

SMARThivPack: A complexity free and cost effective “three tests” combo kit model for improving HIV patients monitoring standards in resource poor settings

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Abstract:

We propose a second method at an implementation level with cost and complexity reductions for monitoring HIV patients in resource-limited settings. The model is SMARThivPack, a “three tests” combo kit. Cost and complexity reductions of HIV patient monitoring technologies were described in a first model (at a technology development stage) proposed earlier. In developed countries, HIV patient clinical management programs comport three laboratory tests containing CD4 count, viral load measurement and pharmacoresistance testing. In most developing countries only CD4 count is performed without the other two tests. Cost and complexity of required technologies are the major challenges to the developing world to meeting the “three tests” standard. SMARThivPack model achieves the “three tests” standard in the developing world by optimizing technology choice as to favour cross-use of equipments, thereby reducing equipment cost at the laboratory implementation level. Equipment cross use also reduces complexity by reducing training time, promoting specialization and substantiating experience in equipment use. The second level cost and complexity reductions model sets the grounds for a third level, global coordination cost and complexity reductions model.

Keywords: HIV monitoring guidelines; resource poor countries; cost and complexity; alternative technologies

Background:

The acquired immuno-deficiency syndrome (AIDS) is a chronic disease requiring long term monitoring. Numerous studies established a link between AIDS and the Human Immunodeficiency Virus (HIV). Chemotherapy-based treatment aiming to inhibit HIV replication exists. However, the virus evolves to develop resistance against AntiRetroVirals (ARVs) used in Chemotherapy, and continues replication in the presence of ARVs. HIV continued replication leads to increase plasma HIV RNA content (viral load) and decrease in the number of CD4 immune cells. Viral load and CD4 number are markers for monitoring HIV replication and disease progression. Pharmacoresistance testing is used to determine patterns of mutations conferring viral resistance to a given, generally three drugs regimens. Interpretation of the mutation patterns allows the choice of alternative drug regimens to further hinder virus replication. [1]

CD4 counting, viral load measurement and, pharmacoresistance testing are three standard tests in the clinical management of HIV patients in the developed world. Standard technologies for performing the three tests are complex and expensive. Cost and complexity are the major challenges to the developing world to achieving the “three tests” standard. Required resources for equipment purchase and expertise for technology implementation, and tests execution are scarce in the developing world. Expert panels therefore recommended simpler and cheaper so called alternative technologies for the clinical management of HIV patients in the developing world. [2, 3, 4] Alternative

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technologies, for CD4 count, viral load measurement, and pharmacoresistance testing for the clinical management of HIV patients in the developing world, have been developed and evaluated. [5]

Despite the availability of experts recommended alternative technologies for the three HIV patients monitoring laboratory tests, few nation level monitoring programs in the developing world, comport the three tests. CD4 count, as the solo laboratory test in the clinical management of HIV patients is the norm in most developing countries. [4]

The World Health Organization (WHO) HIV patients treatment guidelines for the developing world, relied heavily on syndrome-based clinical management through careful symptoms monitoring, over sophisticated laboratory tests emphasized in developed countries. WHO emphasized simplicity and economy, and minimized substantial infrastructure improvement requirements. [6, 7]

However, the forum for collaborative HIV research recommended laboratory monitoring of HIV patients in the developing world, to improve treatment outcomes and avoid drug resistance. [2]

Both proponents and opponents of laboratory testing of HIV patients in the developing countries acknowledge the weaknesses of their approach. The committee that establishes the WHO guidelines acknowledges that setting science-based

different standards for poor patients in the developing world and rich patients in the developed world raised an ethical issue. Dr. Mark Wainberg, an HIV specialist at McGill University and former president of the International AIDS Society, comments on the WHO guidelines: "I was part of the committee that came up with the guidelines. I don't think they are perfect, but I doubt whether any similarly constituted group would improve significantly on the recommendations". [7] Dr. Susan Fiscus, an HIV expert at the University of North Carolina at Chapel Hill and chair of the forum for collaborative HIV research acknowledges that developing countries economy and expertise level are serious challenges to implementing individual-centred sophisticated laboratory testing as performed in the developed world. [2]

Biotech tropicana, Inc proposes an alternative HIV patient clinical management model that overcomes the weaknesses and reconcile the strengths of both the WHO approach and the Forum approach: SMARThivPack, a "three tests" combo kit, consisting of SMARThivCD4mos, SMARThivVLmos and , SMARThivDRmos . A detailed investigation of the available alternative technologies, specially designed for the developing world, showed that the "the three tests" laboratory testing standard is achievable in the developing word, by optimizing a combinatory technology choice as to favour equipment cross-use. SMARThivPack achieves the "three test" standard without substantial increase in cost while creating grounds for improving laboratory implementation and test execution quality. Cross use of equipments reduced equipment cost. Cross use of equipments also reduced training cost while substantiating experience in equipment use, thereby alleviating expertise barrier. Savings in equipments and training costs can be used to increase laboratory number without further investment.

