Press Dossier

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London

Combination therapy in global strategy for treatment of malaria

Every year, malaria kills 1-2 million people. 90% of deaths occur in sub-Saharan Africa. The disease is present in over 100 countries and threatens 40% of the world's population. Malaria remains the single largest cause of death for children under five in Africa. Malaria has a socio-economic impact: patients are often bedridden and incapable of carrying out normal daily activities.

Treatments exist but, in recent decades, drugs such as chloroquine or sulphadoxine-pyrimethamine have become increasingly ineffective due to drug resistance. Resistance to chloroquine now reaches over 90% in many parts of Africa. The spread of resistance is a serious threat to global public health (see map below).

Source: WHO

Scientists and doctors agree that the most effective treatment against malaria is a combination of drugs using artemisinin derivatives, highly potent extracts of the Chinese plant Artemesia annua. This **Artemisinin-based combination therapy (ACT)** is the quickest and most reliable way of clearing malaria infection, and is very well tolerated. Using a combination of drugs shortens the treatment course.

The World Health Organization (WHO) now actively encourages malaria-endemic countries to switch to ACT, and many of them are starting to do so. Overall, 40 countries in the world have included ACT in their malaria treatment protocols and a further 14 are considering doing so.

Why the need for fixed-dose combinations?

Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, patients might take only of one the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of resistance. Fixed-dose combinations (FDC's) combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs in the right

dose.

WHO recommends four therapeutic ACT options for malaria. These include:

- Artesunate – SP
- Artemether-lumefantrine
- Artesunate-amodiaquine
- Artesunate-mefloquine

So far are available only a co-blister artesunate/amodiaquine (Arsucam®) and a fixed-dose ACT artemether and lumefantrine (Coartem®). Although the latter is extremely effective, it needs to be taken with a fatty meal, can cause gastric side-effects, and is relatively expensive. New fixed-dose combinations are urgently needed to offer endemic countries, patients and doctors a wider range of treatment options adapted to their needs.

The Drugs for Neglected Diseases Initiative (DND*i*) is a non for profit drug development initiative focused on developing new tools for neglected diseases. To address the gap in new effective malaria tools, DNDi set up a Fixed-dose Artesunate Combination Therapy or "FACT Project", in association with the UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases (WHO/TDR). The "FACT" Malaria project brings together academics, public and private partners from around the world to develop FDC's for artesunate-amodiaquine and artesunate-mefloquine.

Independently, sanofi-aventis' Impact malaria initiates the development of the same combination.

DNDi and France's leading pharmaceutical company sanofi-aventis have teamed up to develop the artesunate-amodiaquine (AS/AQ) fixed dose combination which should be ready for registration in 2006. Treating infants and children for malaria is one of the key public health challenges. For this reason, AS/AQ will also be made available in special paediatric formulations to treat infants, children and teenagers.

To develop the artesunate-mefloquine FDC, DNDi is working with Far Manguinhos of Brazil.

