



ANTI RETROVIRAL LIFE-SAVING THERAPY; A CURVE FITTING APPROACH IN PAKISTAN

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ABSTRACT... Objectives: Effective implementation of mathematical and statistical models maximizes the likelihood of understanding the trajectory, level and pattern of incurable diseases and their therapies, so that precise demand strategies for costly lifesaving therapies for future, resource allocation and timely intervention could be ensured, a significant concern for less developed countries like Pakistan. **Methods:** The record of monthly number of patients on lifesaving anti-Retroviral Therapy for more than 18 HIV treatment centers in Pakistan was acquired for the period January 2011 to July 2013. A set of eleven curve fitting models namely linear, quadratic, cubic, logarithmic, inverse, exponential growth model, logistics-curve and compound models was carried out for prediction. **Results:** After the execution of various curve fitting models by taking the ANOVA approach along with coefficient of determination and the forecast accuracy measures namely, mean percentage error (MAPE), mean absolute error (MAE) and mean square error (MSE) in the selection of final efficient model. Cubic model was selected for forecasting the monthly anti-retroviral therapy cases for all categories i.e. overall, male female and children. On the basis of final selected model 3% increment is expected number of patients on anti-retroviral therapy annually in HIV treatment center in all Pakistan. Male patients are expected to increase 14% who will get lifesaving anti-retroviral therapies. While the annually expected reduction of 17% and 42% in female and children cases taking anti-retroviral therapy is expected in future respectively. **Conclusions:** The overall number of people on anti-retroviral therapy are expected to increase in Pakistan. Males are expected to have greater risk as compared to female and children in Pakistan.

Keyword: Accuracy measures ; Anti-Retroviral Therapy ; coefficient of determination; curve fitting models ; fatal diseases; HIV; lifesaving therapies; Mathematical and statistical models; Pakistan

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INTRODUCTION

Due to the use of anti-retroviral lifesaving therapy, the numbers of people living with HIV was increased in 2012 globally, but 33% reduction noted in HIV new infection in 2012 as compared to 2011.¹ Worldwide an estimated 35.3 million people were living with HIV and 1.6 million people lost their lives in 2012.¹

Pakistan jumped from low prevalence to concentrated epidemic category with an estimated 98,000 people living with HIV in 2009². The most serious transmission modes of HIV in Pakistan are people who inject drug (PWID), transgender, male and female sex workers with prevalence rate is 27.2%, 5.2%, 1.6% and 0.6% respectively². It is obvious that HIV prevalence is

usually higher among the people who inject drugs in Asian countries, and needle sharing continues at high levels worldwide³ and large population of IDUS in the world live in Asia and the ratio of IDU is higher in low and middle income countries⁴. In Pakistan, people who inject drugs are on top^{2,5}. Many researchers have explored the mutual significant transmission risk factors in the major cities of Pakistan for HIV/AIDS transmission these are inject drug user (IDU) sexual contacts blood transfusion⁶⁻⁷. Few researchers have explored the co-infection among the jail inmates. In a cross sectional prevalence survey, prevalence rate was 2.01% and 77.78% of them were co-infection⁸.

What is ART ?

Anti-retroviral therapy is an international

standard of care for HIV affected patients. It is a combination of three or more medications⁹. The drugs do not cure or kill the virus, but the growth of the virus slows down resulting in significant reduction in AIDS-related illness and death¹⁰⁻¹³. The initial start of antiretroviral therapy not only prevents AIDS-related morbidity and mortality, it also has the potential to significantly reduce the risk of sexual HIV-1 transmission and the spread of tuberculosis¹². Various studies suggest that the use of ART may reduce the HIV incidence among people who inject drugs¹⁴. It is an unresolved issue that when the ART should start. According to the World Health Organization (WHO), anti-retroviral therapy can be started when an individual's CD4 (white blood cells) count falls below 500 cells/ μL . The results suggested in a collaborative analysis of eighteen HIV cohorts concluded that 350 cells/ μL should be the minimum threshold for start of antiretroviral therapy¹⁵.

In 2015 there will be 15 million people accessing ART, while in 2012, 9.7 million people in low- and middle-income countries received antiretroviral therapy. On the other hand antiretroviral therapy prevented 6.6 million AIDS-related mortality worldwide, including 5.5 million deaths in low and middle-income countries from 1996 to 2012¹.

While in Pakistan an increasing trend had been observed there were on the average 40 to 45 new people living with HIV taking lifesaving therapy per month in 2011, majority of them are adult males².

HIV/AIDS Epidemic Modelling

Effectively implementation of statistical models maximize the likelihood of adopting optimum planning, preventative measures and intervention at right time towards the HIV/AIDS epidemic. As HIV/AIDS is a fatal disease so it is significant concern to allocate resources, relevant vaccination, antiretroviral therapy and intervention in affected areas. Development and use of HIV epidemic modelling is significant interest. Adequate modelling allows better understanding of the level and trend and predicting evolution Johnson et al. (2012) used a model based analysis in South Africa to measure the effect of changes

in condom usage and antiretroviral treatment coverage of HIV incidence¹⁶. Hontelez et al. (2013) investigated the prospects for elimination of HIV in South Africa through expanded access to antiretroviral therapy using a micro-simulation model¹⁷. Rao (2003) used mathematical modelling of AIDS epidemic in India¹⁸. UNAIDS reference group on estimates, modelling and projections (2002) gives improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact¹⁹. Alkema et al. (2007) used a Bayesian modelling approach to project the HIV prevalence in Uganda²⁰. Modelling has also been applied to highly active antiretroviral therapy²¹.

