

CLINTON FOUNDATION HIV/AIDS INITIATIVE Q&A

Part 1: Q&A on ACT Treatment for Malaria

Q. *How common is malaria? What geographic areas are affected by malaria?*

A. Malaria is a mosquito-borne illness caused by a parasite that affects an estimated 300-500 million people worldwide each year. More than one million people die from the disease each year, the majority of whom are children, and many more are debilitated, missing weeks of work or school. In addition to its direct impact on individuals and families, malaria has been shown to have a significant impact on the economic growth of affected, costing Africa an estimated \$12 billion in lost GDP growth every year. Sub-Saharan Africa is worst affected by malaria, accounting for more than 80% of deaths from the disease, with large areas of Asia and Latin America also affected.

Q. *Why is CHAI working on malaria?*

A. In 2007, the Clinton Foundation HIV/AIDS Initiative (“CHAI”) assessed the state of the ACT marketplace. Its aim was to see if it could apply its approach and experiences in improving ARV market dynamics to the market for ACTs. It learned that while there were some notable differences – for example, the ACT market was already high-volume, low-margin – there were also critical areas where intervention was needed to improve the extremely low access to ACTs (often less than five percent of patients) in many countries. CHAI identified a number of opportunities to adapt the approach it had taken with ARVs to ensure sustainable supply of low-cost, high-quality ACT products. While working in the ACT market space, CHAI has also identified and initiated other approaches to catalyze changes in the fight against malaria.

Q. *What is ACT and why is it important in the treatment of malaria?*

A. Artemisinin-based combination therapy or “ACT” is the treatment recommended by the World Health Organization (“WHO”) for uncomplicated malaria. ACTs consists of an artemisinin-based derivative, which has a rapid impact on malaria parasites but is quickly cleared from the body, and a slower acting partner drug.

For decades, the simple monotherapy drugs chloroquine (CQ) and then sulfadoxine – pyrimethamine (SP) served as the first line treatment for malaria. However, over time, the malaria parasite developed resistance to these drugs, rendering them frequently ineffective. The problem has grown to the point that in some areas of Africa, the drug will fail to cure 80-90% of malaria infections. This rapid spread of resistance is believed to be a primary cause of increases in malaria deaths witnessed in recent decades.

In contrast, ACTs not only rapidly cure malaria (most combinations have cure rates of 97% or above) but also inhibit the development of resistance by attacking the parasite with multiple agents. Additionally, this combination approach shortens treatment duration from 7 days to 3 days,

improving the likelihood that patients will complete a full course of anti-malarial treatment. As artemisinin-based drugs are currently the only effective treatment against malaria, it is critical that patients be treated with ACT in order to delay the emergence of resistance for as long as possible.

Q. *Why is ACT so expensive?*

A. One reason why ACT is more expensive than older drugs, such as CQ, is that it consists of two separate drugs. The antimalarial “partner drugs” are, on the whole, fairly inexpensive, with the artemisinin-based drug generally accounting for a majority of the cost of producing an ACT. The high cost of artemisinin-based drugs is rooted in the production of raw materials. The cultivation of the plant from which artemisinin is derived is an inherently long and expensive process, with low extraction yields after harvesting. Moreover, uncertainty about ACT demand, climate and high prices for production substitutes (like rice or corn) can all limit the availability of the plant material from which artemisinin is derived, increasing prices due to demand-supply imbalance.

Q. *What are the most commonly used ACT regimens?*

A. The most widely used ACT regimens are:

- artemether-lumefantrine (“AL”), in many areas of the world, including East and Southern Africa where resistance to CQ and similar drugs is particularly high, and
- artesunate-amodiaquine (“AS-AQ”), used primarily in western Africa.

In addition to these two regimens, WHO recommends the use of:

- artesunate-mefloquine (“AS-MQ”), which is deployed in some Southeast Asian countries, and
- artesunate-sulfadoxine-pyrimethamine (“AS-SP”).

In addition to these ACTs that are currently available, it is anticipated that the ACT dihydroartemisinin-piperaquine (“DHA-PPQ”), which has already been adopted in some countries, be recommended for use in the WHO global malaria treatment guidelines in the near future. The clinical development pipeline also includes a number of other promising ACTs.