Advantages of the new artesunate-amodiaquine fixed-dose combination

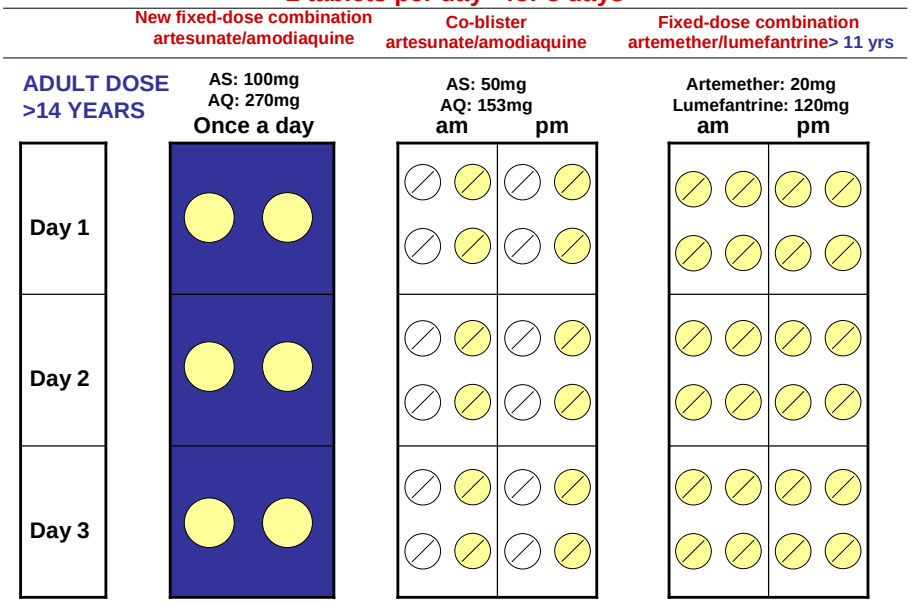
The use of a fixed-dose combination, in strengths adapted to the patients' ages, will allow a simple treatment of just three days, with a single daily administration of two tablets. The advantages are manifold:

- Rapid effect
- High cure rate (over 90%)
- Reduction of potential for transmission (less infective parasite in the blood)
- Ease of use (which increases compliance and therefore treatment effectiveness)
- Coverage of the whole population at risk (treatment can be used in both children and adults)
- Prevention of resistance and therefore further reduction of transmission
    - Cheaper than buying combination of separate tablets or blister pack.

