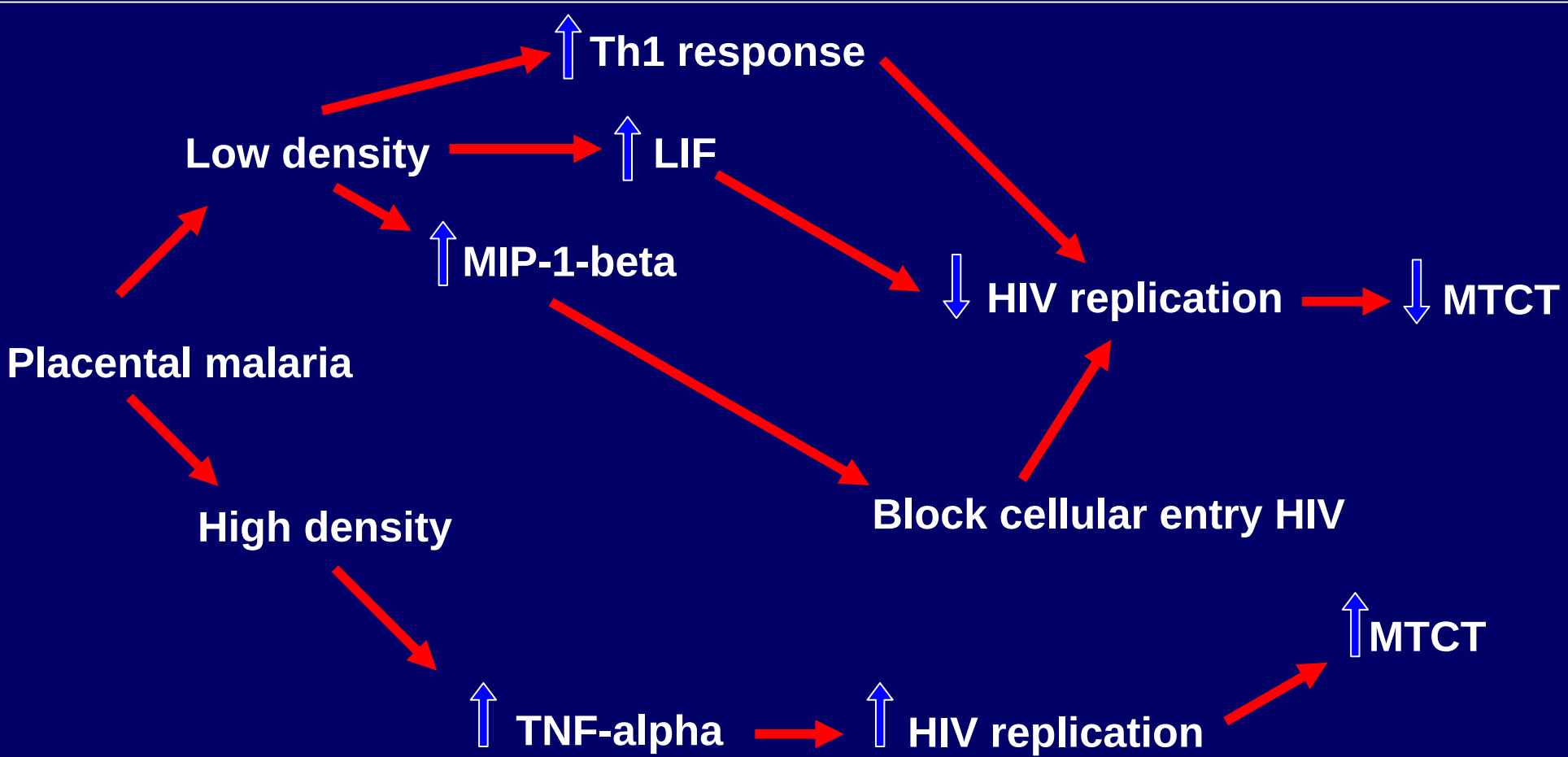
Kisumu, Kenya, 1996-1999
Ayisi et al, in press EID

- 512 mother-infant pairs with known perinatal HIV transmission status
  - 128 women (25%) had placental malaria
  - 102 infants (20%) acquired HIV perinatally by 4 months (HIV DNA PCRs).