Q. *Do people in developing countries have access to ACT today?*

A. Since 2004 when the majority of malaria endemic countries began to transition their treatment guidelines, access to ACTs through the public sector has increased significantly to more than 100 million patients treated per year. This scale-up was made possible by an influx in funding from donors such as the Global Fund, UNITAID and the US President’s Malaria Initiative.

However, there remains a large gap between ACT need and ACT access. Many patients seeking treatment in the public sector are still not receiving ACT due to insufficient funding, supply chain challenges, and other factors. Many facilities frequently spend significant amounts of time without

ACTs in stock. Even where ACTs are available at clinics, long wait times, user fees, and the need to travel long distances to the nearest clinic often drive patients to seek treatment from alternative sources.

As a result of these obstacles to public sector access, many patients seek treatment in the private sector – most commonly small shops or kiosks that sell ACTs alongside less expensive, less effective antimalarials such as CQ. As consumer choice in the private sector is largely driven by price, most patients will opt for the cheaper, less effective therapies (\$0.30-\$0.40) that cost a fraction of the price of ACTs (typically \$8-\$10). Only a small fraction of patients (less than 5%) who seek treatment through the private sector currently receive ACT.

Q. *What is being done to expand access to ACT?*

A. Increased ACT access requires interventions in both the public and private sectors. Existing programs to scale up access through the public sector focus largely on strengthening existing health systems and supply chain management. CHAI is one of many partners supporting governments in these regards, providing technical assistance on forecasting, procurement practices, and other issues. Many countries are also seeking to extend ACT distribution beyond formal health facilities through community health workers and other outreach mechanisms.

Expanding ACT access through the private sector will depend largely on well-designed subsidies given the large retail price differential between ACTs and more affordable but less efficacious drugs. CHAI has demonstrated a model for how this can be achieved through a pilot ACT subsidy program in three districts of Tanzania. CHAI is now supporting the Tanzanian government to roll out a national subsidy with financing from the Global Fund. Through robust evaluation, CHAI is also feeding the lessons learned into the design of a potential global ACT subsidy, known as the Affordable Medicines Facility, Malaria (“AMFm”).

Q. *Will there be enough ACT supply to meet the increased demand created by these access initiatives? What are the challenges to sustainable large-scale supply?*

A. The scale-up of affordable, high-quality ACT supply is threatened by the price volatility of the key input to ACT production – a plant extract called artemisinin. When ACT demand began to increase in 2004, an initial shortage of artemisinin caused prices to increase more than five-fold. In response to the initial shortage as well as demand forecasts that exaggerated the ability of countries to secure and quickly use funding for the purchase of ACTs, Novartis and other suppliers quickly expanded capacity. The capacity boom that resulted left suppliers holding significant extra inventories of product and the price of artemisinin fell precipitously. Many farmers accordingly left the market, starting a boom-and-bust cycle and creating a risk of further price spikes in the future. If increased input costs at the time of the initial shortage had been passed on to purchasers, the price of ACTs would have more than doubled and patients would have suffered from significantly reduced access to the drugs. Instead, Novartis took action to shield patients from the price volatility, absorbing the financial impact rather than passing it on to patients.

Given rapidly but unevenly growing demand and funding, uncertainty surrounding the global ACT subsidy, and shocks that impact artemisinin production such as the recent earthquake in China, the risk of volatility in the future remains high. Since Novartis alone cannot supply the entire market as demand grows to cover need, patients will suffer without the entry of new suppliers. However, the volatility has been a profound disincentive to new supplier entry, and even where suppliers do enter, they may not have the ability to shield patients from the impact of volatility in input prices.

Q. *What steps is CHAI taking to ensure sustainable and affordable ACT supply in the long term as demand increases?*

A. CHAI has taken a multi-pronged approach to address problems in the ACT supply chain. This will help ensure the sustainable supply of high-quality ACTs to meet growing demand. This approach involves:

1. Publishing robust forecasts of global ACT demand in order to increase demand predictability and avoid large artemisinin shortages;
2. Providing technical assistance to help accelerate the entry of new high-quality suppliers into the ACT market;
3. Negotiating agreements with key suppliers at every level of the supply chain (i.e., raw material, processed ingredient, and final formulation).