EASIER TO USE

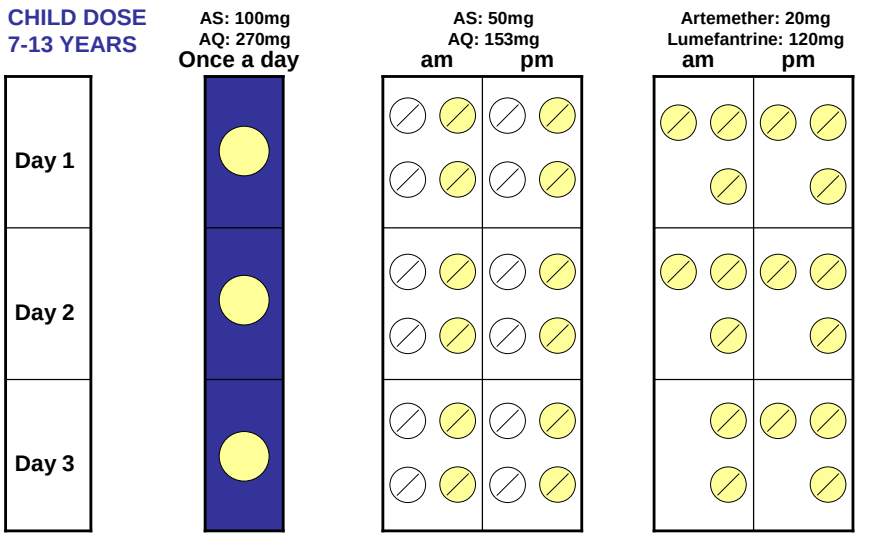
Simplifying malaria treatment for adult

2 tablets per day - for 3 days



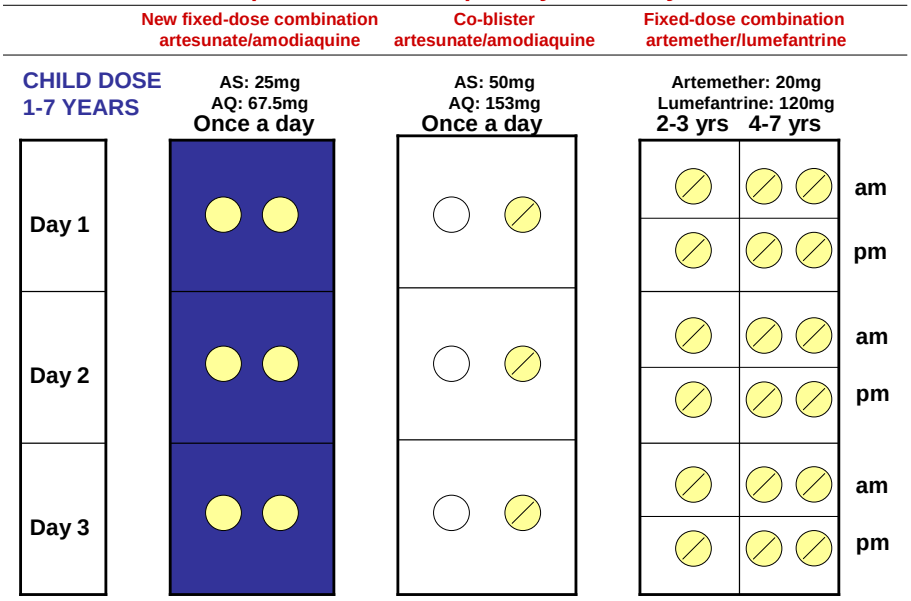
Simplifying malaria treatment for 7-13 yrs

1 tablet per day - for 3 days



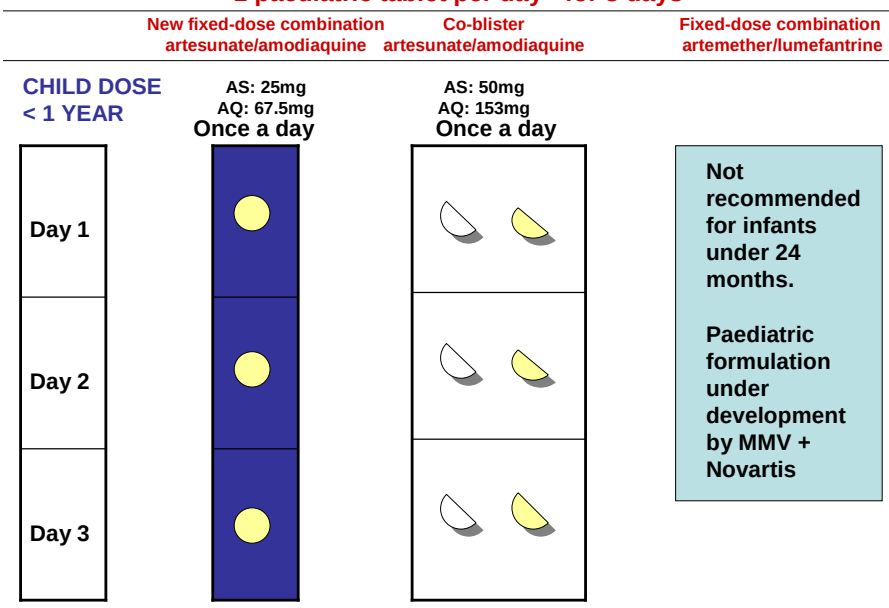
Simplifying malaria treatment for under 7s

2 paediatric tablets per day - for 3 days



Simplifying malaria treatment for infants

1 paediatric tablet per day - for 3 days



The collaboration between sanofi-aventis and DNDi

DNDi and sanofi-aventis are collaborating closely on industrial, preclinical and clinical product development to optimise the quality of the drug and to expedite its availability.

Product development by sanofi-aventis
Following the signing of the agreement, sanofi-aventis and DNDi exchanged product data in their possession. Sanofi-aventis will carry out the agreed development programme, which takes into account available findings and comprises ongoing work as well as new studies. The formulation chosen is that developed by DNDi.

In the months to come, DNDi will pursue the pharmaceutical and clinical investigations and sanofi-aventis will carry out the preclinical, clinical and industrial studies.

Drug registration
The development studies will be used to compile the marketing authorisation application. Sanofi-aventis will be responsible for applying for WHO prequalification and registering the drug with the regulatory authorities of the countries concerned. The aim is to submit the first marketing authorisation applications by late 2005/early 2006.

