MOST EFFECTIVE UTILITY FUNCTION FOR HIV DRUG USING COST AND EFFICACY ANALYSIS

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ABSTRACT

The fight on HIV/AIDS globally is on increase everyday. Many research activities are pioneered to put the scourge under control. In the present paper an exposition is made on the need to fight HIV/AIDS is presented and the role which Operations Research experts can play to reinforce research on HIV/AIDS. The paper also considers a mathematical modeling problem arising from Operations Research. It is that of constructing most effective utility function for HIV drug using cost and efficacy analysis. The problem is a typical max min problem of the utility function and also exploited the Piyavskii's algorithm for finding the most efficacious drug and used four minimization algorithms namely gradient, Newton's, Conjugate gradient and quasi-Newton's algorithms to find the most cost-effective drug.

1 INTRODUCTION

The human immunodeficiency virus (HIV) epidemic is still out of control in most sub-Saharan African countries. In Africa, poverty and food shortages are rampant ([4], [16]) and AIDS is striping whole societies of the parents, farmers, and teachers who could turn things around, as former USA Secretary of State, Colin Powel once declared , HIV is more destructive than any army, any conflict, any weapon of mass destruction [4]. AIDS has remained global crisis since the mid 1980s. World Health Organization (WHO) estimated in 1986, that about 100,000 AIDS people are present worldwide and from 5 to 10 million cause of infection with HIV ([5], [12]).

Ever since HIV was discovered the world is constantly in the state of pandemonium and disarray. Almost 70 million people have been infected with HIV virus and about 35 million people have died from AIDS and over 35.3 million people living with HIV/AIDS (PLWHA) at the end of 2012 by WHO estimate. The epidemic continues to vary from country to country and region to region. 1.6 million people died of AIDs related illness in the same period and 119 countries reported a total of 95 million people tested positive in 2011.Sub-Sahara Africa remains most severely affected with nearly 1 in every 20 adults (4.5%) living HIV and accounting for 69 % of the people living with HIV worldwide (Global Health Observatory (GHO, 2011)).There is continuous reduction in death rate because of scale up antiretroviral treatments.

The youth comprise about one - four of the world's population and UN Department of Economics and Social Affairs reported that in 1998 that fifty percent of HIV infection world wide are between the ages of 15 and 24 (UNAIDS and WHO, see [9]). It is estimated that 39 % people between age 15 and 24 are living with HIV/AIDS globally. Young women are twice likely prone to HIV infections than male counterpart. It is undisputable that socio-cultural factors have had greater influence on young people vulnerability to HIV infection.

1.1 The Global need to fight HIV/AIDS

AIDS has irreparably maimed about 22 million people, since it appearance. Since 1981, over 39.4 million people are now living with HIV/AIDS. The potential danger HIV/AIDS poses to the victims is:

- If DNA of HIV virus aligns with that of patient's DNA the provirus will remain in the patient for life.
- Cardiovascular problems associated with HIV therapy i.e. the use of antiretroviral drugs and highly active antiretroviral therapy (HAAT).
- The drug must be taken consistently for long period. There are strong indications that the virus may not be completely eliminated since; some HIV cells will still remain in tissues and

muscles of the patients when taking of the drug stops.

1.2 THE ROLE OF MATHEMATICAL MODELLER IN THE CONTROL OF SPREAD AND TREATMENT OF HIV/AIDS

The fight against HIV/AIDS is multi-sectored in nature; it cuts across of all sectors of economics and sphere of human endeavour. The multi-disciplinary approaches to fight HIV have been strongly advocated from several quarters ([1], [11-13]).

There are, indeed, several problems that can be solved using mathematical modeling especially, by the use of Operations Research methods to simulate and analyze the strength, weakness and the impact of any intervention strategy targeted to fighting the HIV scourge.

Several intervention strategies are proposed and put in place, some of which are the use of condom and other safer reproductive and sex practices. Proper management of sexually transmitted diseases, (STDS) maternal intervention and other behavioural interventions will reduce HIV incidence.