This approach ensures that artemisinin prices, which have ranged from \$155/kg to \$1,100/kg over the past four years, will remain below a sustainable ceiling price in the future. The increased stability of raw material costs will enable drug suppliers to commit to lower long-term prices.

Q. *Is CHAI working on malaria outside its work on ACT pricing and supply?*

A. Studies have shown that a significant proportion of patients treated for malaria may, in fact, suffer from another type of infection and not have malaria at all. This over treatment not only wastes resources as expensive drugs are used unnecessarily, but, critically, also costs lives – some patients who are given malaria treatment presumptively end up dying of pneumonia or other illnesses that also cause fever and were mistaken for malaria. CHAI is working to help solve this challenge by working with country governments to identify bottlenecks to effective diagnosis and with suppliers and key partner organizations to understand and improve the quality of rapid diagnostic tests and enable rapid scale-up of production.

In addition, CHAI, in partnership with the Global Health Group of the University of California, San Francisco, is providing management support to Southern African countries at the margins of the malaria-endemic zone to plan, resource, and execute malaria elimination programs. In order to ensure that malaria does not return once it has been eliminated, CHAI is also helping these countries to create cross-border collaborations to control the disease in neighboring high-burden countries.

Part 2: Q&A on New ACT Supply Agreements

Q. *What is the purpose of signing these agreements?*

A. As outlined above, the historical volatility in artemisinin production and pricing poses a threat to the ramp-up of high-quality ACT supply. Though Novartis has admirably shielded patients from much of this volatility in the past, Novartis will not be able to meet rapidly growing demand on its own—and new suppliers will not necessarily be able to shield patients from future volatility. CHAI's goal in pursuing these agreements has been to reduce future price volatility to ensure that the continuing scale-up of ACT access is not jeopardized.

Q. *What impact will these agreements have on pricing and price volatility?*

A. CHAI has signed agreements with 6 suppliers that are structured to reduce by 70% the price volatility of artemisinin. Fluctuations in artemisinin price, which ranged between \$150/kg and \$1,100/kg in recent years, have led to unpredictable and unexpectedly high drug production costs. By reducing the price volatility of artemisinin, CHAI has decreased this financial risk to suppliers, which will accelerate the entry of new suppliers and enable suppliers to commit to low but sustainable prices. Without these agreements, if prices of artemisinin were to hit \$1,100/kg again, it would translate into an increase in ACT price of 70%-105%, depending on the specific formulation. The risk reduction provided by these agreements has already enabled formulators to offer a price reduction of more than 30% for one key ACT formulation.

Q. *How do these agreements produce lower volatility and lower prices?*

A. CHAI has negotiated agreements with suppliers at every level of the ACT supply chain. The deals are rooted in agreements with artemisinin suppliers in China and India, with whom we have negotiated a sustainable long-term ceiling price. This will ensure that artemisinin prices, which have swung by as much as 700% over the past four years, will not spike during times of demand-supply imbalance. We then translated the agreed artemisinin pricing into prices at the active pharmaceutical ingredient (API) and formulation level on a cost-plus basis. By stabilizing the artemisinin price, we are able to offer API and formulation suppliers greater stability in their production costs and were able to secure lower long-term price ceilings.

Q. *Why can't drug suppliers negotiate agreements for raw materials on their own?*

A. CHAI has secured long-term price commitments from artemisinin suppliers by aggregating demand across more than one buyer, providing privileged access to that demand, and creating other value for these suppliers through technical assistance and market analysis. The only way lone drug suppliers could secure such pricing commitments would be to commit to large volumes and long time horizons in return, which is financially risky, especially in the context of uncertain demand.

Q. *With whom is CHAI signing these agreements?*

A. CHAI is signing agreements with high quality suppliers at all levels of the ACT supply chain – including artemisinin extractors as well as manufactures of active pharmaceutical agreements (APIs) and drug formulations. These companies include:

- Ipca Laboratories and Cipla for ACT formulation;
- Calyx and Mangalam Drugs for APIs; and
- Holleypharm and PIDI Standard for artemisinin

Q. *Why has CHAI chosen to work with these specific companies?*

A. CHAI is working with these companies because it believes that these companies can deliver on commitments to both quality and price. Over time, it expects to add additional suppliers into its ACT agreements.