Description:

The internet is a gold mine of information on HIV/AIDS basic research, HIV related technologies, and clinical data collected from HIV patients. [8] We used web-based data mining and detailed investigation of existing protocols on HIV laboratory monitoring technologies, to design an optimized laboratory model for monitoring HIV patients in the developing world. Our investigation focused on essential components of the indicated technologies and cost of implementation programs expressed as cost per test. The optimisation process aims to favour "user friendly" "automated" technologies that can carry as many tests as possible. Our model assumes HIV patient monitoring laboratory implementation within an existing health centre. Therefore, our model does not take into account essential components such as refrigerator, electrical supply and, computers which may be shared with other medical services.

In the SMARThivPack model presented in table 1 (see supplementary material), equipment cost is reduced by choosing technologies that share essential equipments for the three tests. Elisa plate reader is the essential equipment for CD4 count and the viral load measurement. Viral load measurement capability is created without any further capital investment in essential equipment by choosing an elisa-based viral load measurement technology. The elisa plate reader can also be used for detection of HIV drug resistance conferring mutations in the OLA and ELMA technologies. Transferring

the savings in viral load capability to establishing a PCR set up creates HIV drug resistance monitoring capability.

Compared to the non optimized alternative technology model, optimization of equipment choice does not reduce the cost per three tests. However, SMARThivPack substantially reduces training cost. The elisa plate reader is an "alternative" "automated" technology that does not require long term training. Use of microscope in the "appropriate" dynabeads CD4 technology adds the requirement of a different skill, thereby increasing training cost. SMARThivPack requires two essential skills, PCR and elisa for execution of the three standard laboratory tests. Furthermore, the elisa plate reader can be used for qualitative hiv test.

Compared to the standard reference technology model, SMARThivPack is far cheaper. Based on our model, thirty (30) SMARThivPack laboratories can be implemented from the total cost of one (1) standard reference laboratory.

The \$42/3tests using our SMARThivPack model, is within the cost range of classical diagnostic tests in monitoring other chronic diseases such as diabetes. In Benin Republic, a resource-limited country, cost of required tests in monitoring diabetes and other chronic diseases typically ranged between CFA 5000-10.000 (\$USD 10-20) (Aboubakar YARI Biotech tropicana, Inc, personal investigation at Cotonou CHU, Benin). Diabetes is not health insurance covered and is paid for directly from patient's income. [9] HIV patient with average income in developing countries can similarly afford to pay for the \$42 per three tests, particularly in light of the special subventions accorded to developing countries HIV/AIDS programs.

The Biotech tropicana, Inc SMARThivCD4mos, SMARThivVLmos, and SMARThivDRmos, are dynamic structures of the Biotech tropicana, Inc SMARThivPack model. The CD4, VL, and DR technologies are chosen from the pool of available indicated technologies, based on existing equipments in a specific health centre, to overcome cost and complexity barriers.

We demonstrate the feasibility of the individual-centred "three laboratory tests" in the clinical management of HIV patients in the developing world. Our SMARThivPack model overcomes cost and complexity barriers. Compared to programs implementing reference technologies, or non optimized alternative technologies, our model is far cheaper. Furthermore, by optimizing "technology choice" our model achieves substantial reduction of training period, while improving test execution quality. SMARThivPack is an ideal companion to generic AntiRetroViral drugs.

It is now well accepted by all parties that alternative HIV patient monitoring strategies and technologies are the ultimate solution to the HIV/AIDS crisis in the developing world. However, approaches to applying these strategies and technologies toward achieving the objectives are an evolving area of sciences. Cost and complexity of the indicated alternative technologies are the major challenges to the developing world. Cost and complexity issues in the clinical management of HIV patients in the developing world were previously overcome with respect to AntiRetroViral drugs (ARVs) accessibility to the developing world. [4] Two

conflicting approaches addressed the ARVs drugs accessibility issue; the pressure on pharmaceutical industry approach (“pressure approach”) [10], and the negotiation with pharmaceutical industry and developing countries government approach (“negotiation approach”). [11] The World Health Organization favours generic drugs, while the George W. BUSH PEPFAR program restricted funding of generic drugs that were not approved by the United States Food and drug Administration (FDA). The Clinton Foundation negotiation approach overcomes the weaknesses and reconciles the strengths of the WHO and BUSH approaches. The Clinton foundation succeeded in reducing cost and complexity of FDA-approved ARVs through a third level, careful coordination of drug development in the developed world and drug purchase by governments in the developing world. [11] Applying the Clinton Foundation strategy to laboratory monitoring, could promote the achievement of the individual-centred “three-test” laboratory monitoring standard, in the developing world, by further reducing cost. Per unit cost of laboratory implementation will decrease, but the number of laboratories can be increased, thereby increasing the quantity of sales. Increase market will motivate private industry to further increase investment in research to improve alternative technologies for the developing world. Small and disorganized market so far limited industry interests. [4] Increase number of monitoring laboratories will increase treatment benefits. Morbidity and mortality will decrease. Decrease in morbidity will alleviate demands on already weak developing world public health systems, and put back HIV patients in the active developing world economy. Tangible results will be achieved. Results achievements will motivate further donations from the developed world public sector. Substantial proportion of the funds, invested in the fight against HIV/AIDS in the developing world, arose from the developed world public sector in the form of AID. [12] Biotech tropicana, Inc is in the process of investigating a third level, laboratory monitoring cost and complexity reduction strategy for the developing world.

