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• D I S C U S S I O N P A P E R •

# INDIA AND SECOND-LINE ART

## Evaluating the Way Forward

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# Discussion Paper

## **COMMISSIONED BY**

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Indian Network for People Living with HIV/AIDS (INP+)

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## LIST OF ACRONYMS AND ABBREVIATIONS

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3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ANVISA	National Sanitary Supervision Agency
API	Active Pharmaceutical Ingredient
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASA	Approved Stringent Authority
ATV	Atazanavir
AZT	Zidovudine
BMS	Bristol-Myers Squibb
CHAI	Clinton Foundation HIV/AIDS Initiative
ddI	Didanosine
EFV	Efavirenz
ENF	Enfurvitide
FVP	Fosamprenavir
GFATM	Global Fund for AIDS, TB and Malaria
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IDV	Indinavir
INP+	Indian Network for People Living with HIV/AIDS
ITPC	International Treatment Preparedness Coalition
LPV/r	Lopinavir/Ritonavir
MSF	Medecins Sans Frontieres
NACO	National AIDS Control Organisation
NACP-3	National AIDS Control Programme-Phase 3
NFV	Nelfinavir
NtRTI	Nucleotide analog reverse transcriptase inhibitors
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NPAC	National HIV/AIDS Policy And Advocacy Centre
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
PI	Protease Inhibitor
PLHIV	People Living with HIV
PQ	Pre-qualified
PSU	Public Sector Undertaking
RNTCP	Revised National Tuberculosis Control Programme
RTV	Ritonavir
SQV	Saquinavir
d4T	Stavudine
TDF	Tenofovir Disoproxil Fumarate
TRIPS	Agreement on Trade-Related Intellectual Property Rights
TB	Tuberculosis
USD	United States Dollars
WHO	World Health Organisation

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## PREFACE

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This discussion paper was commissioned by the Indian Network for People Living with HIV/AIDS (INP+) to address the feasibility of introducing second-line ART into NACO's public-sector treatment programme. INP+'s primary objective for this paper is to advocate for the rapid introduction of second-line regimens into the public-sector treatment programme and to support NACO in its endeavor to ensure that second-line ART is introduced. Over the past year, it has become increasingly clear that the lack of consolidated technical information—from which an evidence base could be established—has prevented more effective advocacy for second-line ART. The data lacunae persists in several overlapping areas: accurate estimation of numbers of patients requiring second-line treatment, the factors contributing to the cost barriers of second-line ART, the impact on the NACO programme if these drugs are patented, and the gaps plaguing the utilization of funding to procure these drugs. This discussion paper aims to fill some of the existing gaps by consolidating technical information pertaining to second-line regimens, thereby providing a basis for INP+'s constructive recommendations to support NACO's efforts to introduce second-line ART.<sup>1</sup>

Since 1986, the Government of India has worked to respond to the epidemic that now affects approximately 5.2 million people in India.<sup>2</sup> Today, the government's public health intervention demonstrates mixed results: in the area of preventing infection amongst persons who are uninfected, India's efforts are recognised globally; yet in the care, support and treatment of those who are actually living with HIV/AIDS, India is lagging woefully behind, with fewer than 10% of those who require ART receiving treatment.<sup>3</sup> Three years after the commencement of the free treatment programme, 62,731<sup>4</sup> people are receiving treatment through national ART centres, receiving a limited regimen of first-line ART: AZT, 3TC, and D4T, in combination with NVP and EFV.<sup>5</sup>

As PLHIV go untreated, India's pharmaceutical sector continues to be the world's leading producer of generic ART, laying bare an unforgivable paradox that remains to be rectified. The access issue in the Indian context is quite different than in other developing countries that actually lack the ability to obtain affordable medicines. In India, access to medicines is a resource allocation issue. Scaling-up ART is feasible, if decision-makers

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<sup>1</sup> The cost concerns are different for pediatric and adult second-line ART. Because price reductions recently transpired for pediatric ART, and provision for children in India has commenced, this paper focuses on adult second-line ART.

<sup>2</sup> See <http://www.nacoonline.org/about.htm>; see also Chandrasekaran et al., "Containing HIV/AIDS in India: the unfinished agenda," *The Lancet Infect Dis.*, 6:508-21 (2006).

<sup>3</sup> See WHO and UNAIDS, "Progress on Global Access to Antiretroviral Therapy: A report on "3 by 5" and beyond" (Mar. 2006). See also the proposal submitted for GFATM funds at [http://www.theglobalfund.org/search/docs/4IDAH\\_793\\_0\\_full.pdf](http://www.theglobalfund.org/search/docs/4IDAH_793_0_full.pdf) for an explanation of why ART was not widely used.

<sup>4</sup> Latest figure obtained through correspondence with Dr.B.B. Rewari, NACO, dated 12 Mar. 2007. Figures obtained from NACO in February 2007: 56,916 PLHIV are receiving first-line ART from 117 centres, 3700 from intersectoral/NGOs, and roughly 20,000 in private sector.

<sup>5</sup> Figures dated 31 Oct. 2006. See *Missing the Target #3*; see also Correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," and [http://www.nacoonline.org/guidelines/art\\_guidelines.pdf](http://www.nacoonline.org/guidelines/art_guidelines.pdf), at p.28.

allocate available resources differently, by opting to overcome obstacles such as the current high cost of second-line ART, the looming threat of patents, and related clinical, operational and ethical issues.

In December 2006, however, the Ministry of Health announced that it was not considering the option of providing free second-line ART as part of its public treatment programme.<sup>6</sup> The Ministry of Health made this determination despite the fact that India is witnessing deaths of PLHIV across the country due to lack of affordable, accessible second-line ART.<sup>7</sup> Both INP+ and the NACP-3 consultations have highlighted the need for second-line ART on multiple occasions, and clinicians across the country are affirming this need by vocalizing concerns about drug resistance, viral load monitoring and complex case management due to HIV co-infection. As patients move from needing first- to second-line ART in India, there are serious questions about the country's ability to scale up the delivery of treatment and sustain the ART programme. The arguments against introducing free second-line ART are not convincing, however, as this discussion paper will demonstrate. The cost and related obstacles are not insurmountable, as we demonstrate in this paper through several findings, including:

- The low achievable cost in the short-term to provide second-line ART will be **\$2-3million USD/year**. The Clinton Foundation and UNITAID<sup>8</sup> have already committed these funds for the first two years of second-line ART provision.
- In the first five years of the programme, it will cost NACO an estimated **\$14million USD** to provide second-line ART after accounting for the two-year donor contribution. NACO/HSCC's successful track record in effectively negotiating lowest prices for first-line ART indicates that lowest prices can also be achieved for procurement of second-line ART.<sup>9</sup> The tentative NACP-3 ART budget provides for \$302.6 million USD for ART overall. Some of these funds should be used to procure second-line ART.
- The patenting of ARVs primarily threatens the access of LPV/r – most other drugs are still legally capable of production by Indian generic companies. In this document we set out the options for NACO to ensure that LPV/r is provided in the national programme.

Since we show that providing second-line ART is feasible, to withhold treatment from the patients who currently need second-line ART is an unconscionable travesty. There are more resources available today than ever before: donor support, generic production and growing civil society momentum and involvement. INP+ advocates that change is possible, and that barriers to introducing second-line ART can be overcome.

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<sup>6</sup> See Government of India, Ministry of Health and Family Welfare, Lok Sabha Parliamentary Question, Starred Question No. 320, "Provision of Second Line Drugs for HIV/AIDS," 13 Dec. 2006, on whether the government intends to provide high-priced drugs such as ddI and ABC. The National HIV/AIDS Control Programme is implemented by NACO under the Ministry of Health and Family Welfare.

<sup>7</sup> See email from K.K. Abraham, INP+, to Solution Exchange for AIDS Community, posted 16 Jan. 2007.

<sup>8</sup> UNITAID is a recently created international drug purchase facility. For more information, see [www.unitaid.eu](http://www.unitaid.eu).

<sup>9</sup> HSCC (India) Ltd is NACO's procurement agency. For more information, see <http://hsccltd.co.in>.

INP+ strongly urges NACO to examine these issues with a critical eye and to endorse the introduction of second-line ART into the national programme, while continuing the scale-up of first-line ART. To support NACO in this endeavor, INP+ submits this discussion paper as a first attempt toward raising the issues and finding solutions. This paper is not an attempt to provide comprehensive answers, but to consolidate information, raise key questions and initiate discussion on this important topic. This paper can be used by NACO as well as by advocates who have some familiarity with ART issues and wish to learn more about the issues standing in the way of PLHIV in India accessing ART that they urgently require.

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## 1 Introduction

There is an undisputed urgency for second-line ART to treat people living with HIV in India.<sup>10</sup> Yet the Government of India, through NACO, has not introduced second-line regimens into the public sector treatment programme.<sup>11</sup> At the forefront of the government's hesitation to introduce second-line ART is the seemingly prohibitive cost of these medications.<sup>12</sup> After Indian companies drove down the price of first-line ART in 2001, prices have steadily declined for those first-line drugs, with a year's course averaging \$130-200USD/year.<sup>13</sup> Second-line ARVs are still more expensive, with some estimates placing second-line at five to ten times the cost of first-line ARVs.<sup>14</sup> Significantly, however, there is no concrete data quantifying the number of patients requiring second-line ART or assessing drug resistance, two critical public health lacuna requiring immediate attention for calculating costs.

Although NACO is currently not providing second-line antiretroviral drugs through its ART programme,<sup>15</sup> free second-line ART is being provided by some external donors and agencies. For example, the Children Investment Fund Foundation, a UK-based non-profit organization, provides funds to the Tamil Nadu State AIDS Control Society so that it can administer ART, including some second-line drugs, to 1000 PLHIV in India. The non-governmental organization MSF also provides free second-line ARVs in its Mumbai project.<sup>16</sup> Further, the Indian non-governmental organization Freedom Foundation is providing free second-line ART to 62 PLHIV.<sup>17</sup> The resources contributed by these

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<sup>10</sup> See ITPC's second six-month update to AIDS treatment report, "Missing the Target #3: Stagnation in AIDS Treatment scale up puts millions of lives at risk," at 19; *see also* Richard Stern and Eugene Schiff, Agua Buena Human Rights Association, "NACO in Denial About Realities of ARV Access in India;" letter exchange between Richard Stern, Agua Buena, and GFATM, 5 Dec. 2006, and 18 Dec. 2006; correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," ¶ 2.5.

<sup>11</sup> See correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," ¶ 2.5.

<sup>12</sup> See correspondence from GFATM to Richard Stern, 18 Dec. 2006; *see also* "NACO wants to ensure adequate supply of second-line drugs for AIDS treatment," [www.redribbon.org.in/news/april06/025040601](http://www.redribbon.org.in/news/april06/025040601).

<sup>13</sup> See Dionisio, Daniele, "Profit Rules and the Right to Appropriate Antiretroviral Treatments – Suitability of Incentive-Bound WHO-Mediated Voluntary Licenses For Equitable Long-Term Solutions," at 1 (2006); *see also* MSF, UNTANGLING THE WEB OF PRICE REDUCTIONS: A PRICING GUIDE FOR THE PURCHASE OF ARVs IN DEVELOPING COUNTRIES (9th ed.). New York, NY (2006)(clarifying that using an improved first-line regimen—e.g. TDF—as recommended by WHO, will raise the current cost of first-line therapy by at least 2.5 times); *See also* "Access to AIDS Medicines stumbles on trade rules," *available at* <http://www.who.int/bulletin/volumes/84/5/news10506/en/index.html>.

<sup>14</sup> *Id.*

<sup>15</sup> See ITPC's second six-month update to AIDS treatment report, "Missing the Target #3: Stagnation in AIDS Treatment scale up puts millions of lives at risk," at 19; *see also* correspondence from GFATM to Richard Stern, 18 Dec. 2006; correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," ¶ 2.5.

<sup>16</sup> See Interview with Leena Menghaney, MSF, 20 Feb. 2007. MSF is currently providing TDF to 5-6 patients in Mumbai. *See also* "Missing the Target #3."

<sup>17</sup> See e-mail correspondence between author and Ashok Rau, Executive Trustee/CEO, Freedom Foundation-India, Nigeria and Botswana. According to Mr. Rau, there are currently 96 PLHIV

groups do not diminish the need for NACO to introduce, develop and sustain the second-line ART component of the public sector programme. Aside from having limited resources, external organizations are not a substitute for a government's commitment of resources. The responsibility for initiating and continuing patients on ART lies first and foremost with NACO.

NACO's desire to provide second-line ARVs, and its concerns about the costs of these drugs, are evidenced by a recent letter from the GFATM to health activists.<sup>18</sup> The letter states "the Government of India is committed to introducing the second-line drugs but they want to make sure they have the resources."<sup>19</sup> The letter also states "the Government of India wants some assurances from UNITAID that the support will be continued beyond two years."<sup>20</sup> Based on this correspondence, it appears that NACO is considering obtaining second-line ART, with support from UNITAID and CHAI, but believes that its ability to implement second-line ART depends on the duration of that support.<sup>21</sup> NACO's primary concern appears to be the ability to provide an uninterrupted supply of ART, given NACO's estimate that the cost for second-line ART will be \$3million USD in the first year, \$7 million USD in the second year, and in subsequent years, \$70+ million USD.<sup>22</sup> However, the basis for these estimates is unclear. GFATM funds likely will be used to build human resource and related capacity for this transition. NACO is due to receive \$17 million USD from GFATM by mid-January, of which \$8 million USD has already been spent by NACO.<sup>23</sup> Unfortunately, although Rupees 1334 crores (\$302.6million USD) are allocated in NACO's budget for the third phase of the National AIDS Control Programme's for ART, no allocation is made specifically for second-line ART.<sup>24</sup>

NACO appears to be pursuing alternative approaches for overcoming the cost and providing second-line ART through its public programme. In a recent letter to INP+, NACO stated that the Health Ministry and NACO are considering, amongst other options, the possibility of public sector production to bring down the prices of HIV drugs.<sup>25</sup> Although NACO is exploring the feasibility of introducing the second-line drugs into the public treatment programme, this exploratory phase has been ongoing for more than a year. There remains an urgent need to arrive at some conclusions and introduce second-line ART.<sup>26</sup>

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waiting to be enrolled in the free second-line Freedom Foundation programme. The programme offers IDV and RTV, supplied by Ranbaxy and Cytomed.

<sup>18</sup> See correspondence from GFATM to Richard Stern, 18 Dec. 2006.

<sup>19</sup> Id.

<sup>20</sup> Id.

<sup>21</sup> At the time of this writing, UNITAID can only commit to covering the costs of second-line ART for two years.

<sup>22</sup> See correspondence from GFATM to Richard Stern, 18 Dec. 2006.

<sup>23</sup> Id. See also [http://www.theglobalfund.org/search/docs/4IDAH\\_793\\_0\\_full.pdf](http://www.theglobalfund.org/search/docs/4IDAH_793_0_full.pdf), to access the proposal for nearly \$1 million USD for second-line ART. See also [http://www.theglobalfund.org/search/docs/4IDAH\\_793\\_0\\_summary.pdf](http://www.theglobalfund.org/search/docs/4IDAH_793_0_summary.pdf), proposal for GFATM funds for five years requesting \$77 million USD.

<sup>24</sup> See Draft NACP-3 Budget, "Financial requirements," Ch. 18, available with author.

<sup>25</sup> See also correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," ¶ 2.5.

<sup>26</sup> See NACO/WHO Draft Minutes, National Consultation on Need and Feasibility for Second Line Antiretroviral Drugs, 24-25 Nov. 2005 (Delhi, India); see also correspondence from

## 2 Background

The *Background* section presents up-to-date information on India, the national ART programme, and second-line HIV drugs. Beginning with an overview of India's ART programme, this section offers basic definitions of how second-line HIV drugs are classified globally and in India. This section emphasizes the need to estimate the number of PLHIV in the country for forecasting purposes while initiating second-line ART into the programme. The section also provides details about the ART programme, including what drugs are offered, who supplies ART to NACO, and what first- and second-line drugs are currently patented, marketed, and/or available in India.