A variety of factors were evaluated in selecting partner suppliers. First, CHAI sought companies with a strong track record of production at high quality. Second, these companies have proven that they can optimize production in ways that reduce costs and increase manufacturing process efficiency. Third, these companies have been willing to commit to supplying high-quality products at or below low long-term ceiling prices, and also to other provisions including improved packaging, prohibitions on sales oral artemisinin monotherapies (as recommended by the WHO), and data sharing to help CHAI monitor demand and improve its global ACT forecasts.

Q. *Which ACT formulations do the agreements cover?*

A. The agreements cover AL and AS+AQ, which are the two most commonly used formulations. For AL, the agreements cover a “coformulated” product in which the two drugs are combined into a single pill. For AS+AQ, the agreements cover packages (called “co-blister packs”) that contain separate pills of AS and AQ.

Q. *Why has CHAI not included a single tablet fixed-dose combination of artesunate and amodiaquine?*

A. Although co-formulated versions of artesunate and amodiaquine already available in the market, none of these products has yet achieved stringent regulatory approval (e.g., from WHO or U.S. FDA). The most convenient WHO-approved formulations are the co-blister packs which are included in the CHAI ACT agreements. CHAI’s partner suppliers and others are actively pursuing development and stringent regulatory approval for co-formulated versions of AS and AQ. As these approvals are obtained, CHAI expects to add these new formulations into its agreements to help the market move rapidly toward the best available quality-assured products.

Q. *What are the new prices?*

A. The long-term CHAI price ceilings for AS+AQ and AL are listed below. Note that short-term prices will be below these long-term ceilings. Eligible purchasers may contact CHAI to inquire about short-term pricing for these products.

<u>Artesunate-amodiaquine co-blisters</u>		<u>Artemether-lumefantrine</u>	
<u>Pack size</u>	<u>Price per pack (US\$)</u>	<u>Pack size</u>	<u>Price per pack (US\$)</u>
3x3	0.24	6x1	0.37
6x6	0.42	6x2	0.74
12x12	0.78	6x3	1.11
		6x4	1.40

Q. *Who has access to Clinton Foundation prices?*

A. All 69 CHAI Procurement Consortium member countries can purchase the full range of products including the ACTs announced today.

Q. *Why is there a price reduction on AS-AQ and not AL?*

A. On World Malaria Day in April 2008, Novartis announced that it would reduce its prices to the public sector by an average of 18%. This is a great development for the international malaria community and malaria patients. Ipca and Cipla have agreed to meet Novartis' prices today and to continue their commitment to cost reduction by achieving greater efficiency in their manufacturing process.

Q. *Will the prices in these agreements now make ACT affordable to all patients?*

A. Ensuring that every single patient has access to life-saving ACT requires a multi-pronged approach to address both the volatility of supply and barriers to access within countries. In many countries, more than half of patients do not access malaria treatment through the public health system, where drugs are often distributed free of charge or at nominal cost, but instead purchase drugs at small private shops. Most of these patients live on less than \$2 per day and cannot afford to spend more than a fraction of that on treatment. Even with the maximum possible price reductions and the full commitment of suppliers, ACT will still be unaffordable to those patients once they have been distributed through the private supply chain.

The only way to further lower the price of ACT and make these drugs accessible to the tens of millions of patients who use the private sector is through subsidies. The Government of Tanzania and CHAI have demonstrated, through a pilot program in three districts in Tanzania, that such a subsidy approach can lead to higher patient access. The piloted subsidy decreased the retail price of ACTs by 95% and increased ACT access among children under five from negligible levels to nearly two-thirds of those obtaining treatment through the private sector.

