

## Q&A on New Pediatric Formulations

**Q.** *What are the advantages of the new pediatric formulations included in today's agreements compared to existing drugs, and how will they contribute to greater access to and higher quality HIV/AIDS treatment for children?*

**A.** The six new pediatric formulations included in today's agreements represent an important improvement to the quality of treatment available to children on antiretroviral (ARV) therapy. The new formulations include: (1) AZT+3TC+NVP (60/30/50mg); (2) AZT+3TC (60/30mg); (3) ABC+3TC (60/30mg); (4) ABC 60mg; (5) ddI EC 125mg; and (6) ddI EC 200mg.

While stavudine (d4T) has until now been a central component of first-line pediatric treatment in developing countries, there is increasing evidence demonstrating that this drug causes significant side effects for children with long term use and produces inferior outcomes to those achieved with zidovudine (AZT). The World Health Organization (WHO) has recommends that countries using d4T in first-line pediatric therapy move instead toward the use of AZT. The AZT-based pediatric fixed dose combination (FDC) combines pediatric doses of the three individual drugs – AZT, lamivudine (3TC) and nevirapine (NVP) – into a single dispersible tablet form, providing greater convenience and more accurate dosing than individual syrups. To facilitate lead-in dosing for children (required due to issues of toxicity with NVP), a dual FDC containing AZT and 3TC has also been made available through these agreements.

The WHO recommends the use of abacavir (ABC), in combination with 3TC, as an alternative first-line regimen for children. The availability of a pediatric FDC containing ABC and 3TC will offer another option for first line treatment and may become increasingly common as future pediatric treatment guidelines may well place even greater emphasis on this regimen.

For children who experience treatment failure on first-line drugs, there is a need to switch to a “second-line” combination of ARVs. The treatment options for children on second-line therapy have been limited and expensive, with limited investments in research for new formulations due to low demand. Previous second-line formulations were also very inconvenient to dose, administer and store, if they were available only in liquid form, or had a high pill burden. The availability of second-line drugs in tablets and capsule form at affordable prices will enable improved access to second-line treatment for children and promote greater adherence.

**Q.** *Why is the introduction of a pediatric AZT fixed dose combination important, when among adults d4T is still the preferred backbone for first-line regimens in developing countries?*

**A.** The WHO has recommended a shift away from d4T to AZT-based regimens for both adults as well as children on first-line treatment. This recommendation is relatively recent, so larger numbers of adults compared to children are on d4T-based regimens, as adult treatment began scaling up in 2002, whereas pediatric treatment only exceeded 100,000 children in 2006.

Particularly in the historical absence of a technical recommendation away from d4T, the uptake of AZT-based regimens among adults has been constrained by the significantly higher price compared to the d4T FDC. By comparison, the pediatric AZT FDC announced today is only modestly more expensive compared to the pediatric d4T FDC. This, combined with the technical recommendation of the WHO, makes the AZT-based alternative particularly important among children. As the pediatric d4T FDC was introduced in late 2006, today's agreements represent a critical step forward so that both first-line regimens can be administered as FDCs.

## Q&A on Second-line ARVs

**Q.** *What are second-line antiretrovirals (ARVs)? Why do they cost more than first-line ARVs, and why are so few people on second-line treatment in developing countries?*

**A.** Over time, a patient's initial regimen of ARVs may start failing to control the level of the HIV virus in the body as the virus develops resistance to the first-line drugs. When this occurs, there is a need to switch the patient to a new combination of ARVs that together comprise "second-line" therapy. Drugs included in second-line regimens, particularly protease inhibitors, are typically bigger and more complex than first-line drugs at a molecular level. A number of second-line drugs are also dosed at higher levels, requiring more active pharmaceutical ingredient (API) per day of treatment. These features help to explain the greater cost of second-line medicines. Low production volumes, due to limited demand to date from developing countries, also play an important role, preventing suppliers from achieving volume-based efficiencies and cost savings.

In 2006, 80,000 of the two million patients receiving ARV treatment in low and middle income countries, or 4% of the total, were on second-line therapy. Most of these two million patients began treatment within the last five years and have not yet experienced treatment failure. The need for second-line regimens is expected to rise significantly across developing countries in coming years as the initial wave of patients reached during the early years of the scale-up of HIV/AIDS therapy begins to experience treatment failure. CHAI estimates that nearly half a million people will require second-line therapy in 2010.

In addition to the relatively low need for second-line therapy, the need that does exist has been under-addressed. Weak diagnostic and laboratory capacity in many countries has made it difficult for healthcare workers to diagnose treatment failure promptly. Thus, some patients stay on first-line regimens beyond the point of virologic or immunologic failure, until clinical failure becomes evident. And even where treatment failure is accurately diagnosed, the high cost of second-line medications has led some countries to hesitate in making second-line treatment widely available.

