USAID
FROM THE AMERICAN PEOPLE

HEALTH SYSTEMS 2020
better systems, better health

info@HealthSystems2020.org
www.HealthSystems2020.org

Cost and Efficiency of ART Regimens

1. OBJECTIVE OF ACTIVITY

The aim of this document is to explore how the HIV/AIDS Program Sustainability Analysis Tool (HAPSAT) should factor cost and efficiencies of the different ART regimens in the HAPSAT tool. The HAPSAT approach provides policy-related recommendations on the sustainability of HIV programs at the national level. Assessing the cost-effectiveness of various ART regimens – in addition to other considerations such as international guidelines, clinical appropriateness, and commodity availability – can assist national ART programs in determining the most appropriate ARV regimens for their unique settings. This paper details and elaborates on the research done as part of updating the HAPSAT software on this aspect of cost and efficiency of ART regimens and how HAPSAT teams should address this issue.

2. BACKGROUND ON ANALYSIS OF COST AND EFFICIENCY OF ART REGIMENS

Numerous studies have shown that ART is cost-effective compared to HIV treatment regimens that do not prescribe ARTs (e.g. Cleary et al. 2006; Goldie et al. 2006). Conducting a cost-effectiveness analysis comparing various clinically-preferred ARV regimens proves to be complex. There are numerous variables including, but not limited to, CD4 count, viral load, opportunistic infections (including TB), drug resistance, as well as other medical conditions that clinicians must factor into their patient diagnosis (Zhang et al. 2008; Walensky et al. 2010b).

As such, patient considerations are crucial and necessary to investigate and factor into decisions made regarding the selection and timing of an individual's most clinically appropriate and effective HIV treatment regimen. For example, when comparing Emtricitabine (FTC) with Lamivudine (3TC) – both clinically efficacious nucleoside analog reverse transcriptase inhibitors (nRTIs) – 3TC emerges as the cheaper option (Global Fund Price and Quality Reporting). Despite the relatively low cost, it is not always the best, efficient option: clinical considerations and supply-chain issues come into play for instance. Moreover, Stavudine (d4T) is the most commonly used (and cheapest) nucleoside analog reverse transcriptase inhibitor (NARTI), but may not be appropriate for patients who experience peripheral neuropathy or are at risk of lipodystrophy. Although the World Health Organization (WHO) has recommended the phase-out of d4T due to its long-term, irreversible side effects, some national governments are still using it due to its low cost and widespread availability (Walensky et al. 2010b). Zidovudine (AZT) or Tenofovir (TDF) are recommended as equally effective alternatives with lower toxicity.

Based on the priority considerations, particularly the clinical dimensions, in choosing an ARV treatment regimen, it is important to identify the preferred and prioritized treatment lines as per national and international protocols (World Health Organization [WHO] 2010), which will most likely be the following:

1st line will be one of the following preferred WHO combinations:

1. AZT(Zidovudine)–**3TC**(Lamivudine)–**EFV**(Efavirenz)

OR

AZT(Zidovudine)–**3TC**(Lamivudine)–**LPV/r**(Kaletra: Lopinavir/Ritonavir)

2. TDF(Tenofovir)–**FTC**(Lamivudine)–**EFV**(Efavirenz)

OR

TDF(Tenofovir)–**FTC**(Lamivudine)–**LPV/r** Kaletra: Lopinavir/Ritonavir)

*** TDF/FTC combination pill is available under trade name Truvada.*
***d4t (Stavudine) will likely have been phased out in most countries, but would be used in replacement of AZT or TDF.*

2nd line is more complicated and should be checked against the country protocols and in relation to system issues such as the availability of cold chain, but it would likely entail the following drugs:

ATV/r(Atazanavir Sulfate, also called 'Reyataz')

OR

LPV/r(Kaletra: Lopinavir/Ritonavir)

Plus either:

a) **TDF**(Tenofovir)+**3TC**(Lamivudine) or **FTC**(Lamivudine)

OR

b) **AZT**(Zidovudine)+**3TC**(Lamivudine)