Expert panels recommended simpler and cheaper technologies for the clinical management of HIV patients in the developing world. [2, 3] Simpler technologies tend to demand substantial human input. Lab technicians in developing countries are

getting infected, and the under staff developing world health systems put an extra burden on laboratory technicians who must also perform testing on other endemic diseases such as malaria and tuberculosis. There arose the “technology type” question. The so called “Appropriate Technologies” for the developing world tends to combine “low tech” with “simplicity” and “low cost”. The drawbacks of these technologies are that they tend to demand substantial human input and are therefore error-prone. “Alternative technologies” as defined by Biotech tropicana, Inc are “user-friendly”, “cutting-edge techs” that combine “automation” with “simplicity” and “low cost”, thereby reducing human input. Biotech tropicana, Inc is investigating the issues of “technology type” and “technology choice” for the developing world.

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Supplementary material

		Standard reference technology	Non optimized alternative technology	SMARThivPack ^a
Essential Technology (Equipments)	CD4	Standard Flow	Dynabeads (fluorescent microscope)	Capcellia (elisa plate reader)
	VL	Cobas Amplicor HIV-1 Monitor Test v1.5 (Cobas system)	Exavir (gel filtration system, elisa plate reader, elisa plate washer ^b)	P24 (elisa plate reader ^c)
	DR	ViroSeq (Automatic Sequencer, Thermal Cycler, gel electrophoresis system)	OLA ^d (pcr set up, elisa plate reader, elisa plate washer)	ELMA ^d (pcr set up, elisa plate reader,)
Equipment Cost	CD4	\$USD 60.000 ^e	\$ USD 6000	\$ USD 3.000
	VL	\$ 90.000 ^f	\$ 7000 ^g	\$ USD 0 ^h
	DR	\$ USD 100.000 ⁱ	\$ 5000 ^j	\$ USD 5000
	Total	\$ USD 250.000	\$ USD 18.000	\$ USD 8000
Implementation Cost (cost/test)	CD4	\$ USD 26/test	\$ USD 4.5/test	\$ USD 17/test ^k
	VL	\$USD 26/test ^l	\$ USD 15/test	\$ USD 12.5/test ^m
	DR	\$USD 350 ⁿ	\$ USD 12.5/test ^m	\$ USD 12.5/test ^m
	Total	\$ USD 402/ 3 tests	\$ USD 32/ 3 tests	\$ USD 42/ 3 tests

Table 1: Comparison of essential equipments choice in a standard HIV patient monitoring laboratory with SMARThivPAck model HIV patient monitoring laboratory in developing countries is given. (a) The SMARThivPAck model presented in this table is an illustration of the SMARThivPAck concept and should not be construed as a universal developing countries HIV patients monitoring laboratory model. The SMARThivPAck model should be adjusted to specific laboratory setting, particularly in light of existing equipments and cost of consumables. (b) A plate washer is a recommended not essential equipment in performing an elisa test. Most elisa kits come with a manual washing protocol. (c) The elisa plate can be used for CD4, VL, and DR assays. (d) Details on OLA and ELMA technologies are available at, [13] and [14] respectively. (e) Unless otherwise specified all costs are averaged from <http://www.hivforum.org/publications/QAAC.pdf> appendixes B and C. Cost is averaged from http://mednet2.who.int/sourcesprices/sp_1b.pdf. (f) From web survey of 5 manufacturer catalogues, cost of elisa plate reader/washer is averaged to \$USD 3000 each, and cost of the gel filtration system is averaged to \$1000. (g) See c). (h) Cost is estimated based on specific requirements of DNA sequencing facility and cost of genetic analyzers. (i) From web survey of 5 manufacturer catalogues, cost of the pcr set up is average to \$USD 5000. (j) Cost as applied in South Africa. <http://www.aidsinfonyc.org/fiar/croi11-app3.html>. (k) Cost is averaged from same reference as in f); (l) Cost is estimated from same reference as in f) based on similarity of essential steps (pcr amplification and elisa detection). (m) Cost range is \$USD 200-500 from [15]