Sanofi-aventis will make the drug available at cost price in the public sector
Sanofi-aventis has agreed to make the product available at cost price to the national health services of the countries concerned, NGOs, and international organisations.

This new co-formulation will be less expensive than existing combinations containing artemisinin derivatives since it combines two well-known active ingredients that are already widely used in monotherapy and in two-tablet blister packs.

A target price of less than one dollar for adults and 50 cents for children is envisaged on the basis of WHO market projections and within the framework of the cost price strategy[1] of sanofi-aventis. This goal will only be achieved if international organisations provide financial aid to the countries concerned to enable them to implement the changes required for malaria treatment, thereby stabilising the raw materials market. This price will therefore greatly reduce the budgetary impact of malaria treatment worldwide.

[1] The cost price must enable sanofi-aventis to cover all production and direct distribution costs. It does not cover any research and development costs or commercial expenses other than direct distribution costs, with no profit margin.

DNDi commits to a reduced cost price in the public sector

Sanofi-aventis will fix the price of the new drug in the private sector. As stipulated in the contract, and in return for the use of information and findings provided, sanofi-aventis has agreed to pay DNDi 3% of the net private sector turnover over a period of seven years.

DNDi's Board of Directors has decided to use this payment to lower the drug's public sector sale price.

Non-exclusivity of the product

As there is no patent covering this artesunate + amodiaquine combination, a reference marketing authorisation will enable third parties to submit a simplified application for a generic version of this product.

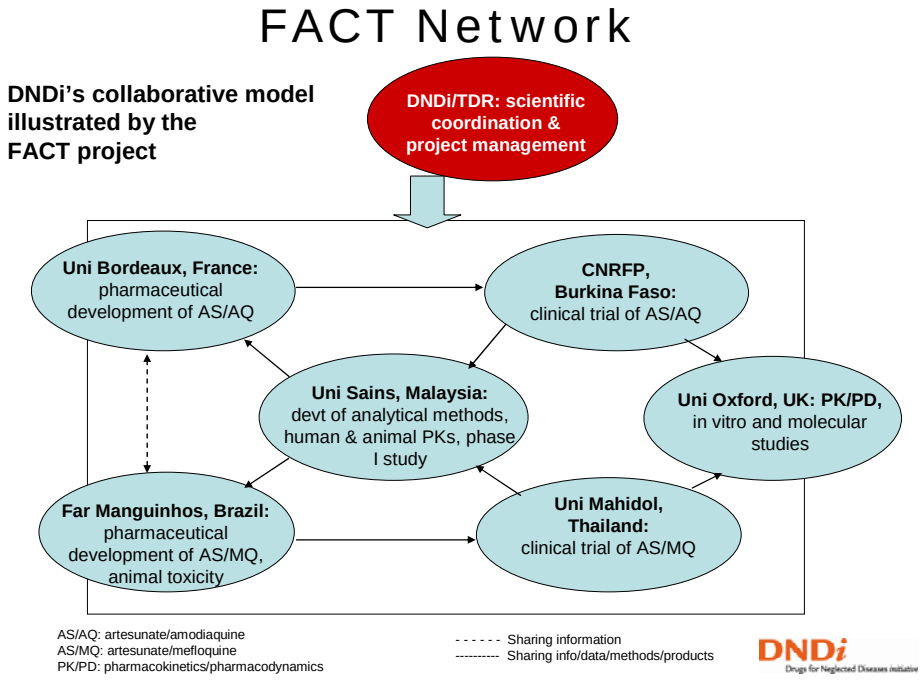
An international network to develop two new anti-malarial fixed-dose combinations AS/AQ and AS/MQ by 2006

Two new malaria treatments - DNDi's FACT (Fixed Dose Artesunate Combination Therapy) project aims to develop two new artesunate-based formulations to treat chloroquine-resistant falciparum malaria. These drug combinations should be registered in 2006 for distributed and use in developing countries at an affordable price. These combinations are WHO recommended artesunate amodiaquine (AS/AQ) and artesunate mefloquine (AS/MQ).