**Q.** *The price of second-line treatment, even after the current announcement, still seems high compared to first-line regimens. Are these prices expected to come down further? If so, how will this be achieved?*

**A.** CHAI and UNITAID have announced cumulative price reductions of more than 30% on second-line ARVs over the last 12 months. Price reductions for middle income countries are more significant with cumulative reductions on the order of 75%. Still, the price of second-line treatment – at roughly \$700 per patient annually – remains high compared to first-line regimens.

Lopinavir/ritonavir (LPV/r) is currently the dominant protease inhibitor used in second-line therapy and has been the driver of its cost, representing 75% of the total regimen price. New WHO recommendations present ritonavir-boosted atazanavir (ATV+RTV or ATV/r) as an emerging alternative to LPV/r. ATV/r is clinically comparable to LPV/r. Because the ATV/r dose (300mg ATV + 100mg RTV) is so much lower than that of LPV/r (800mg LPV + 200mg RTV), much less API is required; API typically represents 60-80% of final drug prices. The per kilogram costs of producing LPV and ATV will likely be comparable once ATV is produced at high volumes. For this reason, CHAI expects ATV/r to be substantially cheaper than LPV/r, with a growing price difference over time. CHAI is working closely with partners to bring a FDC of ATV/r to market before the end of the year, which will be a once-a-day heat-stable pill.

The introduction of ATV/r, combined with further price reductions on other second-line ARVs, particularly TDF, will further lower the price of second-line HIV/AIDS treatment.

## Q&A on New Antiretroviral Pricing Agreements

**Q.** How do CHAI's new prices compare to current prices in the market?

**A.** CHAI's newest agreements include price reductions for 40 ARV formulations – covering pediatric and adult, first and second-line treatments. To determine the degree of reduction, new CHAI ceiling rates are compared to the lowest available prices per market (low income and middle income) listed in several publicly available sources, including analysis of purchases captured in the WHO's Global Price Reporting Mechanism and the lowest approved generic price reported in Médecins Sans Frontières' "Untangling the Web of Price Reductions."

Adult Formulations	Strength (mg)	CHAI ceiling price (per pill)	CHAI ceiling price from May 2007 & Reduction		MSF lowest generic price & Reduction		Low Income Prices & Reduction		Middle Income Prices & Reduction	
							GPRM LI Average <sup>1</sup>	GPRM L/UMI Average <sup>1</sup>		
ABC	300	\$ 0.42	\$ 0.46	9%	\$ 0.59	28%	\$ 0.57	26%	\$ 0.59	28%
ddI EC	250	\$ 0.42	\$ 0.43	2%	N/A	N/A	\$ 0.59	29%	\$ 1.42	70%
ddI EC	400	\$ 0.67	\$ 0.69	3%	N/A	N/A	\$ 0.81	17%	\$ 2.12	68%
EFV	200	\$ 0.16	\$ 0.22	27%	\$ 0.19	17%	\$ 0.25	36%	\$ 0.25	35%
EFV	600	\$ 0.42	\$ 0.46	9%	\$ 0.51	17%	\$ 0.57	27%	\$ 0.70	40%
3TC + d4T + NVP	150+30+200	\$ 0.14	\$ 0.18	22%	\$ 0.14	0%	\$ 0.17	17%	\$ 0.16	11%
3TC + d4T	150+30	\$ 0.09	N/A	N/A	\$ 0.09	0%	\$ 0.10	7%	\$ 0.09	3%
3TC + AZT + NVP	150+300+200	\$ 0.22	\$ 0.24	8%	\$ 0.27	17%	\$ 0.25	12%	\$ 0.30	26%
3TC + AZT	150+300	\$ 0.17	\$ 0.18	6%	\$ 0.18	7%	\$ 0.18	3%	\$ 0.55	69%
3TC	150	\$ 0.05	\$ 0.05	0%	\$ 0.06	15%	\$ 0.07	25%	\$ 0.15	66%
LPV/r	200+50	\$ 0.38	\$ 0.48	21%	\$ 0.71	46%	\$ 0.37	-2%	\$ 0.69	45%
NVP	200	\$ 0.06	\$ 0.06	0%	\$ 0.07	9%	\$ 0.07	17%	\$ 0.15	60%
d4T	50	\$ 0.05	\$ 0.05	0%	\$ 0.04	-25%	\$ 0.03	-47%	\$ 0.10	51%
TDF	300	\$ 0.38	\$ 0.41	7%	\$ 0.55	30%	\$ 0.70	46%	\$ 0.57	34%
TDF + 3TC	300+300	\$ 0.44	\$ 0.50	12%	\$ 0.65	32%	N/A	N/A	N/A	N/A
TDF + FTC	300+200	\$ 0.55	\$ 0.63	13%	\$ 0.75	27%	\$ 0.88	38%	\$ 0.96	43%
AZT	300	\$ 0.13	\$ 0.13	0%	\$ 0.14	8%	\$ 0.15	11%	\$ 0.17	23%
TDF+FTC+EFV	300+200+600	\$ 0.97	\$ 1.07	9%	\$ 1.33	27%	N/A	N/A	N/A	N/A
TDF+3TC+EFV	300+300+600	\$ 0.83	\$ 0.94	12%	\$ 1.17	29%	N/A	N/A	N/A	N/A