### 2.1 What is the background of the ART programme in India?

India, classified as a low-income country, has a population of over 1 billion persons and an estimated 5.2 million people living with HIV.<sup>27</sup> Currently, both treatment coverage and the number of persons requiring treatment are on the rise.<sup>28</sup> Unfortunately, India is still treating fewer than 10% of persons requiring treatment, with only 62,731 persons receiving treatment through the public sector programme.<sup>29</sup> Government spending on HIV/AIDS was approximately \$79 million USD in 2004, comprising \$0.15 USD per capita of the adult population in India.<sup>30</sup> This figure is much lower than other countries, such as Thailand, which spends \$1.74 USD per capita treating AIDS.<sup>31</sup>

The inception of the Indian government's response to the HIV/AIDS epidemic can be traced back to 1986, when the first case of HIV was identified in Chennai, and soon thereafter, NACO was established.<sup>32</sup> The National AIDS Control Programme was introduced in 1992 and has undergone two stages. The first stage focused on basic prevention, including condoms and blood surveillance, and building capacity to create an effective AIDS programme. Most intervention undertaken during this phase focused on awareness efforts amongst the general population. In 1999, the second phase of the programme began, with a significant shift from awareness-raising to targeted interventions amongst high-risk groups. During this period, from 1999 to 2006, two significant developments, relevant to treatment, arose: a human-rights based approach

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GFATM to Richard Stern, 18 Dec. 2006; correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," ¶ 2.5.

<sup>27</sup> See [www.worldbank.org/data/countryclass/classgroups.htm](http://www.worldbank.org/data/countryclass/classgroups.htm); see also Chandrasekaran et al., "Containing HIV/AIDS in India: the unfinished agenda," *The Lancet Infect Dis.* 6:508-21 (2006).

<sup>28</sup> See [www.nacoonline.org](http://www.nacoonline.org); see also correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006," UNAIDS, 2006 Report on the Global AIDS Epidemic, Annex 3: Country Progress Indicators, at 558.

<sup>29</sup> See WHO and UNAIDS, "Progress on Global Access to Antiretroviral Therapy: A report on '3 by 5' and beyond" (Mar. 2006); see also correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006." See also latest data available with NACO.

<sup>30</sup> See also Chandrasekaran et al., "Containing HIV/AIDS in India: the unfinished agenda," *The Lancet Infect Dis.* 6:508-21, at 513 (2006). This low figure for India is in consonance with overall low government expenditure on health of \$7 per capita.

<sup>31</sup> *Id.*

<sup>32</sup> See [www.nacoonline.org/about](http://www.nacoonline.org/about); see also Chandrasekaran et al., "Containing HIV/AIDS in India: the unfinished agenda," *The Lancet Infect Dis.* 6:508-21 (2006).

endorsed by NACO, and the introduction of a care and support component into the AIDS programme.<sup>33</sup>

In 2003, NACO began to assess the feasibility of introducing free ART into the programme. The NACO-sponsored ART programme was formally launched in April 2004, and has slowly grown over the last three years.<sup>34</sup> Today, the programme provides free access to first-line ART, but the number of patients on the drugs is limited. Currently, 62,731 people are receiving ART through 117 NACO-supported ART centres.<sup>35</sup> Aside from the NACO programme, approximately 5,544 PLHIV are receiving ART through NGOs or other government-related sites, and an estimated 20,000 persons are receiving ART through the private sector.<sup>36</sup> In 2007, CHAI, an international organization committed to supporting the Government of India on ensuring access to treatment, with support from UNITAID, will be increasing treatment coverage to reach 10,000 children.<sup>37</sup> The number of patients requiring treatment is expected to grow due to a combination of factors— existing patients not yet receiving treatment, the spread of infection, and an increasing number of people identified as positive and seeking access to treatment.<sup>38</sup>

Presently, India's treatment programme is under intense scrutiny by Indian and international advocates for treatment access. The creation of the ART programme was an important step towards reaching the goal of universal access. NACO has worked to develop the programme, scaling up institutional and human-resource capacity, instituting treatment delivery sites in several states, and expanding treatment coverage nationally. Persistent failures, however, continue to plague the programme, including repeated shortages and stockouts at treatment sites.<sup>39</sup> The Government of India, like governments around the world, is still grappling with the challenges of sustaining and scaling up the ART programme. INP+ would like to bring to NACO's attention that despite this common challenge facing countries globally, other countries are initiating patients on second-line ART in public programmes.<sup>40</sup>

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<sup>33</sup> See [www.nacoonline.org](http://www.nacoonline.org).

<sup>34</sup> See [http://www.nacoonline.org/guidelines/art\\_guidelines.pdf](http://www.nacoonline.org/guidelines/art_guidelines.pdf).

<sup>35</sup> Figures dated 12 Mar. 2007 and 22 Feb. 2007. For documented figures from 31 Oct. 2006, See Missing the Target #3; see also correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006."

<sup>36</sup> No private sector data is officially available. See correspondence from NACO to INP+, "Reply to INP+ request for information on ART for their next ITPC report 2006."

<sup>37</sup> See CHAI press release, "Former President Clinton Announces Breakthroughs in HIV/AIDS Treatment for Children: 3-in-1 Pill for Less than \$60 Annually and 45% Price Reductions for Other Pediatric Drugs", 30 Nov. 2006, Delhi, India.

<sup>38</sup> This number will be offset with the number of AIDS deaths every year. From 1993-2006, approximately 10,224 AIDS deaths are reported in India. See "Reply to INP+ request for information on ART for their next ITPC report 2006", Annex II, Deaths Due to AIDS, available with INP+.

<sup>39</sup> Further issues and challenges can be found at [http://www.who.int/hiv/HIVCP\\_IND.pdf](http://www.who.int/hiv/HIVCP_IND.pdf).

<sup>40</sup> Brazil, Thailand and South Africa all provide second-line ART in the national treatment programmes. South Africa is reported to provide ddI and LPV/r. See, e.g. National Antiretroviral Treatment Guideline, National Department of Health, 2004, South Africa; See Also <http://www.retroconference.org/2007/Abstracts/30137.htm>.

## 2.2 What drugs are currently provided by India's public treatment programme?

India's treatment programme currently includes a limited number of first-line drugs—AZT, 3TC, and D4T, in combination with NVP and EFV.<sup>41</sup> These treatment regimens are more limited in number and therapeutic advantage than those offered in other countries, such as Brazil, where treatment guidelines include PIs in the first-line regimen and offer PLHIV options of LPV/r, ATV, TDF and ENF.<sup>42</sup> Similarly, Thailand has introduced ABC, DDI, LPV/r, and SQV/r into its national treatment programme and, more recently, issued compulsory licenses<sup>43</sup> for LPV/r to lower the cost of HIV treatment.<sup>44</sup> These countries are following the WHO recommendation that the second-line regimen be initiated when patients start showing treatment failure, but in providing only basic first-line ART, India is falling short of international guidelines. Although India has an estimated 5.2 million PLHIV, its response pales in comparison to Brazil and Thailand, whose responses of HIV care surpass those outlined by WHO's recommended guidelines.

There are numerous factors that affect other countries' decisions to include a broader range of ARVs. Both Brazil and Thailand have mature epidemics, with longer histories of treatment delivery, necessitating the introduction of newer therapies.<sup>45</sup> Prior to its current progressive regimen utilizing PIs in the first-line ART regimen, Brazil offered only first-line ART, but responded to the maturation of the epidemic and advances in drug development.<sup>46</sup> Additionally, civil society activism and judicial decisions requiring governments to provide the latest ARVs placed considerable pressure on governments in

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<sup>41</sup> See [http://www.nacoonline.org/guidelines/art\\_guidelines.pdf](http://www.nacoonline.org/guidelines/art_guidelines.pdf).

<sup>42</sup> See "Recomendações para Terapia. Anti-Retroviral em Adultos e Adolescentes. Infectados pelo HIV. 2006", Programa Nacional de DST e Aids, Brasília – DF, at 13, 27, available at <http://www.sbmt.org.br/consenso2006.pdf>.

<sup>43</sup> A compulsory license is a license issued by a government to a third party to allow the production of a patented product, upon payment of a royalty to the patent holder. See [http://www.wto.org/english/tratop\\_e/trips\\_e/public\\_health\\_faq\\_e.htm](http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm).

<sup>44</sup> See The World Bank "The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand", Ch. 3, at 63, 82 (Aug. 2006), available at <http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/EASTASIAPACIFICEXT/EXTEAPREGTOPHEANUT/EXTEAPREGTOPHIVAIDS/0,,contentMDK:21024879~pagePK:34004173~piPK:34003707~theSitePK:503157,00.html>; see also Apiradee Treerutkuarkul, "Ministry pushes ahead with patent breaking," Bangkok Post, (Feb. 13, 2007), available at [http://www.bangkokpost.com/News/13Feb2007\\_news16.php](http://www.bangkokpost.com/News/13Feb2007_news16.php). Thailand has also issued a compulsory license on EFV. See [http://www.ip-watch.org/weblog/index.php?p=499&res=800\\_ff&print=0](http://www.ip-watch.org/weblog/index.php?p=499&res=800_ff&print=0).

<sup>45</sup> See The World Bank, "The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand," Ch. 2, at 26-37 (Aug. 2006); see also M. Scheffer and A. Salazar, et al., Q REMÉDIO VIA JUSTIÇA. Brasília: Programa Nacional de DST/AIDS (2005). See also Bermudez et al, "Essential medicines and AIDS care in Brazil: recent lessons learnt", UNAIDS, 2002, available at <http://hivinsite.ucsf.edu/pdf/cr05-br-01.pdf>. See Also Bastos et al, "Treatment for HIV/AIDS in Brazil: strengths, challenges, and opportunities for operations research," AID Science Vol.1, No.15, Nov. 27, 2001.

<sup>46</sup> *Id.* See also Bermudez et al, "Essential medicines and AIDS care in Brazil: recent lessons learnt", UNAIDS, 2002, available at <http://hivinsite.ucsf.edu/pdf/cr05-br-01.pdf>. See Also Bastos et al, "Treatment for HIV/AIDS in Brazil: strengths, challenges, and opportunities for operations research," AID Science Vol.1, No.15, Nov. 27, 2001.

these countries.<sup>47</sup> The governments of both Brazil and Thailand also responded to public health concerns, namely the increase in treatment failure, drug resistance, and the challenges of long-term AIDS and opportunistic infection (OI) treatment.<sup>48</sup> These countries, in response to various factors, have created treatment guidelines that are more advanced than India's.

In India, the development of treatment failure (or the failure of patients to respond to first-line ART), the concomitant emergence of resistant strains of HIV, and the need for more options to treat patients co-infected with tuberculosis and viral hepatitis all signal the need for the introduction of second-line ARV treatment options.<sup>49</sup> This need is magnified by the growing Indian civil society movement demanding second-line ART.<sup>50</sup> NACO should draw from the experiences of Brazil and Thailand and introduce second-line ART into the free treatment programme. The experiences of these countries in providing latest second-line therapy demonstrates that it is possible for a developing country to ensure access to second-line treatment for PLHIV.

### **2.3 Where do the drugs come from that are used in India's public treatment programme?**

Currently, the first-line ARVs used in India's free programme are procured from multiple suppliers. All of these suppliers are Indian generic companies offering low-cost drugs. A complete table of suppliers and procurement prices is offered in **Section 3.5**. There is reportedly no procurement plan in existence at this time.<sup>51</sup>

At the time of this writing, all funding for ARV procurement is primarily derived from the Government of India and/or the GFATM. No partnerships or donation programmes are being used to obtain first-line ARVs.

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<sup>47</sup> *See id.* *See also* "The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand," Ch. 2, at 25. *See also* <http://www.cptech.org/ip/health/c/brazil/>. *See Also* Bastos et al, "Treatment for HIV/AIDS in Brazil: strengths, challenges, and opportunities for operations research," AID Science Vol.1, No.15, Nov. 27, 2001. *See Also* Jane Galvao, "Brazil and Access to HIV/AIDS Drugs: A Question of Human Rights and Public Health", AJPH, Vol.95, No.7, July 2005.

<sup>48</sup> *See id.* *See also* "The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand," Ch. 3, at 63. *See Also* Bastos et al, "Treatment for HIV/AIDS in Brazil: strengths, challenges, and opportunities for operations research," AID Science Vol.1, No.15, November 27, 2001. *See Also* Jane Galvao, "Brazil and Access to HIV/AIDS Drugs: A Question of Human Rights and Public Health", AJPH, Vol.95, No.7, July 2005.

<sup>49</sup> *See* NACO/WHO Draft Minutes, National Consultation on Need and Feasibility for Second Line Antiretroviral Drugs, 24-25 Nov. 2005 (Delhi, India).

<sup>50</sup> *See* ITPC's second six-month update to AIDS treatment report, "Missing the Target #3: Stagnation in AIDS Treatment scale up puts millions of lives at risk," at 19; *see also* Press release, "Access Denied to Crucial New HIV/AIDS Medicines Under the Indian Government's AIDS Treatment Programme, Positive People Rally In New Delhi as Many Face AIDS and Death," 1 Dec. 2006 (New Delhi, India); description of World AIDS Day rally organized by INP+ for second-line ART at [www.fhi.org/en/HIVAIDS/country/India/res\\_WAD\\_IndianNGOs2006.htm](http://www.fhi.org/en/HIVAIDS/country/India/res_WAD_IndianNGOs2006.htm).

<sup>51</sup> Despite efforts made by INP+ no procurement plan was available from either NACO or HSCC. We were informed via telephonic conversation on 2 Mar. 2007 with HSCC that it does not use an official procurement plan.

## 2.4 What are “second-line” drugs?

The term “second-line ART” has many definitions. Generally, second-line ART refers to a regimen of drugs recommended for patients who experience treatment failure with the first-line of drugs, and require new drugs for treatment to be effective. Both the WHO and national AIDS programmes such as NACO have precise recommendations for what constitutes second-line ART. Second-line ART under both WHO and NACO refers to specific NRTIs and PIs. It should be noted here that when advocates in India lobby for policy changes to introduce second-line ART, they are referring primarily to PIs, such as LPV/r, which have the potential to significantly improve treatment outcomes. It is access to these PIs that are generating the controversy in India. This is because they are considerably more expensive than first-line ARVs, and because the government has not introduced PIs into the free ARV programme.

In 2006, the WHO issued revised ART Guidelines, entitled “*Antiretroviral Guidelines for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach.*”<sup>52</sup> The ART Guidelines classify second-line ART as treatment recommended when patients experience treatment failure on the first-line of drugs and require new drugs for treatment to be effective. In order to assist in understanding the comprehensive treatment regimen recommended globally, the chart below provides a snapshot view of what drugs are classified as first- and second-line by WHO:

**Table 1. Detailed Recommendations for Switching to Second-Line ARV Regimens in Adults and Adolescents**

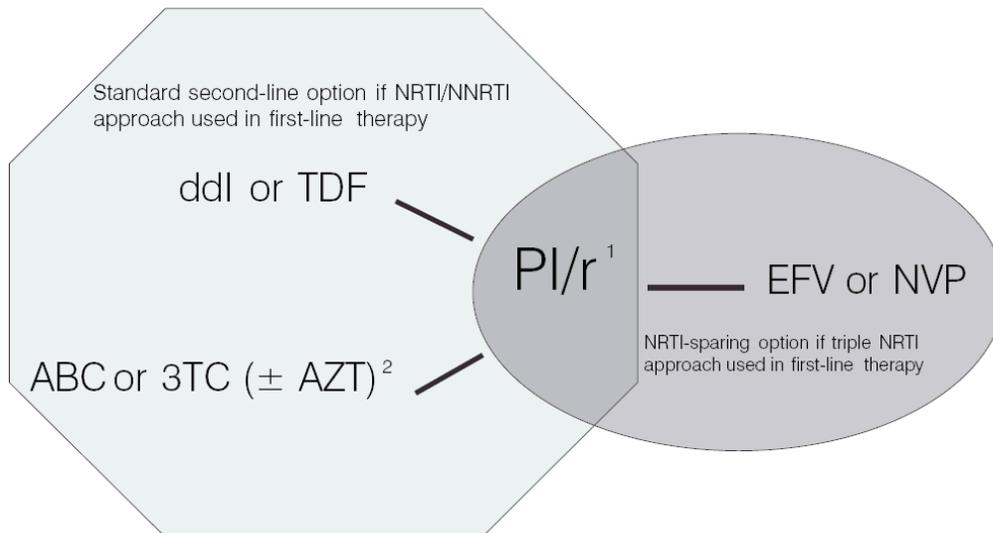
First-line regimen		Second-line regimen	
		NRTI component	PI component
<b>Standard Strategy</b>	AZT or d4T + 3TC +NVP or EFV	ddl + ABC or TDF + ABC or TDF + 3TC (+/- AZT)	PI/r
	TDF +3TC + NVP or EFV	ddl + ABC or ddl + 3TC (+/- AZT)	
	ABC +3TC+ NVP or EFV	ddl + 3TC (+/- AZT) or TDF + 3TC (+/- AZT)	
<b>Alternative Strategy</b>	AZT or d4T + 3TC + TDF or ABC	EFV or NVP +/- ddl	

Reproduced from WHO, “*Antiretroviral Guidelines for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach,*” Table 11 (2006).