Funding – Drug development is an expensive business. A key element of the project is that FACT products are intended for the poorest of the poor and to become public goods. Partners in the FACT project therefore contribute both in kind (expertise, facilities etc) and through direct financing and try to find the most efficient and cost effective ways of moving forward, while maintaining quality or work and end products.

Thanks to this innovative collaborative model, DNDi estimates that it will cost 4 million Euros to develop to develop adult and paediatric formulations for AS/AQ and AS/MQ. One million of this budget is still needed.

The FACT antimalaria project received financial support under the European Union's 5th Framework Programme for Research and Technological Development, from Médecins Sans Frontières, and from WHO/Tropical Diseases Research. , an encouraging example of different global stakeholders successfully working to meet global health needs.



FACT Funding Partners

The Drugs for Neglected Diseases Initiative (DNDi) estimates that the total budget of the FACT Project from start to finish (2002 – 2006) will be 4,0 million EUROs (ME). So far, the project has been supported by the following:

EU funding - 1,2 ME
In 2002, the European Union committed €1.2m over three years to the development of the two FACT drugs. The EU (EC) Directorate General for Research funds projects through its International Cooperation Programme (INCO), a part of the EU Framework Programme for Research and Technological Development., a 5- year plan outlining the EC s priorities and budget for research activities. The FACT project was approved under the FP5 (1997-2001) under the INCO DEV programme set up to encourage international cooperation in research with developing countries.

Tropical Disease Research-WHO (TDR) funding: 0,45 ME
In addition to its financial contribution, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has shared its extensive experience with this project either directly or through consultants, and contributed to the scientific coordination with DNDi.

Far Manguinhos funding: 0,40 ME
Far Manguinhos contributed to the pharmaceutical development and scale up of one of the FDC's and provided funding for drug substance. Management of some pre-clinical activities was also done by them.

Médecins Sans Frontières (MSF) funding: 0,15 ME
MSF provided initial management of this project before the creation of DNDi in 2003. MSF has also provided financial management and support.

DNDi funding: 0,8 ME
DNDi provides overall project management, scientific coordination and financial support.

Still to be fundraised: 1 ME is needed over 2005-6 to complete the FACT projects which means getting the two new products registered and to patients during the course of 2006.

AS/AQ Project Partners

The success of the AS/AQ project fulfils DNDi's goal to bring together the skills and know-how of various scientific, university, public and private partners in developing and developed countries. This success was made possible by the participation of the WHO/TDR programme, TropiVal, Université de Bordeaux 2, Universiti Sains Malaysia, the University of Oxford, and Burkina Faso's National Malaria Research and Training Centre.

TropiVal of the University Victor Segalen of Bordeaux 2 (France), a centre for pharmaceutical projects focused on developing drugs for tropical and neglected diseases, and one of the principal FACT contractors. TropiVal helped identify several public institutions and private companies and contributed to the coordination of their work to insure completion of the various pharmaceutical steps of the project. It contributed to coordinate the pharmaceutical development of fixed-dose combinations of artesunate and amodiaquine

Universiti Sains Malaysia (Centre for Drug Research, CDR): The Centre for Drug Research, Universiti Sains Malaysia, established in 1980 by the Government of Malaysia is an independent research and training centre within the administrative governance of USM. The CDR developed analytical methods which were the base of the quality control of the finished products. It also developed the bioanalytical methods for the project to carry out all the trials of biological samples from animal studies as well as the bio-availability and various clinical studies. It is also responsible for the phase 1 pharmacokinetic study of the new FDC and the bioanalytical and pharmacokinetic analysis.

The Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ougadougou, Burkina Faso : *The "Centre National de Recherche et de Formation sur le Paludisme (CNRFP)* is part of the Burkina Faso Ministry of Health. The CNRFP participates in the formulation, implementation, supervision and evaluation of the national programme for malaria control. This includes carrying out operational and basic research projects to identify new malaria control tools and to adapt existing ones to local conditions and ensuring training on malaria for local health staff and scientists from Burkina Faso and other African countries. CNRFP is working on Phase III clinical trials and pharmacokinetics in patients. It contributes to the organization and the performance of the field study in patients comparing the safety/efficacy of the new FDC with the free combination. CNRFP is also responsible for the clinical part of the Population pharmacokinetic study.

Tropical Disease Research-WHO (TDR) shared its extensive experience by:

- Using a large data-base to determine the best fixed-ratio composition of both components in the combination and design optimal weight/age adapting dosing schedule
- Using its capacity building programs and networks to identify possible individual partners and activities to participate in the project. Contributing to the scientific plan and management of the program and particularly to the clinical components of the FACT project.

University of Oxford, Centre for Tropical Medicine: Experts from Oxford have been heavily involved in research on Artemisinin combinations in South East Asia, the starting point of the FACT project. Professor N.White is also the Chairman of the annual FACT team meetings. Oxford will continue to be involved in the AS-AQ fixed dose combination project through the analysis of the population PK data and possible pharmacokinetic-pharmacodynamic relationships.

Future use and needs of fixed-dose combinations in malaria-endemic countries

According to WHO, forty nine countries have already adopted Artesunate combination Therapy as their national first-line treatment[1] .

12 African Countries and Indonesia have already adopted AS/AQ. Other countries are expected to switch to fixed-dose combinations once these become available, and many other countries may choose to adopt them.

Assessing the future need for ACT, the World Health Organization has forecast that in 2005, 90 to 150 million treatments will be needed (based on total morbidity estimates). Africa, the worst-hit continent, makes up 60-70% of this global need. To meet the high demand several industrial partners will need to be involved in the manufacture of both combinations at low cost.

All malaria-endemic countries will benefit from the availability of a wider range of safe, effective and easy to use fixed-dose combinations.

Thirteen countries have already adopted the combination of artesunate/amodiaquine as their national first line treatment and five have adopted artesunate/mefloquine.

49 countries have adopted ACTs

Continent	Countries	Options	Level
AFRICA 28: 1st-line 6: 2nd-line	Burundi, Cameroon, DRC, Eq. Guinea, Gabon, Ghana, Liberia, Madagascar, Sao Tome, Sierra Leone, Sudan (S), UR Tanzania (Zanzibar)	ART + AQ	1st-line
	Angola, Benin, Burkina Faso, Comoros, Ethiopia, Gambia, Kenya, Mali, Namibia, Niger, Nigeria, South Africa, Tanzania, Uganda, Zambia	AM+LM	1st-line
	Côte d'Ivoire, Mozambique, Sudan (N), Sao Tome, UR Tanzania (Zanzibar)	AM+LM	2nd-line
	Mozambique, Sudan (N), South Africa,	ART + SP	1st-line
ASIA 12: 1st-line 2: 2nd-line	Cambodia, Thailand	ART + MEF	1st-line
	Bangladesh, Bhutan, Laos, Myanmar	AM+LM	1st-line
	Indonesia	ART + AQ	1st-line
	Afghanistan, India (5 Provinces), Iran, Tajikistan	ART + SP	1st-line
	Vietnam	CV-8	1st-line
	Papua New Guinea	ART + SP	2nd-line
	Philippines	AM+LM	2nd-line
SOUTH AMERICA 6: 1st-line	Ecuador, Peru	ART + SP	1st-line
	Bolivia, Peru, Venezuela	ART + MEF	1st-line
	Guyana, Surinam	AM+LM	1st-line

Impact Malaria : Un programme d'actions pour aider les pays en voie de développement à lutter contre le paludisme

Du fait de sa grande et historique expérience dans le traitement du paludisme, et de sa forte présence dans les PED et singulièrement en Afrique, sanofi-aventis a développé depuis 2001 un programme appelé « Impact Malaria ». Ce programme est conduit par une équipe multidisciplinaire qui lui est complètement dédiée. Il entre dans le cadre de la responsabilité sociale de l'Entreprise, et de sa politique de participation au développement durable.

