Review article

Mathematical Analysis of Side effects of HIV/AIDS Medication

Tirmizi SRH[1], Khan N[2]

Abstract:
Acquired Immune deficiency syndrome (AIDS) is caused by Human immunodeficiency virus (HIV); More than 40 Million people live with HIV world wide. Various antiretroviral classes of drugs are used to treat HIV infection and the prolonged treatment has to be taken for the rest of life. It is very difficult to continue prolonged treatment because of problem of adherence and side effects. The basic purpose of antiretroviral treatment is to maintain the quality of life of a patient. However, these side effects vary from drug to drug and patient to patient. The objective of this research is to be modeled some major drug induced side effects by using fuzzy matrix theory which is one of the best tools to analyze unsupervised data involving imprecision. This study is of interest for HIV Specialist and physician who care for HIV/AIDS patients with an aim to concentrate more on safety profile of HIV/AIDS drugs.

Key Words: Mathematical Analysis, HIV/AIDS, Medication, Fuzzy matrix theory.

DOI: http://dx.doi.org/10.3329/bjms.v13i2.13884
Bangladesh Journal of Medical Science Vol.13(2) 2014 p.119-123

Introduction:

HIV/AIDS is one of the greatest threats to the mankind of the world. The immune system of our body protects us from various kinds of infections and diseases. HIV virus suppresses the immune system and any small infection can cause severe health problem even death. From 1981, more than 25 million people were killed with this disease. Five millions people are becoming infected with this virus every year and presently 40 million people have HIV that causes Aids. HIV/Aids acquired through unprotected sexual contact, blood transfusion, syringes and during child birth and breast-feeding through mother to child.

Antiretroviral toxicity is becoming an important subject in the management of HIV-infected persons. HIV infection is a chronic disease, and the drugs are being used in the patients for longer period of time. A study indicates that although the mortality and morbidity rates have been minimized with advanced Combination antiretroviral drugs treatment but major adverse effects is being increased and up to 25% of patients stop their initial HAART (Highly active antiretroviral therapy) regimen because of lethal[1]. The drugs, which are available in the world market, can be divided into five groups and their table is given below with mode of action.

Table I: (Drugs available in the market with mode of action)

ARV drugs class	Abbreviations	First approved HIV treatment (year)	Mode of action
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	NRTIs, nucleoside analogues, nukes	1987	NRTIs inhibit reverse transcriptase enzyme which is helpful in virus replication.
Non-Nucleoside Reverse Transcriptase Inhibitors	NNRTIs, non-nucleosides, non-nukes	1997	NNRTIs also inhibit the reverse transcriptase prot ein which prevents HIV from replicating within cells.
Protease Inhibitors	PIs	1995	PIs is protease inhibitor
Fusion or Entry Inhibitors		2003	Fusion or entry inhibitors stop HIV from entering and binding with human immune cells.
Integrase inhibitors		2007	Integrase inhibitors inhibits enzyme, which is the requirement of HIV to pop in its genetic material into human cells.

The following data is taken from AIDS info 'A service of the U.S. Department of Health and Human Services', which is helpful in our study. These are some most frequent reported serious side effects with HIV medication.

1. Syed Rizwan ul Haq Tirmizi, Assistant Professor, Applied Sciences Department, National University of Science & Technology, Pakistan.
2. Nasiruddin Khan, Department of Mathematics, University of Karachi.

Corresponds to: Syed Rizwan ul Haq Tirmizi, Assistant Professor, Applied Sciences Department, Pakistan Navy Engineering College, National University of Science & Technology, Pakistan.
Email: tirmizi50@yahoo.com

Table II: (Drugs with their brand names and possible serious side effects)