<sup>52</sup> In 2003, the WHO launched its “3 x 5” programme, intended to put 3 million patients on ARVs in developing countries by 2005. To this end the WHO published a document entitled, “Scaling up of anti-retroviral therapy in resource-limited settings: treatment guidelines for a public health approach,” which is widely implemented and/or adapted into national treatment guidelines across the world. In this document, ART is divided into two categories: first- and second-line therapies.

WHO recommends that PLHIV take three active drugs together in order to retard the reproduction of the HIV virus. The backbone of the WHO's second-line regimen is the use of a PI — LPV, IDV, ATV, FPV, or SQV—boosted with another PI, RTV. This PI regimen is completed with the addition of TDF, ABC, ddi, and 3TC +/- AZT.<sup>53</sup> WHO conceptualizes this regimen visually:

**Figure 1. Strategies for Second-Line ART**



Reproduced from WHO, "Antiretroviral Guidelines for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach," (2006).<sup>54</sup>

Under the WHO's framework, it is recommended that countries treat patients with first-line ART, e.g. 3TC or AZT, and then, if patients experience treatment failure, patients should be switched to a second-line therapy.<sup>55</sup> These WHO guidelines are international guidelines that are either directly incorporated or are adapted into national treatment guidelines. In India, although second-line ART is not supplied through the national programme, the current guidelines recommend a second-line ART regimen of TDF/ABC + ddi + LPV/r (or SQV/r).<sup>56</sup> NACO is currently revising its national treatment guidelines as follows:<sup>57</sup>

<sup>53</sup> The alternative option of NVP or EFV as a second-line regimen is recommended for switching from a first-line triple NRTI combination (e.g. 3TC+AZT+ABC/TDF), which India does not use and is therefore not relevant in the Indian context thus far.

<sup>54</sup> In 2003, the WHO launched its 3 x 5 programme, intended to put three million patients in developing countries on ARVs by 2005. To this end, the WHO published a document entitled "Scaling up of anti-retroviral therapy in resource-limited settings: treatment guidelines for a public health approach," which is widely implemented or adapted into national treatment guidelines across the world. In this document ART is divided into two categories, first and second line therapies.

<sup>55</sup> Further discussion on issues relating to switching regimens can be found in section 4.3.

<sup>56</sup> See Section 9.12, available at [http://www.nacoonline.org/guidelines/art\\_guidelines.pdf](http://www.nacoonline.org/guidelines/art_guidelines.pdf).

<sup>57</sup> See WHO, Pre-final Draft Guidelines for ART (Jan. 2007), available with author.

**Table 2. Proposed Revised NACO ART Guidelines**

First-line regimen	Second-line regimen	
	NRTI component	PI component
AZT/3TC/NVP	<b>Choices</b> 1 <sup>st</sup> TDF/ABC 2 <sup>nd</sup> ddI/ABC 3 <sup>rd</sup> TDF/AZT	<b>Choices</b> 1 <sup>st</sup> LPV/r 2 <sup>nd</sup> ATV/r 3 <sup>rd</sup> SQV/r 4 <sup>th</sup> IND/r
AZT/3TC/EFV		
D4T/3TC/NVP		
D4T/3TC/NVP		
TDF/3TC/NVP	<b>Choices</b> 1 <sup>st</sup> ddI/AZT 2 <sup>nd</sup> ddI/ABC	**NLF where no cold chain available
TDF/3TC/EFV		

Reproduced from NACO Pre-Final Draft ART Guidelines (2007), pending printing.

Clinicians and policymakers in India have advocated for expanding the first-line of ART to include TDF and ABC rather than introducing second-line PIs such as LPV/r. This strategy is presumably meant to minimize the political sensitivity shrouding the discussion of second-line ART in India. It allows for the rapid introduction of drugs such as TDF and ABC without deciding the controversial question of whether to adopt the PI component, which is the most expensive hurdle to introducing second-line ART. INP+ is firmly of the opinion that PIs such as LPV/r and ATV must be rapidly introduced into the national treatment programme, because the actual impact of expanding the first-line regimen is limited for PLHIV without the PI component. If, for example, PLHIV are facing side effects or toxicity, then switching to ABC or TDF is an appropriate option.<sup>58</sup> In the face of treatment failure, however, which PLHIV in India are facing, PIs are the optimal solution and should be provided. Therefore, TDF, ABC and PIs should be introduced into the national treatment programme.

## 2.5 How many people actually require second-line ARVs in India?

There is no concrete data in India on the number of people who need to switch to second-line HIV drugs. The most common reference is to 3000-5000 persons, presumably derived from the figure—10% of the persons on first-line treatment in 2006<sup>59</sup>—used in countries with mature epidemics.<sup>60</sup> However the 10% figure is relatively high considering India does not have a mature epidemic – that is, India has not been providing treatment to PLHIV for the length of time many other countries have been. Another figure of reference discussed in India is that an estimated 1800 persons require second-line treatment. This figure is presumably based on an estimated 2-3% of PLHIV in resource-constrained settings who need to switch to second-line ART.<sup>61</sup> In this case, 3% of

<sup>58</sup> The toxicity concerns refer to long-term toxicity of D4T and hematologic toxicity of AZT in low-income settings.

<sup>59</sup> In 2006 there were approximately 45,000 PLHIV receiving ART in the public programme.

<sup>60</sup> See proposal for GFATM funds,

[http://www.theglobalfund.org/search/docs/4IDAH\\_793\\_0\\_full.pdf](http://www.theglobalfund.org/search/docs/4IDAH_793_0_full.pdf), p 117, discussing the Cape Town model of 9% being too high a figure to apply to India's ART-naïve population.

<sup>61</sup> See, e.g., <http://www.retroconference.org/2007/Abstracts/30137.htm>, showing a treatment failure rate of 2% at 1.5 years in two Johannesburg clinics;

<http://www.retroconference.org/2007/Abstracts/29112.htm>, showing a virological failure rate of 4% for patients in South Africa on first-line ART;

<http://www.retroconference.org/2007/Abstracts/29563.htm>, data from 7 African countries

approximately 62,731 PLHIV receiving treatment results in around 1800 persons requiring second-line ART. Addressing the needs of PLHIV requiring treatment means quantifying this number accurately, a gap requiring urgent attention.

Existing data in India is informal and limited.<sup>62</sup> As mentioned in the previous paragraph, according to one localized study of patients in South India, 2-3% of PLHIV needed to switch ART due to treatment failure.<sup>63</sup> Additionally raw data available from 38 ART centres shows that 900 PLHIV are in need of second-line ART.<sup>64</sup> Such studies are limited because they do not evaluate patients across the entire country. Furthermore, since HIV viral load testing is not generally conducted as part of routine clinical management of ART in India, the manifestation of immunologic failure (with poor CD4 response or CD4 decline) and/or clinical failure (with development of OI) are used as surrogate, and less accurate, indicators of virologic treatment failure.<sup>65</sup> INP+ urges NACO to initiate second-line treatment while simultaneously undertaking an assessment of the number of patients who need, both presently and in the future, second-line ART. Such accurate forecasting will provide a basis for procuring adequate volumes of drugs, and prediction of demand volume could also result in lower prices.

## **2.6 Does drug resistance warrant the introduction of second-line ART in India?**

Aside from PLHIV in India failing treatment, the other compelling reason to offer second-line ART in India is drug resistance. Drug resistance refers to the phenomenon where specific drug regimens stop being effective in treating the HIV virus.<sup>66</sup> The public health consequences are severe: left untreated, drug resistance has the potential to result in new strains of HIV virus that are resistant to first-line ART.<sup>67</sup> Such widespread emergence of drug resistance threatens the sustainability of the national programme. Unfortunately, minimal data is available in India, with a paucity of information available from public ART centres:

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demonstrating that 0-2% of adults and 0-5% of kids need second-line out of 116,000 people in 117 Columbia-sponsored sites.; contrast with <http://www.retroconference.org/2007/Abstracts/30321.htm>, presenting MSF data from Khayelitsha, South Africa, where 14% of patients required second-line ART after 48 months. *See also* [http://www.doctorswithoutborders.org/pr/2007/03-01-2007\\_1.cfm](http://www.doctorswithoutborders.org/pr/2007/03-01-2007_1.cfm), releasing a March 2007 study demonstrating a .44% switch rate to second-line therapy per year.

<sup>62</sup> One informal estimate shows an increase from 2% to 10% of persons requiring a switch to second-line ART between 2005-6 and 2009-10. *See* Presentation, Duggal S, NACO/WHO Draft Minutes, National Consultation on need and Feasibility for Second Line Antiretroviral Drugs, 24-25 Nov. 2005, Delhi, India.

<sup>63</sup> This may mean substitution within the first-line itself or a switch to second-line therapy. *See* “Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India”, Kumarasamy N, et al, *J Acquir Immune Defic Syndr.* 2006 Jan 1;41(1):53-8, in this study “second-line” was used for any change in the treatment regimen.

<sup>64</sup> *See* interview with Dr.Po-lin Chan, WHO, 21 Feb. 2007.

<sup>65</sup> Viral load testing is not given in the government programme due to resource constraints. For purposes of projection, the lack of viral load testing is likely to lower the estimates of people requiring second-line ART.

<sup>66</sup> *See* <http://www.who.int/drugresistance/hiv aids/en/index.html>.

<sup>67</sup> *Id.*

There are currently no published studies that systematically measure the development of HIV drug resistance longitudinally among persons receiving ART in India. A limited number of studies provide cross-sectional data on only 324 of the estimated 5 million Indians infected with HIV. Moreover, only 53 of these 324 patients had received ART, while the remaining patients were treatment naïve. These small evaluations of a few samples are all based on analyses of specimens collected prior to the government ART roll-out and the expanded use of ART in India. One of these studies utilized a cell-based resistance testing method that has neither been standardized nor validated for HIV subtype C. Prospective data from India, linking adherence measures, ART clinical efficacy, and the development of HIV drug resistance mutations are therefore critically needed. The findings of currently published studies are presented in the table below:<sup>68</sup>

**Table 3. Findings of Currently Published Studies on Drug Resistance in India**

City, Year	ART Naïve N	ART Experienced N	Findings
Mumbai, 1997-2003	21	53	Naïve: 7% NRTI resistance, 3% PI resistance. Experienced: 27% NRTI resistance, 19% PI resistance.
Pune, 1999-2001	12	None	No resistance at baseline.
Chandigarh, 2000-2002	60	None	Minor variants with resistance noted in 78%. Unclear significance.
Mumbai, 2003	128	None	2/128 with 3TC resistance mutation.
Chennai, 2002-2003	50	None	Polymorphisms of unclear clinical significance in 100%.

Collated from available data.

Some work is currently being done in this area but further study is necessary to understand the drug resistance landscape and to prescribe options, both at the individual level and for the national programme. In India, second-line ART is available commercially, and prescribed in an unregulated manner, in the private and NGO sectors. There is currently no alternative for PLHIV failing first-line ART to continue treatment in the public sector – patients are either unable to access treatment, or for those who can afford it, they may pay to receive irrational prescription of ART that may or may not be effective. Furthermore, usually no standardized treatment monitoring is used. With the use of non-guided therapy for second-line ART, ultimately there will be a transmission of resistant virus or resistance to second-line, and potentially even first-line, ART. Neglecting drug resistance as a serious issue in India at this stage could result in the need for more expensive, effective drugs in the future to avoid the further development of drug-resistant strains. All of these points support the introduction of government sponsored second-line ART that is standardized and regulated, to maximize the benefits of therapy for the most people.

<sup>68</sup> Interview with Dr.Padmini Srikantiah, University of California San Francisco. Division of HIV/AIDS, University of California, San Francisco

## 2.7 What is the current status of second-line ART in India?

India's draft treatment guidelines indicate the preferred second-line regimens include two NRTIs and one PI. Currently, the regimens are not provided by India's programme. At the time of this writing, none of the second-line HIV drugs appear to be patented in India.<sup>69</sup> We note here that the following ARVs are currently available:<sup>70</sup>

**Table 4. Drugs available in India**

<b>Nucleoside Reverse Transcriptase Inhibitors (NRTI)</b>	<b>Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)</b>	<b>Protease Inhibitors (PI)</b>
AZT/ZDV	NVP	SQV
d4T	EFV	RTV
3TC		NFV
ddl		ATV
FTC		INV
ABC	<b>Fusion Inhibitors</b>	LPV/r
	N/A	
<b>NRTI</b>		
TDF		

Modified and Excerpted from NACO Pre-final Draft ART Guidelines (2007), Cross-referenced with DCGI List, company marketing brochures, INP+ Discussion Paper "Patents and Universal Access: Issues and Concerns", CHAI supplier list, pharmacy data, and USFDA (2006) HIV Drugs List.

A thorough overview of these drugs in India, including which drugs are being produced generically by various Indian manufacturers, as well as up-to-date patent status, is available in INP+'s Discussion Paper, "*Patents and Universal Access: Issues and Concerns*".<sup>71</sup>

<sup>69</sup> According to author's research. For regular updates on patent publication and grant in India, see [www.india.bigpatents.org](http://www.india.bigpatents.org).

<sup>70</sup> Further research is required to determine whether the drugs granted marketing approval in India are approved in India for the originator company and/or generic company/companies.

<sup>71</sup> See K.M. Gopakumar, "*Patents and Universal Access: Issues and Concerns*", INP+, Discussion Paper, March 2007. This information can be used to plan procurement in advance so there are no bottlenecks in availability.

### 3 Cost Overview

This section examines the cost of second-line ART, consolidating and setting out the information currently available. An illustration of a cost scenario is presented to demonstrate that the cost of introducing second-line ART may be relatively low when compared to the NACP-3 ART and overall budgets. This illustration attempts to show that NACO's hesitation to fund second-line ART may be unwarranted, and that NACO should immediately introduce second-line ART while simultaneously undertaking further cost forecasting analyses. Emphasizing the likelihood that prices will decrease, this section proposes recommendations to NACO on cost issues. The section concludes with an overview of what second-line ART can be procured using GFATM funds.

#### 3.1 Why is Second-Line Considered Expensive?

As discussed in Section 2, the recommended second-line ART regimens include TDF, ddI, ABC, LPV/r and other PIs. Prices of these second-line drugs are considerably higher than first-line ART, in part because of patents and the egregious practices of some patent-holder pharmaceutical companies.<sup>72</sup> Two of the key factors contributing to the high cost of second-line ART are the lack of competition in suppliers resulting in excessive profit margins, and the low demand volume for second-line ART.

These factors are not solely responsible for the high cost of second-line drugs. Even with generic competition bringing down prices of ARVs, second-line prices will not come down as quickly as first-line ARV prices fell in 2001,<sup>73</sup> due to the complexity of the molecules that make up the second-line drugs and the number of steps involved in their synthesis.<sup>74</sup> Although an in-depth discussion of these factors is beyond the scope of this paper, we offer an example to illustrate this point. See box below:

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<sup>72</sup> See John Carreyrou, "Older Pill's Price Hike Helps Sales of Flagship, A Probe in Illinois," Wall Street Journal, at A1 (Jan. 3, 2007); see also "Untangling the Web of Price Reductions: a pricing guide for the purchase of ARVs for developing countries," MSF, July 2006, available at [www.access-med-msf.org](http://www.access-med-msf.org).

<sup>73</sup> See "Untangling the Web of Price Reductions: a pricing guide for the purchase of ARVs for developing countries," MSF, July 2006, available at [www.access-med-msf.org](http://www.access-med-msf.org); see also [www.essentialdrugs.org/edrug/archive/200611/msg00063.php](http://www.essentialdrugs.org/edrug/archive/200611/msg00063.php).

<sup>74</sup> See S. Duggal, Presentation, National Consultation on Need and Feasibility for Second Line Antiretroviral Drugs, NACO/WHO Draft Minutes, 24-25 Nov. 2005 (Delhi, India).