Il se déroule selon 4 axes bien définis, dans un esprit de lutte intégrée contre le paludisme :

Axe 1 : **RECHERCHER ET DEVELOPPER DE NOUVEAUX TRAITEMENTS ANTI-PALUDIQUES**

Aujourd'hui les associations de médicaments avec un dérivé d'artémisinine s'imposent comme traitement standard du paludisme. Néanmoins la rapidité du développement des chimiorésistances nécessite de toujours chercher de nouvelles solutions thérapeutiques.
Sanofi-aventis contribue à cette recherche avec 3 projets, menés au sein de sa R&D en collaboration avec des partenaires externes, et entièrement financés par le groupe. Une de ces molécules, la ferroquine vient d'entrer en phase clinique.

Axe 2 : **DEVELOPPER DE NOUVELLES STRATEGIES THERAPEUTIQUES AVEC LES MOLECULES ACTUELLES.**

Les bithérapies : du concept à la réalité
Devant l'émergence préoccupante de parasites résistant à la chloroquine, l'OMS oriente les pays vers un changement de politique de santé en matière de paludisme. Elle positionne désormais en traitement de première intention les associations de deux molécules anti-paludiques et plus particulièrement celles à base d'artémisinine (ACT – *artemisinin-based combination therapy*).

Pour contribuer à la mise en place rapide de ce changement thérapeutique, Impact Malaria propose désormais des traitements constitués de deux antipaludiques conditionnés sous un même blister :

- Le coblister Arsucam® (artésunate + amodiaquine) est maintenant disponible dans de nombreux pays d'Afrique sous trois présentations : adulte, enfants et nourrissons.
  Des études comparatives réalisées en collaboration avec les Programmes Nationaux de Lutte contre le Paludisme ont démontré l'efficacité et la bonne tolérance de cette association. Ces études cliniques seront poursuivies en collaboration avec les réseaux de surveillance des résistances, notamment pour documenter le cas d'administrations réitérées.
- Le coblister Arsudar® (artésunate + sulfadoxine - pyriméthamine) sera prochainement disponible dans les pays où le parasite reste sensible à la sulfadoxine - pyriméthamine.

Parallèlement, une coformulation artésunate + amodiaquine (un seul comprimé contenant les deux principes actifs) est en cours de développement dans le cadre d'un partenariat avec DNDi.

Administration rectale de Quinimax® :
Le traitement du paludisme sévère chez l'enfant nécessite l'injection de sels de quinine dès l'apparition des premiers signes de gravité. En dehors des structures adaptées, ce mode d'administration conduit à des résultats très aléatoires (manque de matériel, conséquences d'injections mal réalisées…) : ainsi l'absence de traitement ou un simple retard dans la prise en charge de l'enfant sont le plus souvent fatals. Pour faire face à cette difficulté, Impact Malaria a développé un kit d'urgence pédiatrique qui permet une administration facile et maîtrisée de Quinimax®.
Pour définir la place optimale de ce kit d'urgence dans la pyramide sanitaire, Impact Malaria a mené, en collaboration avec les acteurs de santé locaux, une série d'études :

- En 2003, une étude en Ouganda a comparé l'administration intraveineuse à l'utilisation du kit chez des enfants atteints de neuropaludisme (forme la plus grave du paludisme sévère). Une équivalence d'efficacité et une très bonne tolérance de l'administration rectale de Quinimax® ont été démontrées.
- L'intérêt de l'utilisation du kit (acceptabilité, tolérance et incidence sur la mortalité) a aussi été confirmé par une étude menée en collaboration avec des infirmiers des centres de santé au Mali. Le taux de mortalité des enfants souffrant de paludisme compliqué a diminué de 50 % par rapport aux données nationales maliennes.
- Des études similaires sont actuellement menées dans des villages par des agents de santé communautaires.