Q. *How does CHAI ensure that the products it supports are of high quality?*

A. All of the products included in today's announcement have either been approved by or submitted to the WHO for regulatory approval. All submissions to the WHO include data establishing bioequivalence, based on tests by contract research organizations that have been successfully audited by the WHO. The APIs and formulations will all be manufactured in facilities that have been inspected and certified as compliant with Good Manufacturing Practice by either the WHO, U.S. FDA, or European Directorate for the Quality of Medicines.

Q. *Is CHAI stifling competition by working with a limited number of suppliers and negotiating long-term prices?*

A. No. First, CHAI expects to add other suppliers to its agreements at each level of the ACT supply chain over time. Second, as is true of all CHAI drug pricing deals to date, the prices specified in the agreements are merely ceiling prices. At each level of the supply chain, suppliers will price their products at or below the maximum allowable prices based on competitive forces. The agreements will thus preserve existing competitive dynamics and incentives.

Q. *Is CHAI entering into an agreement with Novartis?*

A. No. The goals of the agreements being announced are to reduce volatility, ensure quality, and enable low and sustainable prices. Novartis has demonstrated the depth of its commitment to these goals. New suppliers entering the ACT market are often committed to high quality, but do not generally have the ability to absorb the financial losses arising from volatility in the way that Novartis has. Therefore, CHAI has signed agreements with new suppliers to protect them from volatility and enable them to commit to low long-term price ceilings. Although CHAI does not have a formal agreement with Novartis, it will continue to work with Novartis to refine demand forecast methodologies, address key barriers to ACT access, and foster a healthy ACT marketplace.

Q. *How will the launch of semi-synthetic artemisinin impact these agreements?*

A. The development of a synthetic or semi-synthetic version of artemisinin would be a dramatic step forward both in terms of technology and also in terms of reducing price volatility. It would significantly reduce the lead time required to make an ACT. Synthetic or semi-synthetic artemisinin would also not suffer from the impact of weather or natural disasters that create volatility of supply and prices. The Institute for Oneworld Health, Amyris Biotechnologies and Sanofi-Aventis are pursuing one project that targets the incorporation of a semi-synthetic version of artemisinin into an ACT by the end of 2010. However, even if the development and scale-up of this product succeeds—which is far from guaranteed—agricultural artemisinin will remain a primary source to meet global demand. The agreements announced by the Clinton Foundation will therefore have an impact now and for years to come.

Q. *How do these agreements relate to other malaria efforts, including the recent goals articulated by the UN Secretary General?*

A. Malaria can only be controlled - and millions of lives saved - through a comprehensive approach. Scale-up of treatment must go hand-in-hand with expanded coverage of insecticide-treated bed nets, vector control and accurate diagnosis. The Secretary General and other leaders have recently called for renewed commitment to ensuring that 80% of people in malaria affected areas have access to these interventions by the end of 2010. The new agreements CHAI is announcing will facilitate the achievement of those targets by helping to ensure sustainable supply of ACTs at high quality and low cost.

Q. *Are there any hidden or additional costs that purchasers will need to pay?*

A. In general, CHAI prices are ceiling rates at or below the rates at which CHAI partner suppliers must quote in response to tenders. The ceiling prices themselves are in “Free on Board” (FOB) terms, meaning that they do not include applicable shipping and handling charges from the point of export. It is common for the prices of ACTs to be reported on an FOB basis. Shipping and handling fees add to the FOB price of a product. In addition, some purchasers choose to use procurement agents such as UNICEF, IDA or Crown Agents, which typically adds 5-10% to the price. These costs are not particular to products and prices offered under CHAI agreements.

Part 3 - Q&A on the Clinton Foundation HIV/AIDS Initiative (CHAI)

Q. *Who has accessed CHAI drug prices under its previous agreements?*

A. As of January 2008, 1.4 million people living with HIV are benefiting from medicines purchased under CHAI agreements, resulting from purchases made by over 50 countries.

Seven times since October 2003 (most recently in April 2008), President Clinton has announced successive agreements to lower the prices of the most common antiretrovirals (ARVs) and diagnostic tests used in HIV/AIDS care and treatment. Initially CHAI-negotiated prices were available to the dozen countries in Africa and the Caribbean where CHAI was working. Beginning in 2004, access was progressively extended to additional countries, based on commitment to principles of sound procurement – this growing group of countries is called the CHAI Procurement Consortium. Membership in the CHAI Procurement Consortium includes 69 nations in Africa, Asia, Latin America and the Caribbean.