**Fig. 2. The Difference Between First- and Second-Line ART<sup>75</sup>**

"...Making and breaking chemical bonds (the synthetic chemistry of API production) contributes 80% or more to the total cost of typical ARV medications. It is likely that second-line ARVs will continue to be somewhat more expensive than first-line medications because they are more structurally complex – they contain a larger number of atoms in each drug molecule and possess molecular architecture that is more difficult to prepare. The most important cost components of making synthetic APIs are the cost of raw materials, the yield obtained in making and breaking chemical bonds, and 'fixed costs' that relate to capital investment, cost of utilities and labor. The 'yield' obtained in making and breaking chemical bonds contributes to costs significantly. Making and breaking chemical bonds to prepare APIs is carried out in a number of discrete steps.

Synthetic chemistry is not perfect. Each step proceeds in less than 100% yield so that material is lost in every step of making chemical bonds. The more steps needed in production, the more drastically the cost of ARVs increases due to overall losses during production. A typical nucleoside, or ARV for first-line treatment, e.g. 3TC or D4T, is made in about 5 synthetic steps. None of the starting materials is very expensive, and the overall yield from start to finish is very good. LPV/r, by contrast, requires 11 synthetic steps to manufacture. The overall losses due to making and breaking chemical bonds in making LPV/r, therefore, is expected to be higher than that for API syntheses (3TC, d4T) with fewer steps. The synthesis of LPV/r also is inherently costly because two expensive fine chemicals (the wings that flank the central core of the molecules RTV and LPV) that are quite expensive (currently over 3000 rupees/kilogram on metric tonne scale) are incorporated into the API synthesis. The factors of overall yield and number of synthetic steps also cause the fixed costs for API synthesis to rise; giving an inherently greatly increased fully-burdened cost of manufacturing."

In addition, the dosing of second-line ARVs is, on average, higher than that of first-line ARVs. Among first-line ARVs, the average daily dosage is approximately 300mg.<sup>76</sup> The dosage differential is mostly driven by LPV/r, for which the daily dosage is over three times as high as the average first-line ARV (800 mg of LPV plus 200 mg of RTV, or 1000mg total).<sup>77</sup>

Nonetheless, out of the four main factors impacting the cost of second-line ART, at least two factors are expected to diminish significantly in the coming months: excessive profit margins will decrease dramatically with the advent of competition, and volume-based cost savings will materialize as second-line drug prices come down and demand for second-line drugs increases. Longer-term solutions may also emerge as dosage-related cost concerns may be partly alleviated if ATV/r gains acceptance as an alternative to LPV/r. R&D teams are also addressing the chemical complexity of second-line ARVs, hoping to reduce the number of steps required for API synthesis and to improve the yield of each step. However, such chemistry optimization will be a more gradual process and

<sup>75</sup> Interview by author with Associate Professor Joseph Fortunak, Chemistry and Pharmaceutical Sciences, Howard University, 15 Feb. 2007.

<sup>76</sup> See "Antiretroviral Guidelines for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach," WHO, 2006 Revision, p102.

<sup>77</sup> See id.

is less likely to generate substantial short-term cost savings. Overall, the likelihood of achieving significant price reductions for second-line ART remains high.

### 3.2 What will it actually cost NACO to introduce second-line ART?

NACO has expressed concern over the sustainability of providing second-line ART beyond the two years that CHAI/UNITAID propose to fund.<sup>78</sup> Specifically, GFATM notes NACO's position that "the first year alone would cost over \$3m and second year approximately \$7m, and in later years it would cost approximately \$70m or more."<sup>79</sup> NACO has not made explicit the bases for these estimates. Our calculations, below, show that under any set of plausible assumptions in which NACO effectively negotiates lowest existing prices, these numbers are not reasonable. As we will demonstrate, if NACO achieves its targets of scaling up ART overall, the cost of providing second-line ART in the first year the cost is likely to be \$2m, in the second year \$3m, and in the fifth year \$7m.

Consider, for example, the second-line ART regimen TDF+3TC+LPV/r. The total costs of this therapy to NACO would depend on two variables: the size of the patient population requiring ART and the cost of the drug combination.

For the first variable, we use a figure of 3,000 patients who may qualify for second-line ART by the end of 2007.<sup>80</sup> Over the course of the next five years of the NACP-3 programme, we use a total figure of 9,000 persons who may require second-line treatment.<sup>81</sup> These figures are upper-bounds using NACO's own targets for overall ART scale-up, with 100,000 patients projected to be on ART in 2007 and a projected 300,000 PLHIV on treatment in five years. The number of patients here is given as a broad estimate, excluding as a factor the number of AIDS deaths per year of people on first-line ARVs.<sup>82</sup> We use a baseline of 3% of total first-line recipients requiring second-line ART and apply this rate to subsequent years.<sup>83</sup>

For the second variable, we use a low-tier price and an average price. The existing lower-tier price for this regimen is \$745/per patient per year (pppy), using the lowest price offered by Abbott Laboratories for LPV/r (\$500/pppy), the lowest price offered by Cipla Ltd for TDF (\$195/pppy), and the price of 3TC by Cipla Ltd (\$50/pppy). The average price of \$1650/pppy, used for this illustration, is derived by taking the mean of the low

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<sup>78</sup> See correspondence from GFATM to Richard Stern, 18 Dec. 2006. Using these numbers, and the figure of 3000-5000 persons requiring treatment noted in the initial letter, it appears that NACO is arriving at these estimates using the \$745/pppy (per patient per year) figure noted in this section: \$3million (total) / 4000patients = \$750/pppy. But the \$745/pppy number assumes the price of LPV/r is \$500, which it is not. Abbott does not formally recognize India or NACO's programme for its low-tier price, but this has the potential to change depending on NACO's ability to negotiate. Lowering the price of LPV/r will depend on a number of factors, including NACO preparing to work around the potential LPV/r tablet patent.

<sup>79</sup> See correspondence from GFATM to Richard Stern, dated 18 Dec. 2006.

<sup>80</sup> Using a figure of 3% of 100,000 PLHIV projected to be on treatment in 2007.

<sup>81</sup> Using a figure of 3% of 300,000 PLHIV projected to be on treatment in 2011.

<sup>82</sup> Latest information from NACO on 12 Mar. 2007 states that there are 4907 reported deaths of patients receiving first-line ART in the programme.

<sup>83</sup> There is an absence of data on the issue of switch rates in India, as discussed in Section 2.5.

(\$745/pppy) and middle-tier price offered by these companies, acknowledging that NACO’s probable purchase price would not be the middle-income country price but, in the absence of effective negotiation, would also not be the lowest price. This upper-bound price of the second-line ART regimen LPV/r+TDF+3TC is approximately \$2590 USD/pppy,<sup>84</sup> relying on the current middle-tier price offered by Abbott Laboratories for LPV/r (\$2200/pppy),<sup>85</sup> the middle-tier price offered by Cipla Ltd for TDF (\$340/pppy),<sup>86</sup> and Cipla Ltd for 3TC (\$50/pppy).<sup>87</sup>

**Table 5. Breakdown of Existing LPV/r-TDF-3TC Prices**

Prices	LPV/r	TDF	3TC	TOTAL
Middle Tier	\$2200	\$340	\$50	\$2,590
Lower Tier	\$500	\$195	\$50	\$745
Averaged Price	--	--	--	\$1667.5

Moreover, there are good reasons to believe the prices cited above are upper-bounds. This calculation does not account for further decreases in price based on the expected market entry of more Indian generic suppliers and/or negotiations by third party agencies. It is possible that this cost will decrease further with bulk procurement, new combinations and advances in drug synthesis.

In this table we examine the cost to NACO for procuring second-line using lowest available prices, the averaged prices, and two potential scenarios informed by price reductions. For ease of presentation, we use rounded-off numbers:

<sup>84</sup> The prices for TDF and 3TC were obtained from MSF’s “Untangling the Web”, 2006 + update. Individual prices for LPV/r were obtained from Abbott’s publicly available information, as noted in section 4.2.

<sup>85</sup> Abbott offers LPV/r at \$2200/pppy for countries that are not Abbott Access countries, including India. Only one generic version of the LPV/r tablet exists in India—Emcure, which is not WHO pre-qualified. Therefore, we use Abbott’s middle-tier price for this exercise. *See* [http://www.abbott.com/static/content/document/aids\\_care.pdf](http://www.abbott.com/static/content/document/aids_care.pdf); *see also* “Abbott statement regarding new initiatives to expand access and affordability to lopinavir/ritonavir in the developing world,” Aug. 13, 2006.

<sup>86</sup> Gilead offers TDF at \$207/pppy as the lowest-tier price but India is not a Gilead Access Program country. Therefore, we use Cipla’s price of \$340 for purposes of this exercise. (Cipla also offers a lower price to low-income countries but India is not on this list either, and no publicly available information states that India will receive the low-income price).

<sup>87</sup> The price for 3TC were obtained from MSF “Untangling the Web”, 2006 + update.

**Table 6. Estimates of Second-Line ART Costs**

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
Total number of patients projected to be on 1st line ART*	100,000	125,000	150,000	184,000	300,000	300,000
% of patients requiring 2nd line ARV	03%	03%	03%	03%	03%	03%
Total number of patients projected to require 2nd line ART	3000	3750	4500	5520	9000	9000
Low-tier price \$745	\$2,235,000	\$2,793,750	\$3,352,500	\$4,112,400	\$6,705,000	\$19,198,650
Average price \$1,667	\$5,001,000	\$6,251,250	\$7,501,500	\$9,201,840	\$15,003,000	\$42,958,590
10% price reduction off low-tier price = \$670	\$2,010,000	\$2,512,500	\$3,015,000	\$3,698,400	\$6,030,000	\$17,265,900
25% price reduction off low-tier price = \$559	\$1,677,000	\$2,096,350	\$2,515,500	\$3,085,680	\$5,031,000	\$14,405,530

\*Based on NACO targets

Table 6 shows that if NACO is able to effectively negotiate lower-tier existing prices, the total cost over five years would be approximately **\$19M**. NACO's share of this cost will be **\$14M**, as CHAI and UNITAID have already committed to covering the cost of second-line ART for two full years, ensuring that patients in urgent need of second-line ART will receive treatment immediately.<sup>88</sup> However, NACO has not yet agreed to accept this support.<sup>89</sup>

Based on this information, INP+ submits that there is no viable reason to withhold second-line ART from patients in India. Given NACO's track record of successful negotiations of lowest prices for first-line ART, NACO's procurement efforts for second-line ART should achieve comparable success; therefore, the 'middle-tier' scenario should not arise. The cost should not be prohibitive, given that external organizations will bear the cost for at least two years and that by the end of those two years, the cost likely will have diminished significantly. In these first two years, the primary cost that NACO would incur is the training of medical officers, which should not require formidable costs or human resources. Additionally, the costs of providing second-line treatment would be

<sup>88</sup> See correspondence from GFATM to Richard Stern, 18 Dec. 2006.

<sup>89</sup> *Id.*

less than the costs that NACO and the health system would incur if people were denied treatment – for example, the costs of hospitalization or OI treatment.<sup>90</sup>

We note here that the total cost of second-line ART of \$19 million USD is a low sum compared to the overall draft NACP-3 budget in India. The draft NACP-3 budget for the next five years is \$2.6 billion USD (11585 crores), which is \$520 million USD (2317 crores) per year.<sup>91</sup> Out of this budget, only \$60.5 million USD/year (266.8 crores), or \$302.6 million USD (1334 crores) over five years, is allocated for treatment, a sum that comprises only 11.4% of the total NACP-3 budget and is allocated solely for first-line ART.<sup>92</sup> Given that external agencies are willing to bear the financial burden of providing second-line ART, there is simply no reason to delay provision of treatment any longer.

Table 7 presents the comparison between the projected cost of providing second-line ART, assuming that NACO will successfully negotiate lowest existing prices, and the ART and HIV budgets:

**Table 7. Cost Over Five Years to Provide Second-Line ART**

Projected Cost of Providing Second-Line ART	NACP-3 Budget for ART	Total NACP-3 Budget
\$19 million USD	\$302.6 million USD	\$2.6 billion USD

We acknowledge that simply looking at the budget shares oversimplifies the issue, and deflects attention from the benefits of second-line therapy. That is, the more important question from a policy perspective is the cost-effectiveness of second-line therapy, i.e. data is needed on the clinical benefits and (direct and indirect) economic benefits of covering second-line treatment.<sup>93</sup> This is beyond the scope of the current analysis, but the cost-effectiveness of providing treatment is gaining acceptance globally and remains an important topic in India.<sup>94</sup>

<sup>90</sup> There are well-documented benefits of providing treatment. See Teixeira PR, Vitória MAA, Barcarolo J. The Brazilian experience in providing universal access to antiretroviral therapy. In: Moatti J-P, Coriat B, Souteyrand Y, Barnett T, Dumoulin J, Flori Y-A, eds. *Economics of AIDS and Access to HIV/AIDS Care in Developing Countries, Issues and Challenges*. Paris, France: Agence Nationale de Recherches sur le Sida; 2003:69–88. See Also Jane Galvao, “Brazil and Access to HIV/AIDS Drugs: A Question of Human Rights and Public Health”, *AJPH*, Vol.95, No.7, July 2005.

<sup>91</sup> See Draft NACP-3 Budget, “Financial Requirements,” Ch. 18, available with INP+.

<sup>92</sup> See Draft NACP-3 Budget, “Financial requirements,” Ch. 18, available with INP+.

<sup>93</sup> See, e.g., Goldie et al, “Cost-effectiveness of HIV treatment in resource-poor settings-the case of Cote d’Ivoire”, *NEJM*, Vol.355: 1141-1153, No. 11, Sept. 14, 2006, showing cost-effectiveness of delivering ART and a 30% life expectancy increase when second-line treatment was administered after first-line failure; See also Walensky et al, “The Survival Benefits of AIDS Treatment in the United States”, *Journal of Infectious Diseases*, vol.194 (2006), highlighting the cost-effectiveness of providing treatment.

<sup>94</sup> For a brief overview of studies on this issue, see the introduction of “Costing of the Free ART Programme of the Government of India”, Draft, Indrani Gupta et al, Institute of Economic Growth, June 2006.

### 3.3 Will the prices of second-line ART rise or fall in the next five years?

The prices of second-line ART are likely to drop in the next year to five years as demand for second-line increases due to economies of scale.<sup>95</sup> Previous experience with ART prices substantiates this, as first-line ART prices plummeted in 2001 with the advent of generic competition.<sup>96</sup> Recent experiences with pediatric ART price reductions further affirm that ART prices decrease significantly with volume and with the entry of third-party agency involvement.<sup>97</sup> For example, UNITAID is the international health initiative providing financing of HIV/AIDS treatment.<sup>98</sup> The revenues from UNITAID, as demand volume increases, are expected to provide additional “fiscal relief” to companies supplying generic versions of ART and may produce significant price reductions in the near future.<sup>99</sup>

### 3.4 What are bulk procurement prices of second-line ART for India?

There is no available information on bulk procurement prices of second-line ART in India because no tender has been invited and no procurement has taken place for second-line ART.

Through this report, INP+ seeks to make publicly available the information on India’s first-line ART bulk procurement prices. The following is the information we have obtained from NACO for the 2006-2007 period:

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<sup>95</sup> Prices are not expected to drop as low as first-line ART prices, as explained in section 3.1.

<sup>96</sup> See Daniele Dionisio, “Profit Rules and the Right to Appropriate Antiretroviral Treatments – Suitability of Incentive-Bound WHO-Mediated Voluntary Licenses For Equitable Long-Term Solutions,” at 1, (2006); see also MSF, UNTANGLING THE WEB OF PRICE REDUCTIONS: A PRICING GUIDE FOR THE PURCHASE OF ARVS IN DEVELOPING COUNTRIES (9th Ed.). New York, NY (2006)(clarifying that using an improved first-line regimen—e.g. TDF—as recommended by WHO, will raise the current cost of first-line therapy by at least 2.5 times); See also “Access to AIDS Medicines stumbles on trade rules,” available at <http://www.who.int/bulletin/volumes/84/5/news10506/en/index.html>.

<sup>97</sup> See Press Release, CHAI, “Former President Clinton Announces Breakthroughs in HIV/AIDS Treatment for Children: 3-in-1 Pill for Less than \$60 Annually and 45% Price Reductions for Other Pediatric Drugs” (New Delhi, India).