Pediatric formulations	Strength (mg)	CHAI ceiling price (per pill)	CHAI ceiling price from May 2007 & Reduction		MSF lowest generic price & Reduction		Low Income Prices & Reduction		Middle Income Prices & Reduction	
							GPRM LI Average <sup>1</sup>	GPRM L/UMI Average <sup>1</sup>		
ABC	20mg/ml	\$ 0.06	\$ 0.07	15%	\$ 0.085	27%	\$ 0.09	31%	\$ 0.09	30%
ABC	60	\$ 0.11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ABC + 3TC	60 + 30	\$ 0.13	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ddI	100	\$ 0.13	\$ 0.13	0%	\$ 0.160	19%	\$ 0.20	34%	\$ 0.35	63%
ddI	200	\$ 0.25	\$ 0.26	3%	\$ 0.315	20%	\$ 0.45	44%	\$ 0.35	29%
ddI EC	125	\$ 0.19	N/A	N/A	N/A	N/A	\$ 0.69	73%	N/A	N/A
ddI EC	200	\$ 0.22	N/A	N/A	N/A	N/A	\$ 0.45	50%	\$ 0.35	37%
EFV	50	\$ 0.08	\$ 0.08	0%	\$ 0.100	20%	\$ 0.11	25%	\$ 0.10	21%
3TC + d4T + NVP	20+5+35	\$ 0.05	\$ 0.05	0%	\$ 0.057	21%	\$ 0.05	3%	\$ 0.05	0%
3TC + d4T + NVP	40+10+70	\$ 0.09	\$ 0.09	0%	\$ 0.096	8%	\$ 0.09	6%	N/A	N/A
3TC + d4T + NVP	30+6+50	\$ 0.04	\$ 0.04	0%	\$ 0.108	63%	\$ 0.04	1%	\$ 0.04	0%
3TC + d4T + NVP	60+12+100	\$ 0.08	\$ 0.08	0%	\$ 0.125	36%	\$ 0.08	0%	\$ 0.08	-1%
3TC	50mg/ml	\$ 0.01	\$ 0.01	0%	\$ 0.012	17%	\$ 0.01	0%	\$ 0.01	10%
3TC + AZT	30+60	\$ 0.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LPV/r	100/25	\$ 0.27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
NVP	50mg/ml	\$ 0.01	\$ 0.01	0%	\$ 0.013	38%	\$ 0.01	35%	\$ 0.01	25%
d4T	1mg/ml	\$ 0.01	\$ 0.01	0%	\$ 0.010	30%	\$ 0.01	14%	\$ 0.06	88%
d4T	15	\$ 0.03	\$ 0.03	0%	\$ 0.032	22%	\$ 0.04	41%	\$ 0.03	8%
d4T	20	\$ 0.03	\$ 0.03	0%	\$ 0.034	12%	\$ 0.07	59%	\$ 0.04	17%
AZT	50mg/ml	\$ 0.01	\$ 0.01	0%	\$ 0.013	31%	\$ 0.01	25%	\$ 0.01	31%
AZT	100	\$ 0.05	\$ 0.05	0%	\$ 0.075	33%	\$ 0.06	20%	\$ 0.06	21%

<sup>1</sup> Weighted average prices in low income (LI) and lower and upper middle income (L/UMI) countries from WHO Global Price Reporting Mechanism for January - December 2007

<sup>2</sup> Lowest price of a WHO/FDA approved generic (if not approved, lowest price of supplier with a dossier submission is in gray italics) from MSF's Untangling the Web (July 2007 edition with September 2007 revision and update from March 2008)

The average price reduction for the seven formulations of the key second-line ARVs abacavir, didanosine, lopinavir/ritonavir, and tenofovir is 10% compared to the ceiling prices negotiated by CHAI in May 2007 and 33% compared to the lowest available generic price quoted by MSF. The prices negotiated on new pediatric formulations represent reductions of more than 50% from the current market prices of the previously available alternatives.