The business of Mathematical modeling experts in the HIV/AIDS management is to develop models to analyze the strength of any intervention and rank various options into classes of different place values.

Here are some of the examples:
Determine the effectiveness of a given intervention: e.g. the use of condom against sex practices without condom.

STD and HIV cofactor management:
It is a well-established fact that STDs are cofactors to HIV spread ([18]). Thus, if a programme seeks eradicate STD in a given community is introduced, how effective will the programme be? How the cofactor to HIV like tuberculosis can to controlled

The prevalence of infection agents:
infection with virus and parasites e.g. some of which are STDs causative agents e.g. herpes simplex, toxoplasmosis, hepatitis, cytomegalovirus are common in Africa. John ([8]) suggests that exposure to these agents' results in a chronic activity of the immune system, which in turn may lead to greater susceptibility to HIV infection.

Behavioural intervention:
To what extent women with intervention focus on female sex and youth between ages 14 and 24 reduce HIV prevalence in any area? Try to identify any other age group or occupational groups that are most vulnerable to HIV so that reduction of preponderance will make impact in the reduction of HIV/AIDS in the place. There are some highly active antiretroviral therapy (HAART) and intervention that are targeted on morbidity and mortality but may also affect transmission. How can we make such intervention effective?

Mother-to-child intervention: some few years ago,
in India and Botswana mother - to - child transmission programmes has reduced HIV almost by 50% but with no impact on epidemic itself. Such intervention can be tested in some other countries to see whether there will be impact on the epidemic in long run and some to determine what

acceptable level is vertical intervention will reduce the mother-to-child HIV incidence in any country especially in the central and West Africa.

Cost Analysis:

To find out estimates most efficient and cost effectiveness intervention. To study the cost effectiveness of any HIV/AIDS control intervention programme in low and medium income countries. Determine the most effective path to channel resources to combat HIV/AIDS epidemic.

Effectiveness of Community Health Financing:

Estimates the expenditure gap to achieving universal access to Health Services to low income level through such public financing mechanisms range from US$25 - 50 billion ([14]) to over US $100 billion.

Community financing are been advocated to offer viable option for providing some financial protection and access to basic health service to the poor. Several areas of HIV/AIDS intervention outlined above are problems arising from mathematical modeling; some of the problems are of Operation Research type.

Some of the problems could be formulated as linear programming problems or non - linear programming or even convex programming or network analysis problem. In order to illustrate the usefulness of Operation Research in HIV/AIDS Research we will consider a non - linear programming problem for solving a given HIV control problem, especially for Africa countries with large number of HIV/AIDS victims, we develop a given utility function and seek, using our knowledge of optimization, to solve given HIV/AIDS problem in the society.

2.0 Preliminary Definitions and Notations

The following definitions would be used throughout the paper.

Definition 1

The function f(x) defined on the internal [a,b] is said to be Lipschitzian with respect to x in [a,b] if there exist a constant L such that

$$| f(y) - f(x) | \leq L | y - x |; \; x, y \in [a, b]$$

L is said to be the Lipchitz constant for $f(x)$. If, on the other hand $f(x)$ is differentiable with respect to (w.r.t) *x*, then the Lipschitz constant *L* is the maximum bound for the derivative of $f(x)$.

Definition 2

If f is evaluated at x_o it follows from the Lipchitz property that

$$f(x) \leq f(x_0) + L | x - x_0 | = F(x_0)$$

For all $x \in [a, b]$, i.e. *f* is bounded above by two lines of slope - *L* and *L* passing through $(x_o, f(x_o))$. We define a saw - tooth curve by $F_i(x) = f(x_i) + L|x - x_i|$.

