



# Antimalarials for eradication

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# Use of antimalarials



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- Therapy
- Prophylaxis
- Intermittent preventive therapy in pregnancy
- Intermittent preventive therapy in infants
- Seasonal intermittent preventive therapy
- Mass drug administration

And something else ...

# The ideal antimalarial for eradication



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- Safe
- Well tolerated
- Efficacious and effective
- No population restriction
- Cheap
- Active against all Plasmodium species
- Active against all stages
- Active against hypnozoites

# The ideal antimalarial for eradication



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- One dose
- Oral administration
- No resistant parasites present
- Refractory to resistance development
- Fast acting
- Long half life
- Matching pharmacokinetics

# Single Encounter Radical Cure and Prophylaxis



Eliminate the human reservoir of infection

Single patient encounter

Radical cure leading to elimination of persistent asexual blood-stage forms and hypnozoites

Prophylaxis to prevent reinfection for at least 1 month

Suitable for mass drug administration

(PLOS Medicine 2011)

?



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Which drugs are there

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# List of antimalarials (1)



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## Quinolines and combination of quinolines

- quinine
- quinine-clindamycin
- quinine-doxycycline
- quinine-tetracycline
- quinine-sulfadoxine-pyrimethamine
- quinidine
- chloroquine
- chloroquine-sulfadoxine-pyrimethamine
- chloroquine-azithromycin
- chloroquine-doxycycline

# List of antimalarials (2)



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## Quinolines and combination of quinolines

- chloroquine-clindamycin
- amodiaquine
- amodiaquine-sulfadoxine-pyrimethamine
- mefloquine
- mefloquine-sulfadoxine-pyrimethamine
- ferroquine
- piperazine
- AQ 13
- pyronaridine



# List of antimalarials (3)



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## 8-aminoquinolines

- primaquine\*
- bulaquine\*
- tafenoquine\*

## Phenanthrene-methanol

- halofantrine

# List of antimalarials (4)



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## Phenothiazine and combinations

- methylene blue\*
- methylene blue-chloroquine
- methylene blue-amodiaquine
- methylene blue-artesunate
- methylene blue-amodiaquine-artesunate

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# List of antimalarials (5)



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## Endoperoxides and combinations

- dihydroartemisinin
- dihydroartemisinin-azithromycin
- dihydroartemisinin-mefloquine
- dihydroartemisinin-piperaquine
- artesunate
- artesunate-mefloquine
- artesunate-amodiaquine
- artesunate-sulfadoxine-pyrimethamine
- artesunate-chlorproguanil-dapsone

# List of antimalarials (6)



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## Endoperoxides and combinations

- artesunate-proguanil-dapsone
- artesunate-chloroquine
- artesunate-atovaquone-proguanil
- artesunate-azithromycin
- artesunate-fosmidomycin
- artesunate-quinine
- artesunate-pyronaridin
- artesunate-ferroquine
- artesunate-clindamycin

# List of antimalarials (7)



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## Endoperoxides and combinations

- artemether
- artemether-lumefantrine
- arteether
- artemisinin
- artemisinin-naphthoquine
- arterolane (OZ277)
- arterolane-piperaquine
- artefenomel (OZ439)
- artemisone
- trioxane (CDRI 97-78)

# List of antimalarials (8)



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## Antibiotics and combinations

- pyrimethamine
- sulfadoxine-pyrimethamine
- chlorproguanil-dapsone
- trimethoprim-sulfamethoxazole
- clindamycin
- fosmidomycin-clindamycin

# List of antimalarials (9)



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## Naphoquinone combination

- atovaquone-proguanil

## Other new compounds

- spiroindolone: KAE609\*
- imidazolopiperazine: KAF156\*

?



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Which drug is closest to ideal

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# Tafenoquine



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Lancet 2000

426 children divided in 5 groups in Gabon

placebo and 4 different doses of tafenoquine  
(31 mg, 62 mg, 125 mg and 250 mg for 3 days)

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# Tafenoquine



Tafenoquine was safe and well tolerated in G6PDH non-deficient subjects

After 2 months of follow-up:

In the placebo and 31 mg dose groups:  
20 % of subjects had parasites

In the 125 mg and 250 mg dose groups:  
No subject had parasites

# A different use of antimalarials for eradication



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## Chemoattenuation

Controlled human parasite infection under  
chemoprotection

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# A different use of antimalarials for eradication



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## Desired characteristics

- Safe and well tolerated
- Suppress breakthrough
- 100% efficacious
- Prolonged chemotherapeutic activity
- Support development of immunity
- Stage specificity
- Immune modulation
- Revert immunosuppression in malaria-endemic areas

# Chemoattenuation



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NEJM 2009

45 bites of infected mosquitoes per subject under chloroquine prophylaxis

Protection against malaria

# Chemoattenuation



- **Design:** Single center, randomized, placebo-controlled, double-blinded, sporozoite (SPZ) challenge dose finding trial under chemoprophylaxis and subsequent **C**ontrolled **H**uman **M**alaria **I**nfection (CHMI)
- **Population:** Healthy, adult, malaria-naïve

# TÜCHMI-002 – design



## Schedule:

	Start	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Group A1	3200 SPZ	3200 SPZ	3200 SPZ		CHMI		
Group A2		12800 SPZ	12800 SPZ	12800 SPZ		CHMI	
Group A3			51200 SPZ	51200 SPZ	51200 SPZ		CHMI

# TÜCHMI-002 – results



Dose dependent and very good efficacy

Good safety and tolerability

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# Chemoattenuation of malaria parasites



An attractive way towards eradication

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