**Q.** *How did CHAI work with suppliers to reduce prices?*

**A.** CHAI provides cost reduction assistance to partner suppliers, helping to secure lower prices on key raw materials, addressing important chemistry challenges, and modeling volume-based cost savings in anticipation of increased demand.

CHAI's partnership with UNITAID to purchase and provide second-line and pediatric ARVs to 42 countries is built on this cost reduction approach by providing guaranteed purchase volumes to suppliers and creating a competitive bidding process for participation in the program. Acting on behalf of UNITAID, CHAI issued a formal expression of interest to all suppliers producing the relevant ARVs, requesting that they indicate the regulatory status of each product they wish to supply and their ability to supply products to each UNITAID beneficiary country. Suppliers were also asked to either indicate the price at which they would provide the product or indicate their willingness to engage in transparent "cost-plus" price negotiations with CHAI. CHAI then began in-depth conversations with those suppliers willing to engage in these negotiations, reviewing their production cost structures and identifying potential cost reduction opportunities. The prices generated through these negotiations were then compared to those submitted by other suppliers to determine the pool of manufacturers eligible for the UNITAID program.

**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 Carrier" (FCA) terms, meaning that they do not include applicable shipping and handling charges from the point of export. It is common for the prices of ARVs to be reported on a "Free on Board" (FOB) or FCA basis. Shipping and handling fees add to the FOB/FCA 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.

**Q.** *Will CHAI procure products at these prices? Will others be able to procure at the negotiated prices?*

**A.** CHAI is managing the procurement of UNITAID-financed volumes of these formulations for 42 countries in 2008, either through its procurement agent or with CHAI acting directly as a procurement agent. The prices at which CHAI will be procuring for its programs are slightly higher than the ceiling prices announced today. The prices offered to CHAI for the UNITAID programs include a risk premium that suppliers need to bear in case of fluctuations in the exchange rate (which would not allow for a price adjustment through the course of the program), while ceiling prices quoted on the CHAI price list do not include this risk premium.

In addition to the countries benefiting from the UNITAID pediatric and second-line treatment programs, all countries in the CHAI Procurement Consortium, which currently includes 69 nations, will be able to purchase the full range of products included in the current agreements at the negotiated prices. Procurement of the products will be the responsibility of each government or its designated representative using its existing procurement systems and either domestic resources or funds from donors such as the Global Fund.

**Q.** *How does CHAI ensure sustainability of prices negotiated through its agreements?*

**A.** Pricing negotiated by CHAI is based on a 'cost-plus' approach, where suppliers agree to price on the basis of an agreed production cost structure plus a reasonable profit margin. The price

reductions announced today were made possible by improvements in chemistry and raw material sourcing that resulted in lower production costs. These reductions were also made possible despite significant appreciation in the value of the Indian rupee against the US dollar (which resulted in an increase in suppliers' production costs) and despite changes in Chinese export tax policy that resulted in an increase in the cost of intermediates to Indian manufacturers. As a result, average price reductions were higher in rupee than in dollar terms, since Indian manufacturers cost structures are denominated in rupees. (For second-line ARVs, the average reduction of 13% in dollar terms compares to a reduction of 22% in rupee terms.)

**Q.** *How do CHAI and UNITAID ensure that the products they support are of high quality?*

**A.** All of the products included in today's announcement have either been approved by or submitted to a stringent regulatory authority such as the WHO or U.S. Food & Drug Administration (FDA). (Two formulations, not subject to UNITAID-funded procurement, will be submitted to these authorities in the next few months.) Submissions to the WHO or FDA include data establishing bioequivalence of the generic medicines to originator products, based on tests by research laboratories that have been successfully audited by the WHO and/or FDA.

For those products which are being procured with UNITAID funds that have not yet received final regulatory approval, additional conditions have been applied consistent with the quality assurance policy adopted by the UNITAID board. These conditions include certification that the facilities where the drugs are produced meet the international standard of Good Manufacturing Practice and submission of a complete regulatory dossier to the WHO or other stringent regulatory authority. CHAI will also ensure that all products supplied through its partnership with UNITAID are of high quality through a comprehensive quality control process. This will include inspecting shipments to ensure that they meet the required specifications and testing random samples of product batches in independent labs to ensure that the chemical composition of the drugs match these specifications.

**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, following purchases made by over 50 countries.

In October 2003, January 2004, April 2005, January 2006, November 2006 and May 2007, President Clinton announced successive agreements to lower the prices of the most common ARVs and diagnostics 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 extended to additional countries, on a case-by-case basis based on commitment to principles of sound procurement. Membership in the CHAI Procurement Consortium has expanded to 69 countries 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, they stimulated greater competition in the marketplace, which resulted in lower prices. 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.