Perinatal HIV Transmission by Placental Malaria Density
Kisumu, Kenya 1996



Potential Immunologic Basis: Effect of Malaria on MTCT



Conclusions: Malaria & HIV during pregnancy

- Some clear interactions
  - Preventing/managing placental malaria and HIV would reduce maternal anemia and low birth weight
- Some unclear interactions that require characterization
  - Will clearing placental malaria affect MTCT ?

Non-pregnant adults

- HIV with immune compromise (CD4 depletion) does make malaria in adults worse
  - More malaria, higher density parasitemia, more illness, more severe disease
  - Reduced efficacy of antimalarial therapy?
- Malaria may make HIV worse
  - Higher HIV viral load
  - Impact on clinical illness?; survival?; transmission?

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Impact of HIV on malaria in non-pregnant adults

- Advanced HIV immunosuppression is associated with higher density parasitemia and more clinical illness in adults
  - French et al, AIDS 2001; Whitworth et al. Lancet 2000; Francesconi et al, AIDS 2001.
- Advanced HIV immunosuppression is also associated with poorer response to malaria treatment
  - Shah S et al, personal communication 2004

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Malaria contributes to increased HIV Viral Load

- Several intercurrent infections have been shown to increase HIV replication *in vivo:*
  - *Mycobacterium tuberculosis*
  - *Mycobacterium avium* complex
  - *Pneumocystis carini*
  - *Herpes simplex*
  - STIs?

Studies of the effect of malaria on HIV RNA levels

- Malawian adults with acute malaria
  - 7-fold increase in HIV-1 viral load
  - Reversible with treatment (in some patients)
  - Induction of HIV-1 replication in CD14 macrophages

    Hoffman, 1999; Pisell, 2002

- Follow-up study in Malawian adults

  Kublin et al, 2003 Am Soc Trop Med Hyg Mtg

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Clinical & public health significance

- Individual
  - Brief increase in viral load due to malaria may worsen clinical prognosis
- Population
  - Higher viral load associated with higher infectivity
  - Probability of HIV transmission may be elevated around a malaria episode, especially during the lag time post-malaria before RNA levels return to baseline

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Infants and Children

- Difficult to study
  - Low incidence/prevalence of HIV in this group
  - Already highly susceptible to malaria and HIV-associated immune deficiency may not make this susceptibility much worse

- Dual Malaria and HIV is associated with poor outcome
  - Anemia
  - Survival?