Definition 3

Consider stationary linear iterative scheme (SLIS)

$$u^{(n+1)} = Gu^{(n)} + K$$

Where *G* and *K* are constants not dependent on $u^{(n)}$ nor *n*. We define average rate of convergence of SLIS as $R_n(G) = -n^{-1} \log |G|^n$

And the asymptotic rate of convergence by $R_\infty(G) = \lim_{n\to\infty} R_n(G) = -\log S(G)$

$R_\infty(G)$ is sometimes referred to as rate of convergence if $S(G) = max\ |G| < 1$, a rough approximation to the number $T(C_i^{(n)}, C_i^*)$ which is define as

$$T(C_i^{(n)}, C_i^*) = \frac{|C_i^{(n)} - C_i^*|}{|C_i^*|}$$

Where $C_i^{(n)}$ iterative value for C_i and $\lim_{n\to\infty} C_i^{(n)} = C^*_i$

2.1 UTILITY FUNCTION

Consider a two dimensional non-linear function, utility function (UF) defined by variables C_i, the cost of drugs, e_j the efficacy of the drugs.

We define the uf by

$$f_{ij} = f(c_i, e_j), i = 1,2,..., N,\ j = 1,2,..., N \qquad (2.1)$$

From our experience, with HIV drugs, f_{ij} have the property.

$f_{ij} \le f_{i+1,j}$ for fixed j

$f_{ij} \ge f_{i,j+1}$ for fixed i

For most effective f_{ij} we need to find n* and N* such that i = n*, j = N* such that the minimum and maximum properties are satisfied, that is,

$$\max_i \max_j f_{ij} = \min_i \max_j f_{ij} = f(c_{n^*}, e_{n^*}) = f_{n^*,N^*} \qquad (2.2)$$

Algorithms to be used are minimization and maximization algorithms. Consider minimization of the unconstrained scalar cost function.

$F(C_i)$ subject to $C_i \varepsilon R^+ = [0, +\infty)$

The algorithms to be used for the different methods are

$$x_{k+1} = x_k + \eta_n dk,\ x(0) = x_o\ (k = 0,1,2...N)$$

$\eta_k > 0$ Determines the length of steps to be taken in the direction of $d_k \approx \Delta x_k$. to compute η_k in the direction of d_k we consider four basic algorithms using the following standard methods:

Method	**Value for η_k d_k**
Gradient method (GM)	$-\Delta_k f(C_k)$
Newton=s method (NM)	$[^2f(C_k)]^- \Delta f(C_k),\ \eta_k > o,\ \eta_k < \eta_{max}$
Conjugate Gradient method (CGM)	$(\beta_k d_{k-1} - \Delta f(C_k))(arg\min f(C_k - \eta d_k)$

$$\beta_k = \frac{|\Delta F(C_K))|^2}{|\Delta f(C_{k-1})|_2^2}$$

Quasi-Newton's (QNM) $H_k \Delta f(C_k)$,$H_k = \Delta^2 f(C_k)$

For maximization, we consider the Piyavskii=s algorithm given as follows:

Piyavskii's algorithm (Algorithm II)

We define the Piyavskii's algorithm for maximization of programming constraint non-linear follows: input the parameters a and b in f_{ij} and perform the following task:

Step one: Let $e_1 = (a+b)/2$

Step two: Evaluate $f(e_1)$ and

$$F(e_j) = f(e_j^1) + L(e - e_j^1)$$

Step three: Perform n - iteration for $f(e^{(k)})$, k = 1, 2, ... n and determine

$$F_n(e^*) = \min_{k=1,2,...n} f(e^{(k)}) + L|e - e_k|$$

With

$$F_n(e) = f(e^{(k)}) \text{ for } k = 1,2,...,n$$

Define

$$F_n^* = \max_{e\varepsilon[a,b]} F(e) \text{ and } f_n^* = \max_{k=1,2,...n.} f(e_k)$$

Step four: End if $F_n^* - f_n^* \leq \varepsilon$,

ε is the error of approximation.

Step five: Print f_n^* which is the approximate value for f and $e^N = \arg f_n^*$ is the corresponding point,

Else $e^{n+1} = arg \max_{e\varepsilon[a,b]} F_n(e)$

Choose smallest e^{n+1}

Evaluate $f(e^{n+1})$

Repeat step three until ε is attained.

Step six: Stop.