Drug Class	Brand names available in market	Possible Serious Side Effects
Nucleoside Reverse Transcriptase Inhibitors. (NRTIs)	• Abacavir sulfate • tavudine • Tenofovir disoproxil fumarate • Zidovudine	The most frequently reported serious side effects include peripheral paresthesia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, skin rash, and mood disorders. Other less serious side effects include headache,oral paresthesia,GI disturbances, fatigue, and taste disorders
Non-Nucleoside Reverse Transcriptase Inhibitors. (NNRTIs)	• Delavirdine • Efavirenz • Etravirine • Nevirapine	Hepatic failure , acute kidney failure. Pancreatitis, hemolytic anemia, rhabdomyolysis, Substantial increases in liver enzymes and hepatic failure, Skin rashes, suicidal ideation, Severe depression,Granulocytopenia (occurring more frequently in children), Stevens -Johnson syndrome and psychiatric symptoms.
Protease Inhibitors (PIs)	• Amprenavi • Darunavir • Indinavir sulfate • Ritonavir • Saquinavir • Tipranavir	PR Interval Prolongation, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, skinrash, nephrolithiasis/urolithia sis, peripheral paresthesia, acute hemolytic anemia and mood disorders
Fusion or Entry Inhibitors	• Enfuvirtide • Maraviroc	Hepatoxicity,hypocellularity, pancreatitis, Bone marrow, skin papilloma, anxiety, decreased appetite, asthenia, herpes simplex, co ugh expression, pruritis, insomnia, myalgia, and weight loss. Heart rate elevations and blood pressure, Lymphoid atrophy local injection site reactions, sinusitis, conjunctivitis, peripheral neuropathy,.
Integrase inhibitors	• Raltegravir	Psychiatric Dis orders, depression (mainly in patients with a previous history of psychiatric problem) with suicidal ideation.Muscle spasm, Skin and Subcutaneous Tissue Disorders, rash, Stevens -Johnson syndrome,

Description and Methodology:

In this research paper we are going to implement fuzzy matrix theory which is one of the best tool to analyzed raw data with imprecision. These mathematical matrices can be applied to social and natural situations to predict likely outcomes. It was first introduced by W. B.Vasantha and V. Indira to study the passenger transportation problem. They used fuzzy optimization techniques to solve this problem. In this present study we used this fuzzy model for the analysis of adverse effects of HIV/AIDS medication. We have conducted a study on 195 reported cases of HIV/AIDS from Agha Khan Medical University and Hospital and Baqai Medical University and Hospital Karachi (Pakistan). These are very selective patients who are already under regular treatment with antiretroviral medications and facing severe adverse effects of HIV/AIDS medication. As the problem faced by them we feel it can be modeled using fuzzy matrix theory to identify the intensity of adverse effects in different intervals of time of treatment. We transform the collected data into matrix form by taking side effects along rows and duration of treatment along the column. The average time dependent matrix (ATD) is obtained by dividing each entry of the matrix by the time period and taking the average μ_j and standard deviation of each column of the ATD matrix. We select a parameter α from the interval [0,1] and form the refined Time dependent matrix by using the formula

if $a_{ij} \leq (u_j - \alpha * \sigma_j \sigma_j)$ then $e_{ij} = -1$

else if $a_{ij} \in (u_j - \alpha * \sigma_j \sigma_j, u_j + \alpha * \sigma_j \sigma_j)$ then $e_{ij} = 0$

else if $a_{ij} > (u_j + \alpha * \sigma_j \sigma_j)$ then $e_{ij} = 1$.

Where aij are the entries of the ATD matrix. In this way, we form the Refined Time Dependent (RTD) fuzzy matrix. The entries of this matrix are –1, 0, or 1. Entries and the sum of rows gives the matrix of intensity of adverse effects. We also combine these matrices for different values of α select from the interval [0,1], in this way we get the Combined Effective Time Dependent Data (CETD) matrix and the row sum is obtained for CETD matrix. Conclusions are derived based on the row sums. Its graphical presentation is very simple and could be understood by a layman.

ESTIMATION OF SIDE EFFECTS OF HIV/AIDS MEDICATION USING 4X8 FUZZY MATRIX

On the basis of history of patients we have taken the following eight major side effects (A_1,A_2,A_3,A_4,A_5,A_6,A_7,A_8) to study in divided four intervals of time which is given below.