In addition to these direct beneficiaries, many more people have indirectly benefited from the actions of CHAI partner suppliers. By offering drugs and diagnostics for lower prices, suppliers stimulated greater competition in the marketplace, which resulted in further price reductions. The credit for the patients on treatment today in developing countries belongs to people in these countries – from Ministers of Health to countless community health workers. The role of donors and international organizations like CHAI is to support their efforts.

Q. *What has been required of countries buying at these prices?*

A. CHAI purchasers agree to prompt and secure payment terms, and they regularly update and share demand forecasts. In addition, they commit to principles of sound procurement, typically reflected in a memorandum of understanding (MOU) signed with the Clinton Foundation. These include aggregated national orders; secure distribution of product in country (to avoid leakage into high-income markets); compliance with national and international law protecting intellectual property; and movement towards using multi-year tenders and splitting high-volume orders across multiple suppliers.

The procurement process is not cumbersome. National governments maintain autonomy over the procurement process, and CHAI agreements support the practices and preferences of Procurement Consortium members.

Q. *What is the CHAI Procurement Consortium? How does a potential buyer join?*

A. The Procurement Consortium refers to the countries eligible to purchase under CHAI agreements. This includes both “partner” countries, where CHAI maintains a continuous in-country presence to support national efforts to expand treatment programs, and “purchasers” whose

relationship with CHAI is largely limited to procurement. To learn more about joining the CHAI Procurement Consortium, please email procurement@clintonfoundation.org.

Q. *How do the ACT supply agreements fit with CHAI's previous ARV work?*

A. The ARV agreements previously announced have focused primarily on lowering prices for high-quality ARVs through cost-cutting measures and by helping ARV suppliers to build volumes. The ACT deals being announced today, by contrast, focus on reducing the volatility of prices for the key raw material in ACT production, thereby reducing financial risks. As a result, suppliers can commit to entering and supplying the market with high-quality ACT at low prices. Despite these differences in approach, CHAI was able to leverage many aspects of its ARV experience in pursuing the ACT work.

Q. *Is CHAI planning to further expand its drug and diagnostic pricing agreements?*

A. Ensuring improved access to high-quality medicines and diagnostics at affordable prices for patients in the developing world is a key priority. CHAI will continue to pursue new agreements for key drugs and diagnostics used in the fight against HIV/AIDS. With respect to malaria, CHAI will launch an effort to increase the availability of artemisinin-based therapies for severe malaria at a lower cost. CHAI also plans to expand its diagnostic agreements over the coming years to include products such as rapid diagnostic tests that are critical to appropriate and effective malaria treatment.

Q. *In addition to its procurement work, what other work does CHAI do?*

A. The Clinton Foundation began its work in 2002, responding to requests by national governments in Africa and the Caribbean both to make treatment more affordable and to develop detailed operational plans for the scale-up of HIV/AIDS treatment. We set out to be responsive to national leadership and fill gaps in the provision of technical assistance from traditional organizations in the HIV/AIDS community. Initially, we assisted governments in developing national strategies and business plans for scale-up of care and treatment, and helped to get these plans funded through the international donor community. As these plans were developed, adopted, funded and implemented, our role has evolved into providing targeted assistance to address policy and implementation challenges that governments face as they attempt to make treatment more broadly available. Today, we play this role in over 20 countries in Africa, Asia, Eastern Europe, and the Caribbean.

Q. *How many people work for CHAI? Where is it based? How does it support its work?*

A. In addition to its dedicated staff, the Clinton Foundation HIV/AIDS Initiative relies on hundreds of part-time and full-time volunteers. There are presently more than 500 people in developing countries and the U.S. working for CHAI. In the United States, CHAI maintains offices in Boston, Massachusetts, and in Harlem, New York. Ira C. Magaziner is Chairman of the HIV/AIDS Initiative. The work of CHAI depends on private and pro bono contributions, as well as

on the time donated by volunteers. HIV/AIDS care and treatment programs themselves are financed principally by national governments and international donors.