<sup>98</sup> See CHAI, “Q&A on UNITAID and its Partnership with CHAI,” 30 November 2006. CHAI is the lead implementation partner for UNITAID for procurement of both pediatric ART and adult second-line ART. CHAI’s experience thus far is that there has been a 45%-70% price reduction for pediatric ARTs, based on resources committed by UNITAID to purchase large volumes.

<sup>99</sup> See Dinosio p 4.

**Table 8. NACO ARV Purchase Prices, 2006-7<sup>100</sup>**

Sr.No	Name	M/s	Quantity	Unit Price/ Rs	CST
1	NVP 200mg	Hetero Drug Ltd Hyderabad	752400	2.85	Nil
2	d4T 40 mg+ 3TC 150 mg+ NVP 200 mg	Hetero Drug Ltd Hyderabad	1404480	6.15	Nil
3	AZT 300mg+ 3TC 150 mg+ NVP 200 mg	Ranbaxy	21067200	10.70	Nil
4	EFV 600mg	Ranbaxy	4577100	24.66	Nil
5	AZT 300mg+ 3TC 150mg	Aurobindo Pharma	6395400	8.2383	4%
6	d4T 30 mg+ 3TC 150mg	Strides Arco lab	3837240	3.00	Nil
7	d4T 30 mg+ 3TC 150mg+ NVP 200 mg	Cipla	12640360	5.99	Nil
8	d4T 40 mg+ 3TC 150mg	Strides Arco Lab	426360	3.20	Nil

From this Indian procurement data, we now assess the variation from lowest available prices in 2006-7 for these drugs. We find that NACO was able to negotiate lower prices than the lowest available prices listed by the international organization MSF in *“Untangling the Web of Price Reductions: a pricing guide for the purchase of ARVs in developing countries.”*

<sup>100</sup> Prepared by Jacob John, NPAC, INP+. This information was provided over the telephone despite efforts to obtain a written copy.

**Table 9. ARV Price Comparisons<sup>101</sup>**

Drug	NACO Purchase Price (\$USD/pppy)	Lowest Global Reported Price (\$USD/pppy)
NVP 200mg	46.23	56
d4T 40 mg+ 3TC 150 mg+ NVP 200 mg	99.77	140
AZT 300mg+ 3TC 150 mg+ NVP 200 mg	173.58	231
EFV 600mg	200.02	217
AZT 300mg+ 3TC 150mg	133.64	134
d4T 30 mg+ 3TC 150mg	48.67	64
d4T 30 mg+ 3TC 150mg+ NVP 200 mg	97.17	132
d4T 40 mg+ 3TC 150mg	51.91	67

From this comparison, it is clear that NACO and its procurement agency has successfully negotiated lowest prices for first-line ARVs, with the caveat that NACO's lack of a pre-qualification requirement may widen its supplier pool and allow for such low prices.

The procurement prices for first-line ART may serve as a baseline from which to estimate bulk procurement prices for second-line ART in India.<sup>102</sup> If NACO is able to continue effectively negotiating with companies supplying second-line ART, it will be able to bring down the prices discussed earlier in section 3.2.<sup>103</sup>

It should also be noted that none of the first-line ARVs were purchased from patent-holders, a variable that may change in the procurement of second-line ARVs. It is important for multiple suppliers to continue to produce, for competitive pricing to drive down the cost of second-line ART. NACO's options for pro-active measures in this regard are discussed in Section 4.

### 3.5 What are current prices of the APIs of second-line ARVs?

APIs are the core component of a final drug formulation. The addition of intermediates and excipients to the API results in the final drug formulation. APIs make up a significant portion of the overall ART cost, and decline with improved manufacturing processes,

<sup>101</sup> This table assumes that each drug regimen requires 2 pills per day, except EFV which requires 1 pill per day.

<sup>102</sup> Further understanding of India and bulk drug formulations may be found at "The WTO and India's Pharmaceutical Industry: Patent Protection, TRIPS and Developing Countries", Chaudhuri, Sudip, Oxford, 2005.

<sup>103</sup> Older information is also available. India has participated in the *Purchase Price Report* by GFATM, submitting transaction-pricing data on first-line ARVs, available at [http://www.theglobalfund.org/en/funds\\_raised/price\\_reporting/default.asp](http://www.theglobalfund.org/en/funds_raised/price_reporting/default.asp). For that report, India submitted the prices and quantities of first-line ARVs it purchased using GFATM funds.

increased demand and multiple suppliers enhancing competition.<sup>104</sup> The experience of first-line ARVs is illustrative: API costs dropped dramatically as scale-up increased, and API producers began supplying manufacturers of finished products in larger quantities and with more regularity.<sup>105</sup>

India and China are currently the leading suppliers of API for ARV drugs globally.<sup>106</sup> There is, however, no current publicly available data on the prices of APIs of second-line ARVs.<sup>107</sup> It appears that both Indian and Chinese API prices are decreasing and that there are now more entrants into the ART market than there were previously. Chinese companies are moving toward offering significantly lower prices than Indian companies, but the lack of GMP compliance, as well as GFATM and WHO regulatory standard compliance, will prove to be a significant hurdle in assuring procurers of the Chinese-based product.<sup>108</sup>

Comparative data is also useful for understanding the role API prices play in overall ART cost. A recent analysis of API model cost data from a state-owned company in Brazil demonstrates that the API cost comprises at least 55% of the direct manufacturing cost of ARVs.<sup>109</sup> This study shows that price reductions in ART are feasible and are largely dependent on eliminating the indirect costs and profits that often are merged into the final price. The indirect costs and operating margins added 31-53% to the manufacturing cost for Indian generic manufacturers.<sup>110</sup>

### **3.6 What other measures can NACO take to drive down the cost of second-line ART?**

Since it is primarily API costs that drive prices of ARVs,<sup>111</sup> one concrete step that the Government of India can take to help reduce the cost of second-line ART is to remove the duties and taxes on intermediates and APIs, most of which are purchased from China.

What kinds of duties and taxes exist in India for ARVs? There are primarily two types: customs duties and excise taxes. When an API is imported into India, if the final product is used in India, a customs duty of approximately 5% is attached; however, if the same

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<sup>104</sup> See “Manufacturing Costs for Second Line AIDS Drugs”, James Love, February 17, 2007, available at <http://www.cptech.org/blogs/drugdevelopment/2007/02/manufacturing-costs-for-second-line.html>.

<sup>105</sup> Id.

<sup>106</sup> See C. Grace, “The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines,” DFID Health Systems Resource Centre (2004), available at [www.dfidhealthrc.org/publications/atm/Grace2.pdf](http://www.dfidhealthrc.org/publications/atm/Grace2.pdf).

<sup>107</sup> The WHO collates this information from suppliers. For 2005 information, See <http://www.who.int/hiv/amds/en/API.pdf>.

<sup>108</sup> Production of raw materials is believed to be the most technically demanding aspect of ARV production.

<sup>109</sup> See E. Pinheiro, A. Vasan, J.Y. Kim, E. Lee, J.M. Guimier, et al., “Examining the production costs of antiretroviral drugs.” *Aids* 20:1745-52 (2006). Direct costs include API, labor, equipment, excipients, packaging and loss. This data was collected from a variety of global suppliers who provide API to Brazil.

<sup>110</sup> Id. Indirect costs include manufacturing overhead, non-operational overhead, operating margin, as well as funds for sustainability and future growth and development.

<sup>111</sup> See Pinheiro, et al.

final product is exported for use elsewhere, the customs duty is not attached.<sup>112</sup> Excise taxes are waived for ARVs in India. However, for intermediates, a 7.5% customs duty and 16% excise tax is attached.<sup>113</sup> For purposes of NACO's public sector treatment programme, the excise tax and the import duty need to be waived for all APIs and intermediates imported for purposes of supplying second-line ART to NACO.<sup>114</sup>

To illustrate, an important combination drug is the FTC/TDF formulation. For this combination, the intermediate used to make FTC is FCME. Indian companies purchase this intermediate FCME from China, and they must pay a duty and tax on that purchase. For TDF, the API comprises 70% of the overall cost, and the intermediates are imported, adding to the cost paid.<sup>115</sup>

In the past, the Indian Government has eliminated the duty on 3TC, a first-line ARV, but not on the intermediates required to make the final drug. Requests for waivers on second-line ARV duties and taxes from the Indian pharmaceutical industry have not resulted in waivers.<sup>116</sup> INP+ recommends that NACO request that the Ministry of Chemicals and Fertilisers waive all duties and taxes on ARV intermediates and APIs.

### **3.7 Even if second-line is expensive, why is NACO not using GFATM funds to procure the drugs?**

In a recent public letter to GFATM, a health activist<sup>117</sup> inquired as to why GFATM funds were not being used to procure second-line ART for India's programme. Taufiqur Rahman replied on behalf of the Global Fund, but his correspondence did not provide a direct response to this question. It is unclear why GFATM and NACO have not provided a direct explanation, given that a clear answer could clarify questions raised by civil society. One of the outstanding questions is whether funds have specifically been designated for use for purchasing second-line ART.

Here, INP+ would like to address the *regulatory* component of the question of why GFATM funds are not being used to procure second-line ART. Under the 2004 GFATM policies, only drugs that have been subject to the stringent regulatory processes of WHO's pre-qualification process, or a stringent national drug regulatory authority, may be purchased by Principal Recipients using these funds.<sup>118</sup> India's drug regulatory authority does not fall within the category of countries with "stringent" national drug

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<sup>112</sup> See "India Doles out Pharma Incentives", Seema Singh, Red Herring, February 28, 2007. This is known as the duty export passbook benefit, a benefit companies may obtain when they import raw materials for final product export.

<sup>113</sup> The 7.5% is a reduction from 12.5% as per the 28 February 2007 budget.

<sup>114</sup> Brazil, for example, has waived the import tax for purposes of government production.

<sup>115</sup> See C. Grace, "The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines," DFID Health Systems Resource Centre (2004), available at [www.dfidhealthrc.org/publications/atm/Grace2.pdf](http://www.dfidhealthrc.org/publications/atm/Grace2.pdf).

<sup>116</sup> See [http://www.financialexpress.com/fe\\_full\\_story.php?content\\_id=154496](http://www.financialexpress.com/fe_full_story.php?content_id=154496); See also correspondence to Minister Ram Vilas Paswan, Department of Chemicals and Petrochemicals, from Cipla Ltd., requesting complete exemption of customs duty, countervailing duty and central excise duty on raw materials and bulk drug formulations for ARV products.

<sup>117</sup> Richard Stern of the Agua Buena Human Rights Association.

<sup>118</sup> See GFATM "Guide to the Global Fund's Policies on Procurement and Supply Management" (Apr. 2004), available at [www.who.int/entity/hdp/publications/13h.pdf](http://www.who.int/entity/hdp/publications/13h.pdf).

regulatory authorities.<sup>119</sup> Therefore, this rule appears to limit the drugs that NACO can purchase using GFATM funding.

However, during the April 2005 GFATM Board Meeting, an exception was created.<sup>120</sup> If only one or no supplier exists that meet this strict rule, India may submit a representation to the GFATM Secretariat indicating this, and if the Secretariat does not object, India may proceed to purchase the equivalent drug(s) from suppliers who have applied to WHO for pre-qualification, **or** if two or more manufacturers are not available, whose sites meet GMP requirements under WHO or a stringent regulatory authority.<sup>121</sup>

In the current scenario, therefore, what drugs can NACO purchase utilising GFATM funds, and from whom? According to the *GFATM Compliance List for Single and Limited Source Pharmaceutical Products*, ABC and dDI have diverse suppliers, including Indian generic companies Cipla and Aurobindo. Therefore, NACO may freely purchase ABC and dDI using GFATM funds.

For the remainder of the second-line regimen, the following is a summary of TDF, LPV/r, ATV, SQV, IDV and NFV and their GFATM-compliance:

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<sup>119</sup> See [http://www.theglobalfund.org/pdf/guidelines/List\\_of\\_Countries\\_ICH\\_PICS.pdf](http://www.theglobalfund.org/pdf/guidelines/List_of_Countries_ICH_PICS.pdf).

<sup>120</sup> The policy is summarized at <http://www.theglobalfund.org/en/about/procurement/compliance>: “Option A/B: If for any given limited-source product, two or more manufacturers exist for which Option A or B applies AND the product is available from these manufacturers (defined as the ability of the manufacturer to supply a sufficient quantity within 90 days of the date of order), then the product must be procured from this set of manufacturers. Criteria (Ci): If the above condition does not apply (i.e., there is only one manufacturer that meets the Option A/B standard or the product is not available from the manufacturers that meet this standard), then the product can be procured from any manufacturer that has submitted the product for review to the WHO or to a National Drug Regulatory Authority (NDRA) in a country that is member of The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (Access below a list of countries that belong to ICH or PIC/S) AND which manufacturers the product at a site complying with "Good Manufacturing Practices" (GMP-compliant) based on inspection by WHO or an ICH or PIC/S NDRA. Criteria (Cii): If the product cannot be procured from two or more manufacturers based on either of the above scenarios, then it can be procured from any manufacturer that has not submitted an application as described under Ci above but which manufacturers the product at a GMP-compliant site (again, based on inspection by WHO or an ICH or PIC/S member).”

<sup>121</sup> See [http://www.theglobalfund.org/pdf/guidelines/QA\\_Board\\_Decision.pdf](http://www.theglobalfund.org/pdf/guidelines/QA_Board_Decision.pdf); see also <http://www.theglobalfund.org/en/about/procurement/compliance/>.

**Table 10. Summary of Global Fund Compliance for Second-Line ART**

International Non-proprietary Name (INN)	Strength	Dosage Form	Global Fund QA Standard	Supplier	Quality Assurance
<b>Tenofovir DF</b>	245 mg	Film-coated tablet	B	Gilead Sciences	ASA
<b>Tenofovir DF</b>	300 mg	Tablet	A-B	Gilead Sciences	PQ, ASA
		Tablet	<i>Cii</i>	<i>Cipla Ltd</i>	--
<b>Lopinavir/Ritonavir</b>	133.3mg (33mg)	Soft capsule	A-B	Abbott Laboratories	PQ, ASA
		Capsule	<i>Cii</i>	<i>Cipla Ltd</i>	-- --
<b>Lopinavir/Ritonavir</b>	20mg/80mg	Oral solution	A-B	Abbott Laboratories	PQ, ASA
<b>Lopinavir/Ritonavir</b>	200mg/50mg	Tablets	B	Abbott Laboratories	ASA
<b>Atazanavir</b>	50mg/1.5g	Oral powder	B	Bristol Myers Squibb	ASA
<b>Atazanavir</b>	100mg	Hard capsule	B	Bristol Myers Squibb	ASA
<b>Atazanavir</b>	150mg	Hard capsule	B	Bristol Myers Squibb	ASA
<b>Atazanavir</b>	200mg	Hard capsule	B	Bristol Myers Squibb	ASA
<b>Atazanavir</b>	300mg	Capsules	B	Bristol Myers Squibb	ASA
<b>Indinavir</b>	100 mg	Hard capsule	B	Merck Sharpe and Dohme	ASA
<b>Indinavir</b>	200 mg	Hard capsule	B	Merck Sharpe and Dohme	ASA
<b>Indinavir</b>	333 mg	Hard capsule	B	Merck Sharpe and Dohme	ASA
<b>Indinavir</b>	400 mg	Hard capsule	A-B	Merck Sharpe and Dohme	PQ, ASA
		Capsule	<i>Cii</i>	<i>Hetero Drugs Limited</i>	--
		Tablet	<i>Cii</i>	<i>Cipla Ltd</i>	--
		Capsule	<i>Cii</i>	<i>Cadilla Pharmaceuticals</i>	--
<b>Saquinavir</b>	N/A	N/A	N/A	N/A	N/A
<b>Nelfinavir</b>	N/A	N/A	N/A	N/A	N/A

Excerpted from *Global Fund Compliance List for Single and Limited Source Pharmaceutical Products*, January 26, 2007

This table is not exhaustive – the *Compliance List* explicitly urges Principal Recipients to confirm the information listed for single and limited source products.<sup>122</sup> Additionally, multiple suppliers are emerging for second-line ART and the landscape will likely be significantly different one year from now. We assess the data available to understand what potential options exist for India at the time of this writing, with the caveat that more recent and thorough information should be obtained from GFATM and other sources:

- ABC and ddi may be purchased from Indian generic manufacturers using GFATM funds.
- IDV, TDF and LPV/r capsules may be purchased from Indian generic manufacturers using GFATM funds, but the Principal Recipient<sup>123</sup> will have to submit a representation to GFATM and obtain approval. There is precedent for such approval from GFATM for other countries.<sup>124</sup>
- SQV and NFV are not pre-qualified. These drug applications do not fall within the *Ci* or *Cii* categories. These drugs may not be purchased using GFATM funds according to available information.
- LPV/r tablet and ATV must be purchased from the originator when using GFATM funds according to available information.