Malaria in HIV+ infants

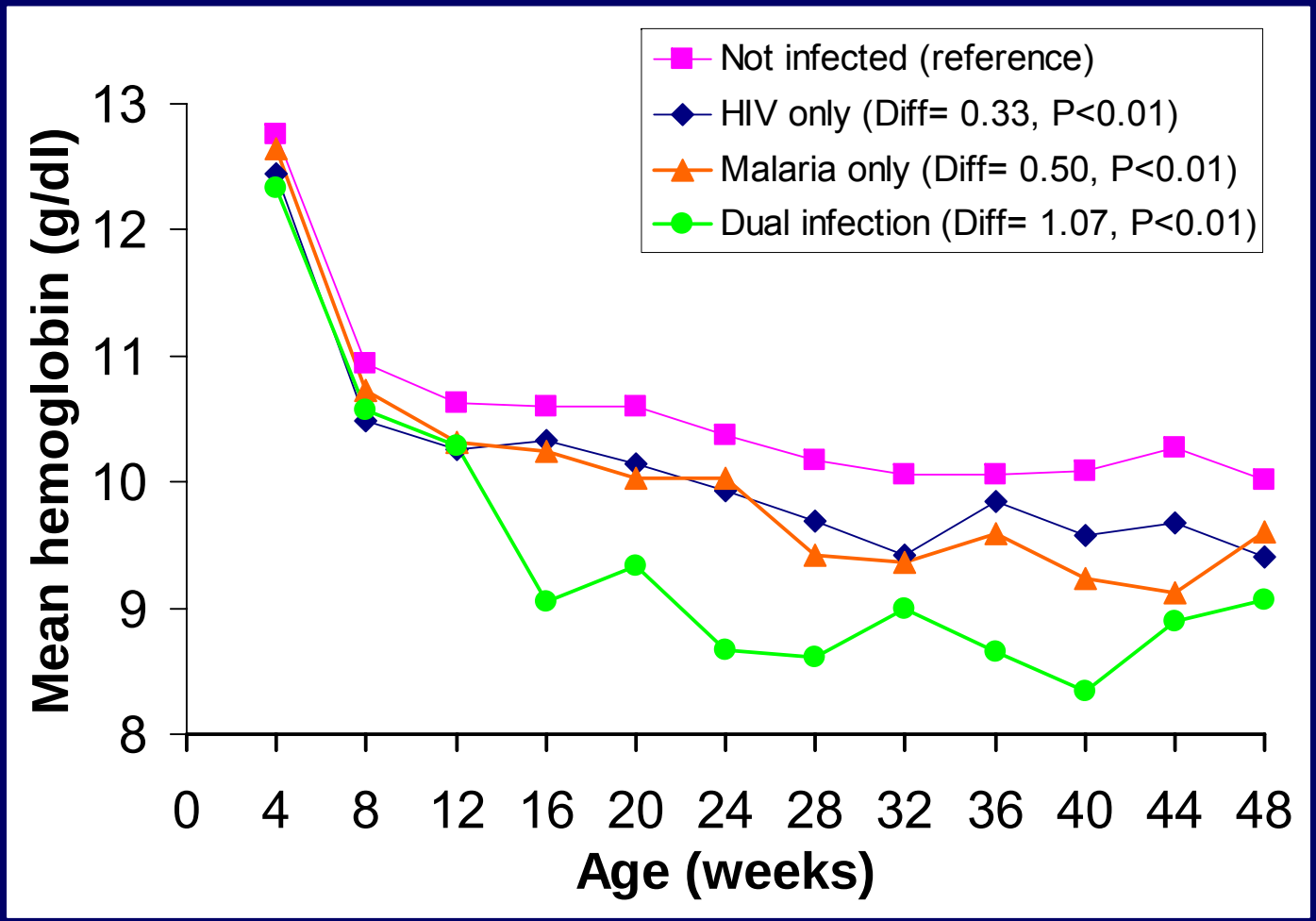
Kisumu, Kenya, June 1996-April 2000

- HIV+ infants were not at risk of
  - more malaria parasitemia
  - higher parasite density
- However, if parasitemic, were at risk to:
  - be febrile
  - have severe anemia
  - have splenomegaly
  - be admitted to the hospital