Based on these first- and second-line ART regimens, the patient's clinical condition and the side effects of the regimens must be prioritized when using the recommended ARV drugs and combinations. The following examples below provide further details on three recommended ART regimes in order to illustrate the complexity of choosing a patient regimen based on their underlying clinical conditions, response to treatment, and potential interactions with other medications:

1. **AZT – 3TC – EFV:** This regimen is the preferred first-choice regimen (in part to "reserve" TDF [Tenofovir] as a possible second-line option). However, in patients with low body mass or low initial CD4 count, there was a higher correlation with AZT-induced anemia. Therefore, if there are underlying issues of anemia (i.e. pregnancy, malaria, malnutrition or advanced HIV presentation with low CD4 count), AZT should not be initiated and/or switched to early on in treatment. Furthermore, EFV will not be used in the first trimester of pregnancy. Finally, no triple drug combination exists for this regimen, so for 'high-risk adherence patients', this may be a consideration related to perceived low-treatment literacy.
2. **AZT – 3TC – NVP:** This regimen is the preferred first-line regimen in pregnant women due to the NVP replacement of EFV except where the patient has a high initial CD4 count. This regimen can be used for

pediatric patients and adults in addition to pregnant women. There is wide programmatic experience with this regimen.

3. **TDF – 3TC – EFV:** This regimen is available as a fixed-dose combination pill taken once daily. TDF has links (albeit low) to renal toxicity. This should therefore be considered when the patient has a history of underlying kidney function issues.

In summary, prioritizing a particular drug or regimen based on cost is conceptually and perhaps ethically questionable. It is reasonable that a national government could (and likely already has) made cost and availability strong considerations in choosing preferred regimens as part of their national protocols. In countries that do not have strong or finalized national protocols (particularly in regards to second-line therapy options), and as developing countries assess the appropriateness of new drugs that become available, an ARV costing exercise could indeed assist in prioritizing various regimens. However, prioritizing particular ARVs or regimens based on cost alone ignores the fact that patient clinical presentation is the most appropriate ART regimen determinant of regimen choice. A concern is that in resource-poor settings, emphasizing cost considerations could potentially lead to poor clinical decision-making and disincentivize clinical competency as well as due diligence in ART selection. This could potentially negatively impact the quality of patient care.

Discussions on the cost-effectiveness of ART would not be complete without mentioning the work and research of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) team at the Massachusetts General Hospital. It uses simulation models to evaluate clinical outcomes, costs, and the cost-effectiveness of strategies for testing and treating HIV/AIDS and its complications, including tuberculosis and other infections. The CEPAC team collaborates with research teams in Côte d'Ivoire, France, India, South Africa, and Zimbabwe, as well as investigators from Brigham and Women's Hospital, the Harvard School of Public Health, Weill Cornell Medical College, and Yale University. The model requires patient level data, including age, sex, CD4 count, and HIV RNA distribution. Also defined are probability distributions for various clinical events such as opportunistic infections and the entrance to or dropping out of care for different patient states. From this distribution of demographic and clinical data, each patient's clinical course is tracked from entry into the model until death. A running tally is maintained of all clinical events and of the cumulative cost and health-related quality of life (or "utility") associated with the months in each health state. This process is repeated until the entire cohort has passed through the model, at which point overall performance measures such as average survival, quality-adjusted life expectancy, and per-patient cost are computed (Cost-Effectiveness of Preventing AIDS Complications [CEPAC] team 2012). Studies of CEPAC include topics such as quantifying the benefits (life expectancy gains) and risks associated with using Efavirenz (EFV) in HIV-infected women of childbearing age (Hsu et al. 2011), review of the cost–effectiveness literature with regard to monitoring the CD4 cell count and HIV RNA level in Africa (Walensky et al. 2010a), and evaluation of the clinical outcomes and cost-effectiveness of first-line ART using TDF in India, compared with the current practice of using Stavudine (d4T) or Zidovudine (ZDV) (Bender et al. 2010).