A_1 - Liver disease
A_2 - Heart disease
A_3 - Kidney disease
A_4 - Septicemia
A_5 - Osteoporosis
A_6 - hyperglycemia
A_7 - Severe depression
A_8 - Pancreatitis

Table III: Initial data based on history of patients (n=195)

Treatment time duration (years)	A_1 Liver diseases	A_2 Heart diseases	A_3 Kidney diseases	A_4 Septi-cemia	A_5 Osteo-porosis	A_6 Hyper-glycemia	A_7 Severe depression	A_8 Pancreatitis
0 - 2.9	13	17	04	19	04	09	22	17
3 - 6.9	69	44	52	78	17	17	35	35
7 - 9.9	48	61	39	45	30	30	39	61
10 - 15	51	70	86	51	41	10	30	72

Average Time Dependent Data (ATD) Matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
4.48	5.86	1.37	6.55	1.37	3.10	7.59	5.86
17.69	11.28	13.33	20	4.36	4.36	8.97	8.97
16.55	21.03	13.45	15.52	10.34	10.34	13.45	21.03
10.2	14	17.2	10.2	8.2	2	6	14.4
4.48	5.86	1.37	6.55	1.37	3.10	7.59	5.86
17.69	11.28	13.33	20	4.36	4.36	8.97	8.97
16.55	21.03	13.45	15.52	10.34	10.34	13.45	21.03
10.2	14	17.2	10.2	8.2	2	6	14.4

Table IV: The Average and the Standard Deviation of the above ATD Matrix

	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
Average	12.23	13.04	11.33	13.07	6.07	4.95	9	12.56
S.D	6.13	6.31	6.88	5.90	3.99	3.72	3.20	6.66

The RTD matrix for $\alpha = 0.1$ the row sum matrix

The RTD matrix for α = 0.1 the row sum matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	−1	−1
1	−1	1	1	−1	−1	0	−1
1	1	1	1	1	1	1	1
−1	1	1	−1	1	−1	−1	1

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	−1	−1
1	−1	1	1	−1	−1	0	−1
1	1	1	1	1	1	1	1
−1	1	1	−1	1	−1	−1	1

−8	−8
−1	−1
8	8
0	0

The RTD matrix for α = 0.25 the row sum matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	−1	−1
1	−1	1	1	0	0	0	−1
1	1	1	1	1	1	1	1
−1	0	1	−1	1	−1	−1	1

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	−1	−1
1	−1	1	1	0	0	0	−1
1	1	1	1	1	1	1	1
−1	0	1	−1	1	−1	−1	1

−8	−8
1	1
8	8
−1	−1

The RTD matrix for α=0.45 the row sum matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	0	−1
1	0	0	1	0	0	0	−1
1	1	0	0	1	1	1	1
0	0	1	−1	1	−1	−1	0

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	−1	0	−1
1	0	0	1	0	0	0	−1
1	1	0	0	1	1	1	1
0	0	1	−1	1	−1	−1	0

−7	−7
1	1
6	6
−1	−1

The RTD matrix for α=0.75 the row sum matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	0	0	−1
1	0	0	1	0	0	0	0
0	1	0	0	1	1	1	1
0	0	1	0	0	−1	−1	0

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
−1	−1	−1	−1	−1	0	0	−1
1	0	0	1	0	0	0	0
0	1	0	0	1	1	1	1
0	0	1	0	0	−1	−1	0

−6	−6
2	2
5	5
−1	−1

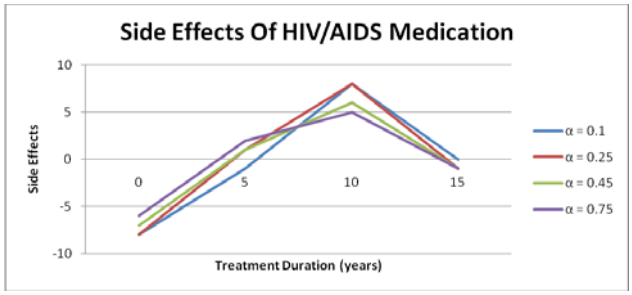

Fig 1: The graph depicting the side effects of HIV/ AIDS medication with the passage of time for different parametric values.