Source: van Eijk et al, unpublished

Hemoglobin in infants by HIV status and malaria

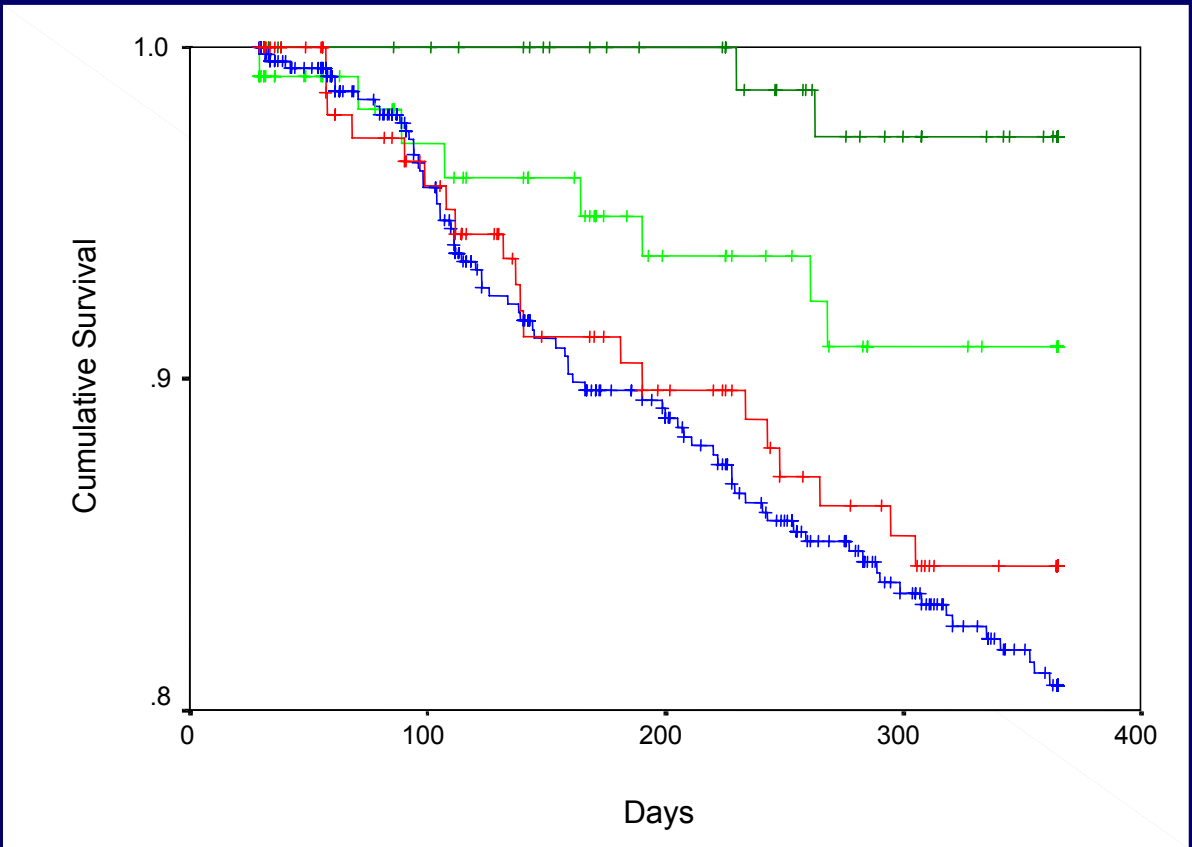
Kisumu, Kenya, June 1996-April 2000



Source: van Eijk et al, AJTMH, 2002

Post-neonatal Infant mortality by maternal HIV-status and placental malaria

Kisumu, Kenya, June 1996-July 2001, N=866



A: No infection (N=96)

B: placental malaria only (N=117)

C: Dual infection (N=159)

D: HIV only (N=494)

Source: van Eijk et al, unpublished

Malaria and HIV biologic interactions – summary 2004

- HIV-associated immunosuppression contributes to more and worse malaria and it's consequences in adults, pregnant women, and children.
- Malaria contributes to stimulus of HIV replication and possibly(?) to its consequences: disease progression, transmission in adults, and MTCT.
- Co-infection with Malaria and HIV in pregnant women contributes to anemia, low birth weight,and their risk for poor infant survival.
- Malarial anemia in children too frequently requires blood transfusion and may still lead to HIV transmission

Malaria & HIV program overlap

- **Population overlaps**
  - Anemic children; pregnant women; adults with ⇓CD4
- **Intervention overlaps**
  - Diagnostics
  - Treatments: complexity and costs of Tx, resistance
    - Protease inhibitors block endothelial CD36 binding of malaria-infected red blood cells
    - OI prophylaxis with co-trimoxazole (an antimalarial)
  - HIV-infected persons need malaria prevention
- **Site of activity overlaps**
  - GFATM and Country Coordinating Mechanisms
  - Antenatal clinics; under-5 clinics; communities, VCT sites? ARV delivery systems

Malaria & HIV program overlap

- **Recommendations for coordinated program action**
  - Jointly strengthen health service delivery:
    - Laboratories
    - Antenatal and delivery care
      - ITNs & IPT for malaria; VCT & MTCT prevention
    - Child care – anemia prevention
- **Specific Interventions**
  - ITN distribution with ARV delivery
  - Use highly efficacious antimalarials in HIV+ persons with malaria infection
  - HIV+ persons on cotrimoxazole for OI prophylaxis who get malaria should receive highly effective antimalarials

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