Axe 3 : **FORMER ET INFORMER TOUS LES MAILLONS DE LA CHAINE DE SOINS**
Donner un accès plus large à l'information et la formation est l'un des objectifs d'Impact Malaria. Une meilleure accessibilité aux médicaments ne permettra de combattre efficacement le paludisme que si les acteurs de terrain disposent en parallèle de toute l'information médicale et sanitaire nécessaire.
Deux approches ont donc été adoptées pour les programmes d'Information – Education – Communication (IEC) :

- Développer une **information médicale pour l'ensemble des acteurs de santé** afin de faciliter une mise en place rapide des réformes thérapeutiques de la prise en charge du paludisme, avec comme thème principal le traitement de la crise de paludisme simple avec les nouvelles combinaisons thérapeutiques.
- Contribuer à la création de **programmes d'information « Hygiène et Santé » destinés aux communautés et aux familles,** pour leur permettre de mieux lutter contre la maladie, d'intégrer toutes les actions indispensables, notamment en ce qui concerne les moyens de prévention.

Plusieurs actions très concrètes viennent soutenir ces objectifs, par exemple :

1. L'information médicale destinée aux médecins au travers

- ☐ du site Internet Impact Malaria : www.impact-malaria.com
- ☐ de l'information thérapeutique sur Arsucam® (artésunate + amodiaquine) dispensée auprès des prescripteurs par nos délégués médicaux.

2. La formation destinée aux infirmiers des postes de santé :
Des kits de formation pour une meilleure utilisation des traitements antipaludiques seront prochainement mis à disposition des infirmiers des dispensaires / postes de santé, voire des personnels soignants des autres réseaux de soins (entreprises, ONG Santé, etc.). Ces guides permettront de former ces personnels de santé pour en faire des relais d'information pour les unités de soin les plus éloignées, notamment les cases de santé des villages.

3. L'information aux communautés et familles :

Les ONG de développement, présentes sur le terrain et proches des familles, ont un rôle important dans ce domaine. C'est pourquoi Impact Malaria travaille en étroite collaboration avec certaines institutions spécialisées afin de contribuer à l'évaluation des connaissances des communautés concernées et à la réalisation de supports permettant la mise en place de programmes de lutte intégrée.

*** Le site Internet Impact malaria : nouvelle version**

2004 a été l'année de la mise en ligne d'une version bilingue (français/anglais) du site d'information et d'éducation sur le paludisme : www.impact-malaria.com

De nouvelles fonctionnalités sont désormais disponibles sur « L'actualité du paludisme » : lettre mensuelle d'information, avis d'experts, bibliothèque virtuelle, l'actualité en temps réel, les tests de connaissance…

Axe 4 : **METTRE EN PLACE UNE POLITIQUE DE PRIX ET DE DISTRIBUTION ADAPTEE POUR FAVORISER UN MEILLEUR ACCES AUX MEDICAMENTS**

La complexité de la mise à disposition de médicaments dans les pays en voie de développement nécessite un partenariat global avec l'ensemble des acteurs de santé : institutions onusiennes, ONG, organismes publics et marché privé.

Ainsi pour les marchés publics, sanofi-aventis s'est engagé à fournir à prix différencié ("no-profit / no-loss") des médicaments antipaludiques destinés aux populations défavorisées. Cette offre inclut les nouvelles combinaisons à base d'artésunate recommandées par l'OMS destinées aux marchés privés et publics.

Pour le marché privé, un programme innovateur de Carte d'Accès aux antiPaludiques (CAP) mis en place au Cameroun en 2003 a été étendu au Gabon et à Madagascar en 2004.

Grâce à un partenariat avec des pharmacies d'officines de centres urbains, ce programme donne un plus large accès de la combinaison artésunate-amodiaquine (Arsucam®) aux populations défavorisées.

Toutes ces actions s'intègrent dans une réelle volonté de donner durablement accès aux populations défavorisés à des médicaments de qualité, leur permettant ainsi de progresser dans la lutte contre le paludisme.