(CETD) matrix

A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8

The Combined Effective Time Dependent Data the row sum matrix

Discussion:

Side effects of antiretroviral medicine have been shown to be a major cause for non-adherence to medications. Understanding of the use and side effects of antiretroviral medicine are therefore essential in managing HIV-infected patient.

Hepatotoxicity are associated with antiretroviral agents PIs in a potential cohort study it was observed that patients who were treated with ritonavir (RTV) and also the patients who were receiving saquinavir, nelfinavir (NFV) or indinavir (IDV) were faced severe hepatotoxicity[2]. Severe hepatotoxicity was also observed in patient using Ritonavir. Hepatotoxicity incidence is observed in other treatment groups, i.e., nucleoside analogs, nelfinavir, saquinavir,and indinavir as well[3]. In another study, highly active antiretroviral therapy (HAART) containing protease inhibitors (PIs) and ritonavir with saquinavir, drug-induced hepatotoxicity was observed with administration of its full dose)[4].

HIV-infected patients also show risk factors for cardiovascular problems. Most recently, studies showed that NRTI, NNRTI and PI drug classes (alone and in combination) are increasing the risk of heart attack in HIV patients[8]. The Food and Drug Administration (FDA) has approved the DAD study (Data collection on Adverse events of anti-HIV Drugs), which indicates that those HIV patient treating with abacavir and didanosine have a maximum chance of heart attack than patients on another medications[5].

Drug-induced renal failure is a common incident in patients with HIV. The antiviral like acyclic nucleoside phosphonates cidofovir and adefovir causes worse nephrotoxicity[6]. A study showed that acute renal failure developed in a patient with HIV using tenofovir[25]. A study showed that Urological complications were associated in majority of patients with the indinavir treatment because of elevated indinavir plasma concentration[1].

Some special metabolic complications like osteopenia and osteoporosis are associated with protease[27]. In the opinion of some researchers lactic academia and proposed mitochondrial toxicity are associated with nucleoside analog (NRTI) which become the main cause of withdrawal from treatment. The PI therapy can cause cumulative incidence of hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy[7]. Antiretroviral medications may cause pathogenesis of hyperglycemia in HIV-infected patients[8,9,10]. In vitro evidence, it is mentioned that ritonavir can caused both insulin resistance[5] and impaired -cell function[11]. In some studies, it is also reported that administration of ritonavir-containing regimens can cause glucose homeostasis[8,9,10-16].

Acute pancreatitis is a life-threatening problem[3]. The annual incidence of acute pancreatitis in the US HIV population is considerably higher than in the general non-HIV–infected population[5]. Some studies show that the use of hydroxyurea with didanosine should probably be discouraged because the risk of pancreatitis is increased[17].

Although, with all complications, we can not ignore the importance of medication. Different numerous studies have reported that there is always a need of treatment with vision of risk-benefit. The net median survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype[18] and the median survival rate after diagnosis of AIDS in resource-limited settings where treatment is not available ranges between 6 to 19 months, depending on the study[19]. But HAART therapy reduced the death rate by 80%, and raised the life expectancy for a newly diagnosed HIV-infected person to about 20 years[20].

Conclusion and Suggestion:

We have observed from the above graphs that adverse effects start from the first day of the treatment and getting peak level after 5-10 years during the treatment. Then some supporting medication is needed to maximize the adherence with the drug. As we know efficacy and tolerability, these are the factors which make a drug ‘the drug of choice. The efficacy of combination ARV regimen is increased but adverse effects of these therapies may cause worse effects on the body organs, we can say its mix blessing because of prolonged treatment and less tolerability, it is very difficult for the HIV positive person to continue the treatment that results in treatment failure. There is a need to continue the efforts in the improvement of medication and better understanding the side effects of ARV regimen for HIV Specialist and physician who care for HIV/AIDS patients.