Table 11 illustrates that for the LPV/r tablet and ATV, NACO may not benefit at this time from more manufacturers producing second-line ART, and likely will not be able to purchase more drugs at better prices. Furthermore, according to available information, the LPV/r tablet has not been registered for marketing approval in India by the originator. The result is that the number of patients on treatment will remain stagnant. However, despite the high cost, NACO can purchase these drugs from originator companies using GFATM funds in the interim period until generic versions meet the GFATM requirements. Several other countries, including South Africa, Botswana and Thailand, are paying comparably high prices for ART in order to meet the needs of PLHIV.<sup>125</sup> India should also ensure that GFATM funds are used for the purpose intended: to purchase ART for patients who urgently require treatment. NACO should use the flexibilities available and include any relevant requests in its procurement plan. GFATM should approve any requests made by NACO to further scale-up efforts.

Additionally, an open issue is whether the Round 4 and Round 6 GFATM grants for India, which have designated funds specifically for ART purchase, include second-line

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<sup>122</sup> See <http://www.theglobalfund.org/en/about/procurement/compliance/>. For purposes of cross-referencing, information regarding WHO prequalification is available at [mednet3.who.int/prequal/lists/hiv\\_suppliers.pdf](http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf).

<sup>123</sup> The principal recipients for Round IV are the Population Foundation of India and the Government of India's Department of Economic Affairs, according to <http://www.theglobalfund.org/programs/countrysite.aspx?lang=en&countryID=IDA>. Therefore NACO would likely make this recommendation to one or both of these entities after taking inputs from civil society, the medical community, and other key stakeholders.

<sup>124</sup> See, e.g., Peru, whose Principal Recipient and Country Coordinating Mechanism (CCM) approached and received approval from GFATM to purchase generic versions of the LPV/r capsule from Cipla (information obtained from correspondence with Lidice Lopez, Colectivo por la Vida, Lima, Perú); see also Informe Trimestral report, at 18 (Dec. 2005-Feb. 2006), available at <http://www.care.org.pe/websites/fondomundial/Fortaleciendo/segavan1.htm>.

<sup>125</sup> See "NACO in Denial about Realities of ARV access in India," Richard Stern and Eugene Schiff, Agua Buena Human Rights Association.

ART or whether the Principal Recipient must submit a separate request. INP+ requests NACO to clarify this issue, and make such a request to GFATM, in order to move forward on effective utilization of GFATM funds.

Lastly, NACO may have concerns about the fact that GFATM funds have not yet been approved for purchasing second-line ART after the CHAI/UNITAID support finishes in two years. INP+ therefore recommends that GFATM publicly commit to approving purchase of second-line ART from the third year onwards.

## 4 Patents and Second-Line ART

This section focuses primarily on the practical outcomes of patent determinations on second-line ART, highlighting the interplay between cost and patents using a case study of an actual second-line regimen. After examining the impact of patent determinations and pre-grant patent oppositions on second-line regimens, the section looks at the effect patents will have on choosing the optimal PI. The section concludes by offering recommendations for NACO to promote access to medicines while staying in compliance with the amended patent laws of India and international legal obligations (TRIPS).

### 4.1 How does the new patent law affect second-line ART?

India's new patent law has activated debate about the impact of patents on access to affordable medicines. Simply put, the new Indian patent law allows pharmaceutical companies to claim sole ownership of a drug. To illustrate, Abbott Laboratories, a U.S. based pharmaceutical company, holds U.S. patents on LPV and RTV, two PIs highly recommended by WHO. Abbott Laboratories has also applied for a U.S. patent on the combination drug of the LPV/r tablet, known as Kaletra. Therefore, if the patent is granted in the U.S., Abbott will be the only company that has the legal right to sell LPV, RTV and the Kaletra tablet. But simply because Abbott holds the LPV and RTV patents, and may obtain the Kaletra tablet patent in the U.S., does not mean they will automatically have the same patents in India. Abbott has to apply to the Indian Patent Office for Indian patents, and only if those applications are granted will Abbott have the sole right to sell LPV, RTV and Kaletra here in India. If no patent is granted, then other companies can also make "generic" versions of LPV/r.

On what basis does the Indian Patent Office decide to grant a patent on a second-line HIV drug? The Patent Office will make a determination for an HIV drug by ascertaining whether it is an *invention*. This determination is not as easy as it sounds. The patent examiner, who is the person in charge of making this determination, uses three criteria in her decision: Is the drug "new"? Would it have been obvious to someone skilled in the art, e.g. an ordinary organic chemist, to make this compound? Does the drug have the ability to be manufactured in industry? For each drug, this inquiry can take months or, in some cases, years. Many drugs, including HIV drugs, are new forms of older compounds, complicating the determination of whether a drug is really an invention.

Advocates for second-line ART drugs are concerned about the granting of patents because the patented version of these ARVs can be, as demonstrated in section 3, formidably expensive, creating tremendous barriers to access for patients.<sup>126</sup> When India came into compliance with its obligations under the World Trade Organisation in January 2005,<sup>127</sup> it exercised its right to introduce provisions into law that would protect the public's right to affordable medicines.<sup>128</sup> Under the new law, there is a strict test that

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<sup>126</sup> Recent studies have examined the correlation between patents and HIV infection rates. *See, e.g.*, "Intellectual Property Organisations and Pharmaceutical Patents in Africa," Robert Deiss, SSM 64 (2007), pp.287-291.

<sup>127</sup> *See* Patents (Amendment) Ordinance 2004, later amended and passed in March 2005 as the Patents (Amendment) Act (2005), available at [www.patentoffice.nic.in/patent/patent\\_2005](http://www.patentoffice.nic.in/patent/patent_2005).

<sup>128</sup> For background on the use of TRIPS flexibilities, *see* S. Musungu and C. Oh, "The Use of Flexibilities in TRIPs by Developing Countries: Can they promote Access to Medicines?"

companies must meet to show the drug they seek to patent is worthy of patent protection.<sup>129</sup> This test, known as the “efficacy test,” makes it more difficult for companies who are seeking to patent new forms of older drugs, as they must demonstrate that the new drug is more efficacious than the older drug. To illustrate, GlaxoSmithKline applied for a patent for Abacavir Sulfate in Kolkata, and the company must now show that Abacavir Sulfate is significantly more efficacious than the older known drugs of the same form, Abacavir and Abacavir Succinate, which were invented in the 1980s-90s.<sup>130</sup> The existence of the efficacy test in Indian law is promising for PLHIV because many second-line ART drugs are new forms of older drugs that may not be more efficacious, including TDF, ddI, ABC and LPV/r.

However, the Swiss company Novartis in the Chennai High Court is currently challenging the “efficacy test”.<sup>131</sup> Thus, at the time of this writing, the future of second-line ART patents remains uncertain. Depending on the outcome of the case, and whether the courts set a higher or lower threshold for the efficacy test, many second-line drugs may be patented or only less important formulations may be patented. Even if these second-line ARVs are patented, all hope for free second-line ART is not lost. There are a number of options available to NACO to ensure second-line ART is available for the government programme.

#### **4.2 Case Study: TDF-3TC-LPV/r, Costing and Patents**

India has not yet finalized which second-line regimen(s) to include in the national ART programme. For purposes of illustration only, to demonstrate why costs and patents are overlapping prohibitive factors, we offer the following case study, using the second-line regimen **TDF-3TC-LPV/r**. We note here that key policymakers and public health officials, as well as the PLHIV community, lack practical information about the impact of the patent law on purchasing and accessing second-line ARVs in India. For purposes of this case study, we focus on the practical outcomes of the new law for NACO’s ART programme.

##### **Case Study**

As a starting point for this case study, we assume that India’s national treatment programme decides in 2007 to introduce TDF-3TC-LPV/r as its preferred second-line ART regimen. NACO therefore begins to assess the feasibility of procuring this regimen from a costing and patent perspective. To do so, NACO examines each individual ARV in turn.

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Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH), Geneva (Aug. 2005).

<sup>129</sup> Section 3(d), Indian Patents (Amendment) Act (2005).

<sup>130</sup> For a detailed history of the development of Abacavir, *see* “Bitter Pills,” Jul. 4, 2001, *available at* <http://www.cptech.org/ip/health/aids/umabc.html>.

<sup>131</sup> *See* Amelia Gentleman, “Battle Pits Patent Rights Against Low-Cost Generic Drugs,” *New York Times*, Jan. 30, 2007, *available at* <http://select.nytimes.com/gst/abstract.html?res=F50A14FB3F5B0C738FDDA80894DF404482>.

## **TDF:**

TDF currently costs \$207/pppy (per patient, per year) in designated ‘access program’ countries and \$360 in middle-tier countries, when purchased from Gilead Sciences, Inc., the U.S.-based patent-holder of TDF.<sup>132</sup> When purchased from the Indian generic manufacturer Cipla Ltd., TDF currently costs \$195/pppy in low-income countries and \$340/pppy in middle-income countries.<sup>133</sup> India is not part of Gilead’s Access Program and does not qualify to receive the low-tier price.<sup>134</sup>

In analyzing the possible cost of TDF, NACO must factor in the possibility that TDF is under patent examination in India. If TDF is *not* patented, Cipla may supply NACO with TDF at the price of \$195/pppy, and there may be scope to further reduce this price, depending on issues like volume. If TDF *is* patented, then NACO can exercise at least two options: (a) NACO may purchase directly from Gilead or the eleven Indian companies Gilead has agreed to let manufacture the drug pursuant to a voluntarily license, or (b) issue Cipla a compulsory license/government use license to produce a generic version of TDF (where a royalty must be paid to Gilead).<sup>135</sup>

In one scenario, where TDF is not patented, NACO decides to buy from Cipla. To lower the price further, NACO decides to recommend that the Ministry of Chemicals and Fertilisers waive the custom duties and excise taxes on TDF’s intermediates and raw materials imported from China. For TDF, the tariffs on the imported intermediates add 12.5% to 15% to the cost already paid. The cost savings here are modest but helpful to bringing down the overall price.

In the other scenario, where TDF is patented, NACO has the choice of one of the eleven companies who received a license from Gilead. Out of the eleven companies, some are only producers of the API (not the final formulation) and some are not manufacturing TDF, narrowing the number of companies from which NACO must choose. The lowest existing available price from a Gilead-licensee, Hetero, is \$365/pppy.<sup>136</sup> NACO chooses not to purchase directly from the originator, Gilead, because precedent demonstrates that patented drugs inevitably are cheaper when supplied by generic companies than from the originator.<sup>137</sup>

It is conceivable, therefore, that if NACO negotiates with the patent-holder or with generic companies, the low-tier price can be used: \$207/pppy if TDF is patented, or \$195 if TDF is not patented.

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<sup>132</sup> See <http://www.gileadaccess.org/wt/page/countries>; see also MSF, “Untangling the Web” (2006); see also <http://www.timetodeliver.org/?p=86>.

<sup>133</sup> See MSF, “Untangling the Web”, 2006 Updates.

<sup>134</sup> See <http://www.gileadaccess.org/wt/page/countries>.

<sup>135</sup> We exclude public production as an option in this case study because, at the time of this writing, no public manufacturing site is undertaking second-line ART production.

<sup>136</sup> See MSF, “Untangling the Web” (2006).

<sup>137</sup> See *id.* See also “Voluntary Licensing Strategies,” Tahir Amin, Oxfam GB (2007), forthcoming.

### **3TC:**

Since 3TC is a first-line ARV, it is produced and sold in high volumes. The price for 3TC is approximately \$50/pppy.<sup>138</sup> The drug is not patented in India.<sup>139</sup>

### **LPV/r:**

LPV/r is the crucial factor in this case study. The price of LPV/r impacts the entire second-line regimen: If the price of this drug remains high, it will be difficult to introduce second-line drugs into the national ART programme. This is the clearest example of how the new patent law threatens the feasibility of introducing second-line ART into the Indian ART programme.

There are two main forms of LPV/r: the soft-gel formulation and the heat-stable tablet. The heat-stable tablet has numerous benefits including no need for refrigeration. Abbott's middle-tier price of heat-stable tablet LPV/r is \$2200/pppy and the low-tier price is \$500/pppy.<sup>140</sup> If Abbott obtains a patent on LPV/r in India, they may maintain their current unaffordable middle-tier price of \$2200/pppy.<sup>141</sup> Currently the only generic version of heat-stable LPV/r, recently introduced onto the Indian market, is by Emcure, a Pune-based pharmaceutical company, priced at \$1774/pppy.<sup>142</sup> However no application has been filed for pre-qualification and this option is therefore not favored by NACO.

The alternative is that NACO could choose not to purchase the heat-stable tablet for LPV/r and could purchase the soft-gel capsule of LPV/r instead. The soft-gel patent has been abandoned in India and the lowest existing price by Abbott is \$500/pppy, and \$1338/pppy by one generic company.<sup>143</sup> Although the soft-gel version may seem to be an appealing option, it creates a risk to PLHIV because of its need for refrigeration, high pill burden and side effects.<sup>144</sup>

The heat-stable tablet is the best option for India's ART programme. The difficult issue before NACO is whether to purchase generic versions of heat-stable LPV/r. The current generic price is higher than Abbott's low-income country price of \$500, which Abbott claims is the "at-cost" price. Generic companies have been working to reduce the cost of

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<sup>138</sup> See MSF, "Untangling the Web" (2006).

<sup>139</sup> 3TC will not be patented in India as it was invented in 1989, and India is not required under TRIPS to grant patents on pre-1994/5 drugs.

<sup>140</sup> See [http://www.abbott.com/static/content/document/aids\\_care.pdf](http://www.abbott.com/static/content/document/aids_care.pdf); see also "Abbott statement regarding new initiatives to expand access and affordability to lopinavir/ritonavir in the developing world," Aug. 13, 2006.

<sup>141</sup> The LPV/r tablet does not have only one patent pending, there may be other "blocking patents" that obstruct the generic production. However under s11(a)(7) of the Indian patent law, it is likely that certain generic companies can continue production of LPV and RTV (as individual components) with the payment of a reasonable royalty to Abbott Laboratories.

<sup>142</sup> Obtained from marketing brochure.

<sup>143</sup> See correspondence from Mumbai Patent Office to INP+ regarding PCT International Application No. IN/PCT/2001/01312/MUM, stating the application is deemed abandoned, available with INP+. See also MSF, "Untangling the Web" (2006).

<sup>144</sup> See "Abbott's New and Improved Kaletra: Only in the US... But What About the Rest of the World?", Briefing Note, 14 Mar. 2006, available at [http://www.doctorswithoutborders.org/news/hiv-aids/kaletra\\_briefingdoc.cfm](http://www.doctorswithoutborders.org/news/hiv-aids/kaletra_briefingdoc.cfm).

generic LPV/r, addressing the challenges involved in optimizing complex chemistry and achieving bioequivalence for the heat-stable formulation. Though generic companies have not yet announced a price competitive with Abbott's \$500 price, the generic prices have been declining rapidly and experience suggests that they will become cost-competitive in the near- to medium-term. Lowering the price of generic LPV/r will also depend on increased demand and guaranteed purchase orders.

Opting to purchase Abbott's version has its problems. Abbott is a company that traditionally has refused to engage in price reductions and may decide, as the manufacturer with the sole ownership if a patent is granted, to maintain its current unaffordable price of \$2200/pppy.<sup>145</sup> This would be troubling news. It also appears that Abbott has not registered the LPV/r tablet for marketing approval in India. Thus the threat of an Indian patent being issued on LPV/r is a source of hesitation for NACO in procuring generic versions of heat-stable LPV/r.