There are other forms of Piyavskill's algorithm we will then adopt algorithm to find solution to the following optimization problem

$$\max_{e_j} f(C_i, e_j),\ e_j \varepsilon [a,b] \subset R+.$$

f is assumed to be Lipchitzian and e_j ε[a, b] for fixed C_i.

3.0 STATEMENT OF PROBLEM

Let us ask the question is it possible to have a most effective and most cost effective drug for managing of HIV/AIDS? The answer will be established later, but it is not easy to answer this

question. We note that, there are several interventions that can be used to find the solution to this question. We will consider cost of procurement of antiretroviral and highly active antiretroviral drugs and their efficacies to answer the question.

There are several options to solving the problem, we consider the chemotherapeutic one; it appears, the attention of the world is focus on how develop most effective drugs or vaccines to combat HIV.

There are several people living with HIV/AIDS who needed life supporting drugs to extend their life, the drugs are expensive hence beyond the reach of poor people in Africa where the HIV/AIDS scourge is most perilous and had reached most calamity stage .Although some generic HIV drugs are in place, but such antiretroviral drugs have many side effects and still beyond the reach of people in the sub-Saharan Africa.

The drug, an antiretroviral pill known as Truvada,was found to interfere with the replication of the most common HIV virus and can reduce the risk of new infection by 62% or more if taken consistently. The consistency required for Truvada to be effective has important implications for real-world use, especially given the drug's annual price tag, which can run as high as $14,000 per year in the United States, says Michael Kolber[19].

Furthermore, the currently recommended treatment for newly diagnosed patients is a single pill (Atripla) taken daily that combines three brand-name antiretrovirals - tenofovir (Viread), emtricitabine (Emtriva) and efavirenz (Sustiva). A generic form of a drug that has a similar mechanism of action to emtricitabine became available in January 2012, and a generic version of efavirenz is expected in the relatively near future. Patients could soon take these two less expensive generic drugs alongside the brand drug tenofovir (see [19-20]).

We intend to come up with a mathematical programming problem which seeks to find the most cost-effective drug (minimization problem) and at the same time most efficient (maximization of efficacy of the drugs). The potency of drugs is measured in terms of their efficacies (see [1] & [10]).

In our paper [12], efficacy of drugs was defined in direction of [10] as

$$k = 1 + \frac{d_x + k_2 - 1}{x_o^1} \qquad (3.1)$$

Where

d_x = natural death rate of HIV cells.
k_2 = the rate of the inhibiting the immune cells
k_o^1 = initial viral load of HIV cells

The non-linear programming problem being

$$\max_{e_j} \min_{C_i} f(c_i, e_j) \text{ subject to } C_i \varepsilon R^+, e_j \varepsilon R^+.$$

Assuming that f is Lipchitzian with respect to e_j.

The problem can be solved in the following way:
Consider

$\min_{C_i} f(C_i,e_j)$ subject to $C_i \varepsilon R^+$ treating$_j$ as constant.

Then
min $f(C_i, e_j) = \min f_1(C_i) = f_2(e_j)$
We find the optimal solution to (2) as C* using algorithm 1.
Solve

max $f_2(e_j)$ treating C_i^* as fixed and find optimal solution as e^* using algorithm II. Therefore eg (1) has optional solution to the max min problem to be
$f(c^*,e^*)$ (3.2)
This is treated as an unconstraint optimization problem. The problem can be also solved as a typical non-linear convex programming problem. If $f(C_i, e_j)$ satisfies some convexity properties as well as some properties imposed on the domain e.g convex or cone. For a domain, which is a cone, we may use the method of monotone iterative technique to find the optimal solution to the max min non-linear programming problem.