3. IMPLICATIONS FOR THE HAPSAT APPROACH

The need for country patient profile data to determine the choice and distribution of ART regimens, rather than the cost alone, prevents us from using the HAPSAT software to recommend on optimal distribution. However, HAPSAT teams should review the distribution of ART regimens and its cost implications using the HAPSAT in order to assess and consider the following questions within the stakeholder engagement process:

1. Is the distribution in line with national ART guidelines, and preferably also the most up-to-date WHO ART regimen guidelines? If not, what are the reasons?

2. Are the major ART regimens administered in a given country the most cost-effective options? If not, what are the reasons?

3. Are the prices and procurement costs of the ART regimens low compared to other countries? Global Fund Price and Quality Reporting may be used as a tool for comparing prices and costs

Posing these questions to the national ART programs and other appropriate stakeholders will at the least provide a platform to review, and potentially improve, this aspect of the country's HIV response and prioritization of various ARV combinations within national protocols. The usefulness of the above process will prove to become much more effective and ethically appropriate in the future when developing countries gain access to additional drugs. Additionally, this approach will become more appropriate as clinical guidelines continue to shift in order to keep up with pharmacological advances and as health information systems allow for a more detailed tracking of patient profiles. In the same vein, as developing countries gain access to better drugs that are currently prohibitively expensive and/or for which there is currently no generic production – using a model like the HAPSAT at the national level in order to compare the cost and efficiency of new ART regimen options vs. existing ART regimen options can assist ministries in determining if and when to change their national protocols.

REFERENCES

Cleary, S. M., D. McIntyre, et al. (2006). "The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa--a primary data analysis." *Cost Eff Resour Alloc* 4: 20.

Cost-Effectiveness of Preventing AIDS Complications (CEPAC) team. (2012). "CEPAC: Cost-Effectiveness of Preventing AIDS Complications." Retrieved 12 September, 2012, from http://web2.research.partners.org/cepac/mainpage.html.

Goldie, S. J., Y. Yazdanpanah, et al. (2006). "Cost-Effectiveness of HIV Treatment in Resource-Poor Settings — The Case of Côte d'Ivoire." *New England Journal of Medicine* 355(11): 1141-1153.

Walensky, R. P., R. Wood, et al. (2010). "Scaling Up the 2010 World Health Organization HIV Treatment Guidelines in Resource-Limited Settings: A Model-Based Analysis." *PLoS Med* 7(12): e1000382.

World Health Organization (WHO) (2010). Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach – 2010 revision.

Zhang, M., X.-X. Han, et al. (2008). "The impacts of current antiretroviral therapy regimens on Chinese AIDS patients and their implications for HIV-1 drug resistance mutation." *Japanese Journal of Infectious Diseases* 61(5): 361-365.

Health Systems 20/20 is a five-year (2006-2011) cooperative agreement (No. GHS-A-00-06-00010-00) funded by the U.S. Agency for International Development (USAID). The project uses an integrated approach to address the financing, governance, operational, and capacity constraints in a health system that impede access to and use of life-saving priority health services.

Abt Associates Inc. leads a team of partners that includes:
| Aga Khan Foundation | Bitrán y Asociados | BRAC University | Broad Branch Associates | Deloitte Consulting, LLC. | Forum One Communications | RTI International | Training Resources Group | Tulane University School of Public Health

This publication was produced for review by USAID. It was prepared by Christina Juan, Itamar Katz and James White for the Health Systems 20/20 project.

DISCLAIMER: The author's views expressed here do not necessarily reflect the views of the United States Agency for International Development or the U.S. Government.

ACKNOWLEDGMENTS: We would like to thank Stephen Resch and Elaine Baruwa for their input, and Maria Claudia De Valdenebro for designing the document.

September 2012

For more information about Health Systems 20/20 please contact:
Health Systems 20/20 | Abt Associates Inc. | www.abtassociates.com | 4550 Montgomery Lane | Suite 800 North | Bethesda, MD 20814 | USA
E-mail: info@healthsystems2020.org | www.healthsystems2020.org