Additionally, India is not an Abbott "access country" and accordingly, will receive the middle-tier \$2200/pppy price.<sup>146</sup> If India negotiates with Abbott, Abbott may drive the price down to \$1379/pppy, the price Brazil reached after negotiating with Abbott. However NACO should assume that Abbott's low-tier price is \$500/pppy, and the population NACO seeks to provide treatment to falls within the lowest-income bracket. Therefore NACO may consider issuing a compulsory license or government use license, as Thailand has recently done for LPV/r, to allow for low-cost generic production of the LPV/r tablet in India.<sup>147</sup>

Although NACO's is inclined to purchase the off-patent option, the soft-gel capsule, it is less technically sound. In the face of uncertainty of the pending tablet patent, NACO should decide to use the window of opportunity to procure and provide the heat-stable LPV/r tablet from a generic company.

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This case study demonstrates the interplay between costing and patenting and its practical impact on India's second-line ART programme. NACO has thus far not publicly acknowledged the potential solutions available to India regarding the impact of patents on its second-line programme. A comprehensive understanding of the impact of patents on second-line ART will enable NACO to exercise legal options available to it and ensure that treatment is provided for PLHIV in India.

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<sup>145</sup> Abbott has reduced its price or made overtures towards reducing its price when Brazil and Thailand threatened to issue compulsory licenses.

<sup>146</sup> See MSF, *Untangling the Web* (2006). See Also <http://www.accesstohivcare.org/en/>.

<sup>147</sup> See <http://www.cptech.org/ip/health/c/thailand/>.

### 4.3 What will be the impact of the patent determinations, and pre-grant patent oppositions, on the second-line ART regimen?

The impact of both patent determinations and pre-grant oppositions is still unknown.<sup>148</sup> Pre-grant patent oppositions, in the view of INP+, are civil society’s contribution towards ensuring that generic production is sustainable. The patent opposition mechanism is not only significant in the short term on a case-by-case basis, but also as a long-term strategy to create systemic checks on the patent examination process – future ART will also be impacted. Pre-grant oppositions will serve an important role, now and in the future, in ensuring that the patent examination process is thorough and rigorous. Patent decisions are expected in 2007 for many ARVs, and the outcome remains uncertain.

The table below sets out the financial implications of patenting for the key second-line drugs. NACO may wish to assume that for LPV/r and ATV, the rejection of the patent will serve to lower the price, as multiple suppliers will enter the market and competition will drive prices downwards. The table below demonstrates that a potential spectrum of impact exists in the wake of patenting – with ddI, ABC and TDF likely to face less impact on prices, and LPV/r and ATV likely to face greater impact on prices.

**Table 11. Financial Implications of Patenting on Second-Line ARVs**

Drug Name	Cost if Patent Upheld (pppy)	Cost if Patent Rejected (pppy)
TDF (300mg)	\$195-\$207*	\$195
LPV/r tablet	\$500-2200*	\$1774 or lower**
ddI EC (400mg)	\$132 ***	\$132
ABC (300mg)	\$456***	\$456
ATV (150mg)	Unknown at this time****	Unknown at this time

\* Obtaining lowest price depends on NACO’s ability to negotiate best prices.

\*\* LPV/r tablet is currently available only from Emcure. NACO may wish to assume that Emcure and other suppliers will be able to achieve Abbott’s lowest price of \$500 in the near future.

\*\*\*The generic companies supplying these drugs may continue production, despite a patent grant, with a payment of a royalty. It is unclear to what extent such a royalty will be built in to the price NACO pays.

\*\*\*\*ATV (150mg) in India, under license from the patent-holder to Emcure, is Rs.2500MRP. This price is significantly higher than NACO’s probable purchase price.

For ARVs such as ABC and ddI, the impact of patenting should be less severe than with some other ARVs, since under the patent law, generic companies can legally continue production even if the drug is patented.<sup>149</sup> These drugs are at a relatively lower risk of patenting in India, assuming the “efficacy test” is retained in the Indian law and is given a strict interpretation.

<sup>148</sup> ‘Patent determination’ refers to a decision made by a patent examiner on a given drug. ‘Pre-grant patent opposition’ is a procedure allowing any person to oppose the granting of a patent, prior to the patent determination.

<sup>149</sup> S11(A)(7) of the Indian patent law.

The impact of patent decisions is unclear for drugs that originator companies have licensed to Indian generic companies. For example, Gilead Sciences has issued eleven voluntary licenses to Indian generic companies to produce TDF for the Indian market. Although the terms of the licenses raise concerns, the scenario for PLHIV is promising, given that there are at least a few companies working to manufacture and sell the final TDF formulation. If the TDF patent is rejected, NACO is free not only to buy from Gilead and its licensees, but also from other generic companies who may price TDF at lower rates. Another example of a licensed drug is ATV, licensed by Bristol-Myers Squibb (BMS) to Emcure.<sup>150</sup> If patented, BMS and Emcure have the sole right to set prices for ATV and NACO will need to be prepared to negotiate.<sup>151</sup>

The harsh effects of the new patent regime will be most pronounced for drugs that, if patented, fall within the sole ownership of the patent-holder, such as the Abbott Laboratories heat-stable LPV/r tablet, which Abbott consistently refuses to license to generic companies. NACO cannot wait for the patent determination on LPV/r to make a decision. Unlike TDF, which the patent office will likely decide on in early 2007, the heat-stable tablet LPV/r patent application is not expected to be decided in 2007.<sup>152</sup> NACO will have to make decisions prospectively.

#### **4.4 Do patents have an impact on what the best PI is for NACO to procure for PLHIV in India?**

As discussed in section 2.1, it appears that LPV/r and ATV/r are the optimal PI regimens for PLHIV from a clinical perspective. Their clinical attractiveness is affirmed by the fact that LPV/r and ATV/r are currently the leading PIs in the developed world. It is possible, based on the WHO and NACO-draft recommendations and the price structures of these PIs, that LPV/r and ATV/r will be the dominant PIs for India in the next few years. The fact that LPV/r is currently the only PI co-formulated in a single, heat-stable tablet is an important reason for its inclusion as the preferred PI regimen in national treatment guidelines. However, heat-stable forms of RTV are expected to become available in the near future.

Interestingly, the complex interplay amongst therapeutic benefit, cost and patents can have an impact on NACO's decision-making process. While assessing clinical suitability for the ART programme, NACO will likely consider the fact that co-dosing ATV with RTV will require less of the drug (100mg daily) than co-dosing with LPV (200mg daily). NACO also will consider that only 300mg of ATV is required daily compared to 800mg of LPV, and, assuming that the costs of ATV and LPV are comparable once demand rises, likely will conclude that ATV will be cheaper to provide.<sup>153</sup> It is therefore possible

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<sup>150</sup> Unlike TDF, the ATV license is not publicly available.

<sup>151</sup> The current price of ATV (150mg) in India is Rs.2500 for 60 tablets. This price was obtained from an Emcure marketing brochure.

<sup>152</sup> Author's assessment based on the examination status of the relevant PCT application, entry into the national phase, and based on the absence of publication in the Indian Patent Journal. The determinations on the "blocking patents," e.g. the individual crystalline forms of LPV and RTV, may take place earlier, but may be covered under section 11(A)(7)'s continued production provision.

<sup>153</sup> See "Antiretroviral Guidelines for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach," WHO, 2006 Revision, p102.

that NACO would consider ATV an attractive option, particularly in the absence of data showing that LPV/r is clinically more beneficial than ATV/r.<sup>154</sup> Yet there exists a risk of patenting for ATV, and in the absence of a price reduction from BMS for NACO's ART programme, the cost may prove prohibitive. There is also a risk of patent issuance for the LPV/r tablet, and the LPV/r capsule patent has been abandoned, so the interplay of these factors should influence NACO's comprehensive decision-making process.<sup>155</sup>

#### **4.5 How can NACO best promote access to medicines while staying in compliance with Indian and international law (TRIPS)?**

NACO may consider any of the following strategies:

- *Negotiations with patent-holders.* As discussed in Sections 3 and 4, for at least a few ARVs, NACO and its partners must be prepared to effectively negotiate with patent-holders. Historically, India has not needed to engage in tough negotiations with patent-holders due to the lack of a product patent regime, but with the impending threat of patenting NACO will need to prepare. First, NACO should assess the availability and pricing of required drugs. If the ARVs are not available or affordable, NACO should seriously consider the option of following Thailand's recent example of issuing a compulsory license on LPV/r. Similarly, Brazil's actions to issue a compulsory license resulted in a settlement with a 46% price reduction from Abbott Laboratories for LPV/r, and a 50% price reduction for TDF from Gilead.<sup>156</sup> Such negotiation strategies should be in the planning stages now so that NACO is ready to act immediately if patents are granted. This forward planning is essential given the legal delays and practical consequences of the steps required to issue such a license.<sup>157</sup> NACO should note the experience of countries that have actually issued compulsory licenses, including Malaysia, Indonesia, Taiwan, Peru, the Philippines, and several African countries.<sup>158</sup> Compulsory licenses offer NACO a strong option to ensure that second-line ART is available in the national programme.

- *Government use.*<sup>159</sup> In India, the government may use a patented drug without violating the law.<sup>160</sup> There are two strategies that the government may use to provide the drug for non-commercial use.<sup>161</sup> Significantly, the first strategy allows the government to initiate provision of treatment after the patent application is submitted to the patent office but before the grant of patent.<sup>162</sup> NACO may use this approach to immediately procure and supply second-line ART in the national treatment programme, despite the pending

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<sup>154</sup> ATV is dosed once daily.

<sup>155</sup> *Id.*

<sup>156</sup> Full accounts of the dispute may be accessed online at <http://www.cptech.org/ip/health/c/brazil/>.

<sup>157</sup> For a discussion of available options to the Government of India, see Shamnad M. Basheer and Tahir Amin, "Taming of the Flu: Working Through the Tamiflu Patents in India," J. of Intellectual Property Rights, Vol. 2, at 113 (Mar. 2006), available at SSRN, <http://ssrn.com/abstract=889868>.

<sup>158</sup> For a thorough overview of countries who have issued or threatened to issue compulsory licenses, see <http://www.cptech.org/ip/health/cl/recent-examples.html>.

<sup>159</sup> For a discussion of government use, see Basheer and Amin at 157.

<sup>160</sup> See Indian Patent Act, sec. 47, ch. XVII and sec. 99-100.

<sup>161</sup> *Id.*

<sup>162</sup> See Basheer and Amin.

patent determinations. In this scenario, a royalty must be paid to the patent-holder.<sup>163</sup> The second strategy waives the royalty requirement but mandates that the drug be imported – given India’s thriving generic industry, this section makes little sense.<sup>164</sup>

- *Voluntary licenses.* NACO likely will not be involved in the voluntary licensing process unless it arises during the issuing of a compulsory license or for purposes of government use, as discussed above. However it may be advisable for NACO to stay apprised of recent developments to inform decision-making. A new business strategy of voluntary licensing has evolved in the last 1-2 years, due in part to the risk of patent challenges, the advent of new business models/strategies for partnerships with local partners and a smooth entrance into a new ARV market, and Indian companies’ desire to create partnerships with patent holders. The voluntary licensing strategy is evidenced by the licenses issued in three notable Indian cases. Gilead Science’s unique offer of eleven non-exclusive licenses to Indian generic companies for TDF, the voluntary licenses issued by Roche to Hetero during the threat of the bird-flu pandemic, and the license issued by Bristol-Myers Squibb to Emcure on ATV. These licenses raise important questions about the benefits and drawbacks for access to medicines using voluntary licensing of drugs prior to the issuance of a patent. Further examination of these developments and the impact on access is advisable.<sup>165</sup>

- *Public production.* Currently in India many of the public producers, known as Public Sector Undertakings (PSUs), are defunct and the government is investing in reviving them. Recently, the government announced that it is investing 3240 crores to revive the dormant PSUs, and that the Ministry of Chemicals and Fertilisers will invest 100 crores to help HAL and IDPL receive pre-qualification by WHO.<sup>166</sup> Although there are a number of important reasons to revive PSUs, including the availability of publicly manufactured ART, this process will involve considerable time and resources. Second-line ART is required immediately and will need to be procured from existing sources. As a long-term strategy for newer HIV drugs, NACO should coordinate with the Ministry of Chemicals and Fertilisers to revive public sector production to lower the prices of medicines in India. Two questions that should be considered in pursuing this option of public production are: how competitive can PSUs be, and what impact does public production have on existing industry? In the case of Brazil, state-production of ART, coupled with exemptions on import duties, has had a negative impact on the private sector Brazilian industry.

- *ANVISA Model.* The patenting of pharmaceutical products in India is now a long-term concern. Institutional mechanisms should be built in to the patent system at this stage. The Ministry of Health may contemplate following the Brazilian model, which mandates that, the National Sanitary Supervision Agency (ANVISA) review pharmaceutical patent

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<sup>163</sup> *Id.* See Section 99-100 of the Indian patent law.

<sup>164</sup> *Id.* See Section 47 of the Indian patent law.

<sup>165</sup> For an in-depth analysis of the benefits and drawbacks of voluntary licensing, see “Voluntary Licensing Strategies,” Tahir Amin, Oxfam (2007), forthcoming.

<sup>166</sup> “Govt will help its ailing pharma firms export anti-HIV drugs”, Mint, 8 Feb. 2007, Bhuma Shrivastava. The ministry has apparently approved a Rs.550 crore revival package for HAL, Rs440 crore for Bengal Chemicals & Pharma and is in the process of approving a Rs2,250 crore package for IDPL.

applications prior to the grant of the patent.<sup>167</sup> We recommend that such a system be adopted in India, requiring the prior consent of the Health Ministry for pharmaceutical patenting on both public health and technical grounds.

- *Propose, support and oppose legislative amendments.* NACO and the Ministry of Health should continue to actively seek civil society input on a number of related issues, including any future amendments to the patent laws, data exclusivity, drug pricing and technical committee reports impacting access to medicines. Based on these inputs the Ministry of Health should propose, support and oppose legislative amendments and policy developments impacting access to medicines.

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<sup>167</sup> See Industrial Property Law, Brasil, Law no. 9.279 (May 14, 1996), Regulating Industrial Property Rights and Obligations, *amended by* Article 229-C, Law 10.196 (Feb. 14, 2001).

## 5 Issues Requiring Further Attention

A diverse range of stakeholders, from clinicians to policymakers, have asserted that the existing first-line ART programme needs to be strengthened so that second-line ARVs can be introduced.<sup>168</sup> INP+ urges NACO to view these objectives as simultaneous, and to approach the existing challenges with the belief that they are capable of resolution—it is possible to achieve the goals of the ART programme with the committed amount of human resources, fiscal investment, and the increasing support of civil society. An examination of the existing programme in-depth is not within this paper's scope; instead of drawing conclusions on the issues impacting the current programme, we highlight here what we believe is required for the ART programme to function more effectively.

First, we recommend evaluation regarding the state of our supply system. Is this system responsive to the operational challenges that scale-up of ART is bringing? The current procurement system is not well-understood in India, a gap that should be addressed as second-line ART is introduced. NACO utilizes services provided by HSCC (India) Ltd., a public sector agency.<sup>169</sup> There is currently no competitive process to select the procurement agency— as a government entity, NACO can commission another public agency such as HSCC to undertake the procurement work.<sup>170</sup> Only if a private sector agency is used would a competitive bid be required.<sup>171</sup> Since there is no transparency in the selection process, no assessments can be made regarding the quality of services or prices paid. Further, the website of the agency is not sufficiently transparent, as it lacks basic information about procedures followed for ART procurement.<sup>172</sup> It also neglects to cite the bulk prices paid and suppliers used for ART in the programme.<sup>173</sup> INP+ recommends that the following factors be made transparent on the NACO website: the bases on which NACO selects its procurement agencies, the forecasting data on which NACO makes procurement decisions, and the actual tender process and bulk purchase prices.<sup>174</sup>

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<sup>168</sup> See NACO/WHO Draft Minutes, National Consultation on Need and Feasibility for Second Line Antiretroviral Drugs, 24-25 Nov. 2005 (Delhi, India).

<sup>169</sup> See <http://hsccltd.co.in>. HSCC is used to procure drugs and HLPPT (Hindustan Latex Family Planning Promotion Trust) is used to procure diagnostics. See also <http://www.hlppt.org/>.

<sup>170</sup> It is reported that NACO is considering the use of International Competitive Bidding. No official documents could be obtained during the course of this research to confirm this information.

<sup>171</sup> It is reported that engaging in competitive bidding using the private sector may increase the bureaucracy of the process.