4.0 MAIN RESULT

We can construct f_{ij} using a family from the conic section as

$$f_{ij} = a_i C_i^2 + 2 b_{ij} C_i e_j + d_i e_j^2 + h_i C_i + l_j e_j + k_{ij} \quad (4.1)$$

Where

a_i, b_{ij}, d_i, h_i, l_j and k_{ij} can be determined whenever the C_i and e_j are known using least square method. To guarantee that optional solution for $i = n^*$ and $j = N^*$ is attained with property (2.2) which satisfied the max min criterion, a simple criterion that guarantee stability can be inferred. That is, if

$b_{ij} < 0, a_i < 0, \; b_{ij}^2 > d_i a_i \; for \; i, j = 1,2,...N$ or

$b_{ij} > 0, a_i > 0, \; b_{ij}^2 > d_i a_i \; for \; i, j = 1,2,...N$

In order to illustrate the usefulness of Operation Research in HIV/AIDS Research we will consider a non - linear programming problem for solving a given HIV control problem, especially for Africa countries with large number of HIV/AIDS victims, we develop a given utility function and seek, using our knowledge of optimization, to solve given HIV/AIDS problem in the society.

UTILITY FUNCTION

Consider a two dimensional non-linear function, utility function (UT) defined by variables C_i, the cost of drugs, e_j the efficacy of the drugs.
We define the UT by

$$f_{ij} = f(C_i,e_j), i = 1,2,...,N$$

$j = 1,2,...,N$

Algorithms to be used are minimization and maximization algorithms. Consider minimization of the unconstrained scalar cost function.

$F(C_i)$ subject to $C_i \in R^+ = [0, +\infty)$

The algorithms to be used for the different methods are

$x_{k+1} = x_k + \eta_n dk,\ x(0) = x_0\ (k = 0,1,2...N), \eta_k > 0$ Determines the length of steps to be taken in the direction of $d_k \approx \Delta x_k$. to compute η_k in the direction of d_k we consider four basic algorithms using the following standard methods **(Algorithm I):**

Method	**Value for η_k d_k**
Gradient method (GM)	$-\Delta_k f(C_k)$
Newton=s method (NM)	$[\Delta^2 f(C_k)]^- \Delta f(C_k),\ \eta_k > o,\ \eta_k < \eta_{max}$
Conjugate Gradient method (CGM)	$(\beta_k d_{k-1} - \Delta f(C_k))(\arg\min f(C_k - \eta d_k)$
Quasi-Newton's (QNM)	$H_k \Delta f(C_k)$, $H_k = \Delta^2 f(C_k)$

For maximization, we consider the Piyavskii=s algorithm given as follows:

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Quasi-Newton=s (QNM)	$H_k \Delta f(C_k)$, $H_k = \Delta^2 f(C_k)$

For maximization, we consider the Piyavskii=s algorithm given as follows:

Piyavskii's algorithm (Algorithm II)

That is, derived from eigenvalues of the characteristic equation obtain for f_{ij}.

To obtain the main result, we define

The utility function by

$$f(C_i) = a_i C_i^2 + C_{ij} C_i + Z_i C_i + g_2$$

Where

$$g_2 = g(e_j) = d_j e_j^2 + l_j e_j + k_{ij}$$

Applying the algorithm 1 we obtain various iterative schemes, conditions for their convergence, stopping time and the number of iteration needed as follows:

Table 1: Some minimization iterative schemes

Method	Iterative formulae	Condition for convergence (|G| ?1)	Stopping time ??	Number of iteration needed
GM	$C_i^{(k+1)} = GC_i^{(k)} + K$ $G = 1 - 2\sum_i \mu_{ji} a_i$ $K = -2\sum_i \mu_{ji}(b_{ij} g_i + Z_i)$	$0 < \sum \mu_{ji} a_i < 1$	$T \le \in$	$-\frac{(\log(\in))}{R_\infty(G)}$