References:

1. Valentina Montessori, Natasha Press, Marianne Harris, et al. Adverse effects of antiretroviral therapy for HIV infection, *CMAJ* 2004;**170**(2):229-38

2. Sulkowski MS, Thomas DL, Chaisson RE, et al.. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000; **283** (1):74-80. http://dx.doi.org/10.1001/jama.283.1.74

3. Mark S. Sulkowski, MD; David L. Thomas, MD, MPH; Richard E. Chaisson, et al., Hepatotoxicity Associated With Antiretroviral Therapy in Adults Infected With Human Immunodeficiency Virus and the Role of Hepatitis C or B Virus Infection, *JAMA.* 2000;**283**(19):2526-2527

4. Mark S. Sulkowski, Semin Liver Hepatotoxicity Associated with Antiretroviral Therapy Containing HIV-1 Protease Inhibitors, *Dis* 2003; **23**(2): 183-194

5. Mark Cichocki, R.N., HIV and Coronary Artery Disease-Why Does HIV Increase Your Risk of Heart Attack? By About.com Guide, Updated January 25, 2009.

6. Steven MD; Perazella, Mark A. MD, Rapid Communication: Acute Renal Failure Associated with Tenofovir: Evidence of Drug-Induced Nephrotoxicity, *American Journal of the Medical Sciences* 2002;**324** (6):342-344.

7. Calmy A, Clement E, Teck R, et al. Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up. *AIDS* 2004;18:2353-2360.

8. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* 2001;**32** :130-139. http://dx.doi.org/10.1086/317541

9. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;**32**: 298-302. http://dx.doi.org/10.1097/00126334-200303010-00009

10. Dufer M, Neye Y, Krippeit-Drews P, et al. Direct interference of HIV protease inhibitors with pancreatic beta-cell function. *Naunyn Schmiedebergs Arch Pharmacol* 2004;**369**: 583-590. http://dx.doi.org/10.1007/s00210-004-0933-6

11. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem.* 2000;**275**: 20251-20254. http://dx.doi.org/10.1074/jbc.C000228200

12. Ilde JT, Lee CA, Collins P, et al. Increased bleeding associated with protease inhibitor therapy in HIV-positive patients with bleeding disorders. *Br J Haematol* 1999; **107**:556-9. http://dx.doi.org/10.1046/j.1365-2141.1999.01748.x

13. Indira, V., Ph.D. Thesis, Guide: Vasantha Kandasamy. W.B., 2000 Department of Mathematics, Indian Institute of Technology, Chennai-36.

14. Klir, G. J., and Yuan, B., 1995, "Fuzzy sets and Fuzzy logic", Prentice Hall, New Jersey.

15. Kosko, B., 2001, "Neural Networks and Fuzzy Systems", Prentice Hall, New Jersey.

16. Lee GA, Seneviratne T, Noor MA, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. *AIDS*. 2004;**18**: 641-649. http://dx.doi.org/10.1097/00002030-200403050-00008

17. Ronald B. Reisler, MD, MPH,* Robert L. Murphy, MD,Incidence of Pancreatitis in HIV-1–Infected Individuals Enrolled in 20 Adult AIDS Clinical Trials Group Studies,*J Acquired Immune Deficiency Syndrome* 2005;**39**(2):159–166.

18. UNAIDS, WHO (December 2007). "2007 AIDS epidemic update" (PDF). Retrieved 2008–03–12.

19. Zwahlen M, Egger M (2006) (PDF). Progression and mortality of untreated HIV-positive individuals living in resource-limited settings: update of literature review and evidence synthesis. UNAIDS Obligation HQ/05/422204. Retrieved 2008-03-19.

20. Knoll B, Lassmann B, Temesgen Z (2007). "Current status of HIV infection: a review for non-HIV-treating physicians". *Int J Dermatol* **46** (12): 1219–28. http://dx.doi.org/10.1111/j.1365-4632.2007.03520.x