<sup>172</sup> See FN 51 regarding the lack of a procurement plan. It is reported that from March, only WHO-prequalified drugs will be used in the NACO programme. No official documents could be obtained during the course of this research to confirm this information.

<sup>173</sup> Only the invitation for bids, dated 2 July 2007, is cited. See <http://www.hsccltd.com/NACO-Non-GFATM-A-08-02-07.htm>. Additionally, even NACO's website does not share the procurement agency used or the process used to select procurement agency. This information would be helpful and should be displayed on the website. See <http://www.nacoonline.org/procurement.htm>. Public agencies should make proactive disclosures regarding their practices. An examination of the Tamil Nadu Medical Services website, for example, provides information regarding stock of essential medicines by warehouse and by drug. See [http://tnmsc.tn.nic.in/drug\\_stk.htm](http://tnmsc.tn.nic.in/drug_stk.htm).

<sup>174</sup> In South Africa, for example, information that has been made available includes tenders awarded, which companies supplied the ART, and what percentage of the tender each company's

Another important issue warranting close attention in India is the ongoing interruptions in the drug supply for first-line ART.<sup>175</sup> This issue should be investigated and resolved in tandem with the introduction of second-line ART. In recent months, reports have emerged that drugs are out of stock or in short supply in numerous locations throughout the country.<sup>176</sup> Such shortages may be caused by several factors including: failures at various supply levels such as the ART centres, delivery mechanisms, procurement and supply agencies. A review is urgently required to understand where the current system is encountering problems. Such a review should answer the following questions: Are stock registers being accurately kept? Are diversions taking place? Is delivery planned properly? Is the supply-chain management system being implemented? These are crucial matters because patients suffer when treatment is interrupted. NACO's responsiveness to this issue will also prove critical for another reason: if treatment interruptions continue, drug resistance will be exacerbated, resulting in rising costs. The government can and should consider quickly undertaking an investigation of the underlying problems causing these crucial drug supply interruptions.<sup>177</sup> Leading experts recommend monitoring and evaluating the performance of the supply system, including procurement and distribution. Depending on the outcome, options for further action may include employing alternative means or improving upon capacity and management.<sup>178</sup>

Another related issue is the lack of pharmacovigilance undertaken in India currently. To illustrate, currently the Ministry of Health has no quality restrictions on procurement of ART. GFATM funds, on the other hand, must purchase, with limited exceptions, prequalified drugs. This can result in situations where the same drug is bought from two different suppliers, or the same drug is bought from two different sites of the same supplier. The quality of the product may therefore differ. INP+ urges NACO to resolve these discrepancies concomitant to the introduction of second-line ART. Quality control studies are necessary to understand the impact; sample testing, what protocols are used, and other findings must be made publicly available on the NACO website. Another important step towards improving the procurement system is the involvement of civil society.<sup>179</sup> In the Philippines, for example, civil society involvement in monitoring

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supply makes up. *See* AIDS Law Project and Treatment Action Campaign, "Let them eat cake: A short assessment of provision of treatment and care 18 months after the adoption of the operational plan," 2003. at 13 (June 2005). *See also* Operational Plan on Comprehensive HIV and AIDS Care, Management and Treatment for South Africa.

<sup>175</sup> The term used by procurement agencies are "shortages" or "stockouts", whereas patient group advocates use the term "drug interruptions". Here we use the terms interchangeably.

<sup>176</sup> *See, e.g.*, Diwakar Tejaswi, posting on AIDS India listserv, "Shortage of First-line Drugs in Bihar," 12 Feb. 2007; *see also* Loon Gangte, posting on AIDS India listserv stating that shortage issue of pediatric ART at RML Hospital in Delhi is resolved, 11 Feb. 2007; *see also* Janabi Goswami, "Assam ART Center" posting on AIDS India listserv, 11 Mar. 2007.

<sup>177</sup> Currently, no central repository is used in India, and the drugs go directly to the government ART sites. This is a positive aspect to the ART supply system but there is no logistical or MIS follow-up which is an important component of a well-functioning supply system.

<sup>178</sup> *See* Yolanda Talyer, Ed., "Battling HIV/AIDS: A Decision Maker's Guide to the Procurement of Medicines and Related Supplies," at Ch. 3, World Bank (2004).

<sup>179</sup> Public disclosure and civil society involvement are two important components to strengthen public procurement. More information is available in "Towards a Medicines Transparency Alliance", Medicines Transparency Alliance (MeTA) Discussion Paper – consultation draft, February 2007.

procurement is not only encouraged, it is mandated by law.<sup>180</sup> INP+ recommends that NACO involve civil society in its efforts to improve procurement mechanisms by following this regional precedent.

In addition, other infrastructural issues must be carefully addressed. NACO's consultation to assess the feasibility of introducing second-line ART in November 2005 was an important first step in this regard. Amongst the numerous infrastructure concerns discussed at the 2005 national consultation were the "increase in lab monitoring needs, pill burden, toxicity/drug interactions risk, drug cost, staffing needs, referral/mentoring needs and cold chain."<sup>181</sup> Exacerbating the infrastructural issues are clinical, social, and operational factors. For example, the lack of a precise definition for treatment failure may result in premature switching of patients to second-line, resulting in increased drug resistance. Other factors resulting in resistance, as discussed earlier, include drug interruptions, quality control, lack of laboratory facilities, and lack of patient adherence.

Multiple strategies must be employed to improve patient adherence as India moves from a first- to a second-line regimen. These strategies should include strong treatment literacy materials which publicize the causes of resistance and the consequences of non-adherence or non-supply of ART.<sup>182</sup> Addressing the needs of patients with HIV-co-infection is also important, as some patients believe that ART is not working due to the persistence of OIs and discontinue treatment as a result. More attention is required to understand the causes of non-adherence to be able to successfully encourage patient compliance.<sup>183</sup> Treatment literacy materials for both first- and line- ARVs need to be made available in local languages and to meet the needs of illiterate populations. Further, both professional and peer counselors must be trained on first- and second-line ART to facilitate treatment adherence for their clients.

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<sup>180</sup> Section 13 of the Government Procurement Reform Act or Republic Act 9184, series 2003, aims to enhance the transparency of the procurement process. The section states that the procuring entity shall invite a civil society representative, a private sector representative, and a representative from the Commission on Audit. The observers must come from a duly registered entity from the Securities and Exchange Commission and must not have any direct or indirect interest in the project to be bid. The inclusion of the civil society representative is to ensure that the provisions of the procurement law are strictly adhered to and protects the integrity of the bidding process. This is affirmed by GPPB, Implementing Rules and Regulations, Part A of Republic Act 9184 (as amended). See e-mail correspondence with Carole Belisario, Procurement Watch, Inc. and Lorraine Hawkins, Consultant Health Economist, dated February 28 and March 3, available with author; See also <http://www.procurementwatch.org.ph/>; See also <http://www.procurementservice.org/gppb/home.htm> for the government procurement policy board's information on public disclosure.

<sup>181</sup> See NACO/WHO Draft Minutes, National Consultation on Need and Feasibility for Second Line Antiretroviral Drugs, Presentation by Ying-Ru Lo, 24-25 Nov. 2005 (Delhi, India).

<sup>182</sup> See Solution Exchange for AIDS Community, compiled by E. Mohamed Rafique and Ritu B. Nanda, "Consolidated Reply to Query on Second-line ARVs in government centres – experiences," 7 Feb. 2007.

<sup>183</sup> Creative new pilot programmes should be initiated to ensure patient adherence. One promising avenue may include using women and children's health NGOs to support individuals through the treatment process to fill important voids, as these NGOs may be able to understand and address the broader causes for non-compliance, such as domestic violence and travel hardship. See interview with Leena Menghaney, MSF, 20 Feb. 2007.

Many of the issues raised in this section require further examination. To this end, there is value in studying India's Revised National Tuberculosis Control Programme (RNTCP) when considering the introduction of second-line ART into India's HIV programme.<sup>184</sup> In combating TB, India's health system has already witnessed the successful implementation of a drug treatment programme. It is possible that NACO's ART programme can succeed in part by drawing on the institutional mechanisms that proved constructive in the fight against TB. From its inception, the Indian TB programme has used a process of external programme review and joint monitoring by WHO and the Government of India.<sup>185</sup> This approach, which relies on experts with actual programme-building experience, has resulted in enormous programmatic benefit for implementation strategies. The group reviews all aspects of the TB programme: structure, function, outcomes, indicators, reporting, management, advocacy and other critical factors.<sup>186</sup> The process is believed to be constructive and participatory and takes place every three years, beginning with a pre-pilot programme mission in 1992, and consistent follow-up meetings in the years that followed. Based on this success, INP+ suggests that the ART programme undergo a similar exercise, to create a treatment-focused external monitoring mission and review. As demonstrated by the TB programme, it is best to conduct such reviews in the early stages of a programme, to ensure constructive feedback, transparency, and more effective programme implementation. Such a process, we believe, will strengthen the ART programme, particularly if recommendations are consciously put into practice.

Finally, all of the issues discussed in this paper – cost, patents, funding, adherence – are capable of resolution. Challenges exist, as we have acknowledged, but they are not insurmountable, and there are alarming consequences to withholding treatment from PLHIV at this critical juncture. The absence of second-line ART, in conjunction with the lack of treatment-related counseling and wider availability of first-line ART, may result in increased drug resistance. Experiences in other countries support the view that the ethical obligation falls squarely on government. For example, in South Africa and Senegal, the lack of a patient-centered approach and withholding of free treatment in the context of XDR-TB and TB led to nonadherence, and ultimately the emergence of drug-resistant strains.<sup>187</sup> Furthermore, India chose to introduce first-line ART in 2004, and

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<sup>184</sup> Such an approach is advocated in Frieden, Editorial: "Tuberculosis Control: Critical Lessons Learnt," *Indian J. Med. Res.* 121, at 140-42 (Mar. 2005). The experience in Malawi of applying lessons from the TB programme is also discussed at Libamba et al., "Scaling up anti-retroviral therapy in Africa: learning from tuberculosis control programmes – the case of Malawi," *Int. J. Tuberc. Lung Dis.* 9(10), at 1062-71 (2005).

<sup>185</sup> See WHO (SEARO), "Joint Tuberculosis Programme Review," held Sept. 2003 in New Delhi, published Feb. 2004.

<sup>186</sup> *Id.*

<sup>187</sup> See Keith Alcorn, "Risk of default on TB treatment halved by patient-centred adherence approach in Senegal study," (*referring to* Thiam S et al., "Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting. A cluster randomized controlled trial." *JAMA* 297 (4):380-86 (2007)), available at <http://www.aidsmap.com/en/news/4EB1147D-16BC-4964-A1E9-1CF28614055A.asp>; see also "World Health Organization and experts call for \$95 million in emergency funding to combat XDR-TB," (*referring to* P. Nunn, "A global emergency response," 37th Union World Conference on Lung Health, Paris (2006), and K. Castro, "Extensively Drug-Resistant TB (XDR TB): A summary report." 37th Union World Conference on Lung Health, Paris (2006), available at <http://www.aidsmap.com/en/news/ADC40507-A617-4065-B4B7-32E8FC7BC9EC.asp>.

implicit in India's commitment was the commitment to continue people on treatment. India has made numerous commitments to provide the highest attainable standard of treatment.<sup>188</sup> Health is a human right- choosing some people over others, or declining to introduce new ARVs that have significantly improved therapeutic benefits, are not ethically sound decisions, nor are they in consonance with India's commitments. India must meet its obligation to providing the continuum of comprehensive care which includes second-line ART for all PLHIV who require it.

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<sup>188</sup> For an overview of these commitments, *see* The Lawyers Collective, "Legislating an Epidemic: HIV/AIDS in India," at 199-203, New Delhi: Universal Law Publishing Co.Pvt.Ltd. (2003). These commitments include the International Covenant on Economic, Social and Cultural Rights, Article 12.2 and General Comment No.14, International Guidelines on HIV/AIDS and Human Rights, UNGASS Declaration of Commitment. India's Supreme Court has reiterated that the State cannot plead financial constraints to justify withholding medical treatment. *See id.* at 202.

## **6 Recommendations**

Many of the issues discussed in this paper are complex, but we are confident that NACO can quickly resolve these issues and promptly introduce second-line ARTs into the programme. INP+ is committed to supporting NACO in doing so and this discussion paper is one of many steps in that direction.

INP+ concludes this discussion paper with the following set of recommendations:

### **Introduce second-line ART including interim mechanisms:**

1.1 NACO should introduce second-line ART for the small number of people who need it as quickly as possible, starting at the latest by **1 May 2007**. The list of network members who are currently on or in need of second line ARVs can be given by INP+ to NACO on **1 April 2007**. NACO should accept the CHAI/UNITAID offer of funding the first two years of second-line ART immediately.

1.2 NACO and donors such as CHAI/UNITAID should introduce a system to reimburse the costs of second-line ARVs purchased by PLHIV who come to the government-supported ART centres, effective **1 May 2007**.

1.3 Donors should immediately contribute funds to the 'Positive Support Fund' created by INP+ to support those PLHIV who need second-line ARVs.

### **Estimate the number of PLHIV who need second-line ARVs:**

2.1 NACO should estimate of the number of PLHIV who are coming to government-supported ART centres and who urgently need second-line ARV regimens by **1 May 2007**.

2.2 Comprehensive longer-term forecasting must be conducted to properly plan ART scale-up. International organisations can provide technical assistance if necessary. These estimates should already be in existence, and if the projections are not current, NACO should create a projection model by **1 June 2007**.

2.3 NACO and WHO should thoroughly examine the issue of drug resistance to understand the present and future treatment needs of PLHIV.

### **Overcome cost and funding issues:**

3.1 NACO should recommend a waiver of duties and taxes on HIV drugs to the Ministry of Chemicals and Fertilizers by **1 May 2007**.

3.2 NACO should request that Principal Recipients submit a representation to GFATM indicating to GFATM the need to buy second-line ARVs, under the GFATM Board Meeting exception allowing for alternative suppliers, by **1 May 2007**.

3.3 NACO should immediately request GFATM to permit the reallocation of resources from the round-4 and round-6 grants to buy second-line ARVs.

3.4 NACO should make public the percentage of GFATM funds spent thus far and indicate what, if any, bottlenecks exist.

**State involvement:**

4.1 State AIDS Control Societies should collaborate with other agencies/funders to give second-line ARVs in their respective states.

4.2 State governments should allocate specific funding for both first- and second-line ARVs. NACO should request state governments to support both first- and second-line ARVs.

**Overcome patent barriers:**

5.1 As the patenting situation of second-line ART unfolds:

- NACO and its procurement agencies must effectively negotiate with pharmaceutical companies to bring down the prices of second-line ARVs, particularly LPV/r.
- NACO and Government of India must issue or threaten the issuance of compulsory licenses in the event of patenting of second-line ART, particularly for LPV/r tablet and ATV.
- NACO should initiate procurement of second-line ART from Indian companies prior to the granting of patents, potentially under the government-use provision of the patent law.

5.2 In the next one year, NACO should:

- support the introduction of a “prior consent” system for pharmaceutical patenting in India, requiring the consent of the Health Ministry prior to grant of patents.
- study voluntary licensing, public production and donation programmes to understand the full import on the ART programme.
- propose, oppose and support legislative and policy changes impacting access to medicines.
- collaborate with relevant ministries related to patent issues (Ministry of Commerce and Industry, Finance Ministry, Ministry of Chemicals and Fertilisers)

**Mobilise new resources:**

6.1 Major donors and international agencies, e.g. the Gates Foundation and CHAI, should support the introduction of second-line ARVs in government-supported ART centres.

6.2 NACO should include second-line ARVs when finalising the NACP-III budget.

6.3 NACO should propose in the GFATM round-7 grant application to introduce second-line ARVs. GFATM should approve this request.

## **Strengthen the treatment programme:**

In 2007, NACO should initiate the following actions:

7.1 Start an external programme review following the WHO-RNTCP model, to effectively develop programme implementation.

7.2 Increase transparency in procurement and supply system, including making publicly available information related to drugs, prices, quality and suppliers. This information should be accessible on the NACO and HSCC websites. The Philippines model of involving civil society in monitoring procurement should be followed.

7.3 Investigate the problem of drug interruptions and expeditiously resolve the issue.

7.4 Accredit more second line providers through trainings and continuing medical education.

7.5 Strengthen treatment adherence by making materials available in native languages for both literate and illiterate audiences, and build capacity of counselors for first- and second-line ART.