SDM	$C_i^{(k+1)} = GC_i^{(k)} + K$ $G = 1 - 2\sum_i \mu_{ji} a_i$ $K = -2\sum_i \mu_{ji}(b_{ij} g_i + \sum_i \mu_i)$	$0 < \sum_i a_i < \frac{1}{\mu_0}$	$T \leq \in$	$-\frac{(\log(\in))}{R_\infty(G)}$
QNM	$C_i^{(k+1)} = GC_i^{(k)} + K$ $G = 1 - \sum_i \mu_{ji} H_i a_i$ $K = \sum_i (b_{ij} g_i + Z_i)$ $H_i = \sum_j [a_{ij}]$	$0 < \sum\sum \mu_{ij} a_i u_i = \beta < 2$	$T \leq \in$	$-\frac{(\log(\in))}{R_\infty(G')}$
CGM	$C_i^{(k+1)} = GC_i^{(k)} + K$ $G = 1$ $K = -(B_k d_{k-1} - \frac{\partial f}{\partial C_i} C_i^{(k+1)})$ $\times (\arg\min \frac{\partial f(C_i + \eta_k d_k)}{\partial C_i})$ $B_k = \frac{4}{3}\alpha_j C^{2(k)} + b_{ij} g_i^2$	for all n	$T \leq \in$	$-\frac{(\log(\in))}{R_\infty(G')}$

Experiment

Considering cost of some antiretroviral drugs can run a simple experiment and their tested proven efficiencies as displayed in the table below:

Table 2: The utility matrix

	C_1	C_2	C_3	C_4	C_5	C_6	C_I
e_1	(C_1, e_1)	(C_2, e_1)	(C_3, e_1)	...	...	...	(C_i, e_1)
e_2	(C_2, e)	(C_2, e_2)	(C_3, e_2)	...	...	...	(C_i, e_2)
e_3	(C_1, e_3)	(C_2, e_3)	(C_3, e_3)	...	...	...	. . .

e_4	(C_1, e_4)	(C_2, e_4)	(C_3, e_4)	...	...	...	(C_i, e_3)
e_5	(C_1, e_5)	(C_2, e_5)	(C_3, e_5)	...	...	...	
e_6	(C_1, e_6)	(C_2, e_6)	(C_3, e_6)	...	...	...	
.							
.							
.							
e_j	(C_1, e_j)		(C_3, e_j)	...	...	...	(C_i, e_j)

We use the least square method to find the coefficients of f_{ij} and then find $f(C_i,e_j)$ and use the algorithms I and II respectively to find optimal value C*, e* for $f(C_i,e_j)$ then compute f(C*,e*) which is the most effective utility function and the most efficient and cost effective drugs should be cluster around C* and e*. The closer the drug to e* the better.

Antiretroviral drugs (ADs) are classified according to enzymes activities on HIV developmental processes. The ADs contain inhibitors to hamper so the production of HIV cells called provirus. Four types of inhibitors are generally cognized for ADs there are Fusion inhibitors, (FI) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIS), Nucleoside Reverse Transcriptase Inhibitors (NRTIS) and protease Inhibitors (PLS).

We consider some ADs that are duly approved by the US Food and Drug Administration (FDA) for treating or preventing AIDS - related illness or opportunistic infection. We listed ADs according to their generic name although there are different brand names:

PLS	NNRTIS
Indinavir	Efavirentz
Fosamprenavir	Nevirapine
Lopinavir-Ritonavir	Delavirdine
Ritonavir	NRTIS
Fusion Inhibitor (FI)	Abacavir
Enfuvirtide	Lamivudine
	Tenofavir
	Zidovudine
	(Retrobir, A Z T, Z D V)

The twelve drugs sample can be used by assigning C_i each drug for every i=1, 2, 3,... the run our experiment, unfortunately, we cannot lay our hand on the cost of the drugs and the clinical trial of the drugs to determine efficacy of the drugs.

The use of antiretroviral drugs has gained ground in Nigeria, it is hoped that results on clinical application of the Ads and efficacies would be available in future thereby give the opportunity to fully

test the algorithms I and II.The beauty of the present paper is that it provides the public health officers with a tool on how to determine the benchmark values for drug and the cost for given selected drugs. The benchmark should cluster around the optimal values e* and C*.The benchmark or the control limits can be found using quality control techniques.

CONCLUSION

The role the Mathematical modeling experts can play in future is so enormous further areas of application to HIV/AIDS treatment and care need to be explored.

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