Different statistical models are used for forecasting the HIV/AIDS data. Curve fitting models give the better results as compared to other models²². Curve estimation models for forecasting the HIV cases in India and Nepal have given more accurate estimates as compared to Back-Calculation method & State Space models²²⁻²³.

METHOD AND MATERIAL

Source of data: A monthly registered data for the people living with HIV and recently taking Anti-Retroviral Therapy at 18 different HIV treatment centers including Pakistan Institute of Medical Sciences (PIMS) Islamabad from January 2011 to mid of 2013 was taken from Pakistan Bureau of Statistics (Statistics House) government of Pakistan, Islamabad, Pakistan for the present study. Let the dependent variable " y " is representing the total number of reported monthly patient on ART. While " t " is a repressor and taking value 1 = January 2011, 2 = February 2011, 3 = March 2011 and so on 30 = June 2013.

Material

In this study the set of 11 different curves estimation regression models have been applied. The equations are given below. A common notation that is used in these models: Let y_t represent the Anti-Retroviral Therapy cases at time " t " while β_0 , β_1 , β_2 and β_3 are the regression's coefficient, " e " represents regression residual.

Linear Trend Model

This model is define by the following equation $y = \beta_0 + \beta_1 t + e$

Quadratic Trend Model

This model is define by the following equation $y = \beta_0 + \beta_1 t + \beta_2 t^2 + e$

Cubic model

This model is define by the following equation $y = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 t^3 + e$

Growth model

This model is define by the following equation $y = e^{(\beta_0 + \beta_1 t)} + e$

Compound model

This model is define by the following equation $y = \beta_0 \beta_1^t + e$

S-curve trend model

This model is define by the following equation $y = \frac{t_0^a}{\beta_0 + \beta_1 (\beta_2^t)}$

Power model

This model is define by the following equation $y = \beta_0 t^{\beta_1} + e$

Inverse model

This model is define by the following equation $y = \beta_0 + \frac{\beta_1}{t} + e$

Exponential Model

This model is define by the following equation $y = \beta_0 e^{\beta_1 t} + e$

Logistic model

This model is define by the following equation $y = \frac{1}{\frac{1}{U} + (\beta_0 \beta_1^t)}$

U= is the upper boundary value. The value must be positive that is the greater than the largest value of the dependent variable.

Logarithmic model

This model is define by the following equation $y = \beta_0 + \beta_1 \ln(t) + e$

Measures of Forecast Accuracy

Mean square error (MSE), Means absolute percent error (MAPE), and Means absolute Deviation (MAD).

Forecast error = Actual value – Forecast value

Mean absolute deviation = $\frac{\sum |e|}{n}$

Where “e= $y_t - f_t$ ” is a forecast error

Mean absolute percentage error = $\frac{\sum \left| \frac{\text{Error}}{\text{Actual}} \right|}{n} \times 100$

Mean square error = $\frac{\sum (y_t - f_t)^2}{n}$ where y is representing the series of total number of reported monthly Anti-Retroviral Therapy cases and $f_t =$ Predicted values

Coefficient of determination $R^2 = 1 - \frac{\sum e^2}{\sum y^2}$

RESULTS AND DISCUSSION

The basic aim of this study is to understand the trend and magnitude of (i) Overall patients on anti-retroviral therapy (ii) Male patients on anti-retroviral therapy (iii) Female patients on antiretroviral therapy and (iv) children on antiretroviral therapy. The ratio of HIV affected patients taking anti-retroviral therapy at various HIV treatment center for male, female and children were 7:2:1 respectively. The descriptive statistics are given in Table 1 indicates that on the average the overall people taking ART per month cases at HIV treatment center is (2202.08, 3383.72).

A curve fitting estimation has been applied. Among the 11 different models the efficient model is a cubic model for all categories with p=0.001. The accuracy measure is least with forcing mean square error (MSE) mean absolute deviation (MAD) and mean absolute percentage error (MAPE) and a higher value of coefficient of determination for categories.²⁴A detail of all the models along with accuracy measure and the R-square are given in Table III. A cubic model indicates the expected percent increment in overall HIV patients taking anti-retroviral therapy which is 3% from July 2013 to June 2014. While the expected increment for male patients taking anti-retroviral therapy is 14% from July 2013 to June 2014. The expected decrement in 12 month in female and children taking anti-retroviral lifesaving therapy are 17% and 42% respectively.

The graphical illustration of actual verses

predicted on the basis of selected cubic model for overall, male female and children are shown in figure 1 through figure 4 by taking time (months) along x-axis while the number of patients on ART along y-axis.

Cubic models equations for various categories are given in equation (1) to equation (4).

For Overall

$$y = 1960.998 - 0.09t + 5.021t^2 - 0.104t^3 \dots\dots\dots (1)$$

For Male

$$y = 1326.09 + 13.44t + 2.25t^2 - 0.04t^3 \dots\dots\dots (2)$$

For Female

$$y = 527.29 - 8.62t + 2.17t^2 - 0.048t^3 \dots\dots\dots (3)$$

For Children

$$y = 105.93 - 4.1t + 0.516t^2 - 0.011t^3 \dots\dots\dots (4)$$

Cases	Min	Max	Mean	Std. Deviation
Overall	1954.0	3711.0	2792.90	590.82
Male	1338.0	2595.0	1931.70	408.42
Female	514.0	955.0	735.27	160.68
Children	91.0	154.0	122.67	21.27

Table-I. Descriptive statistic

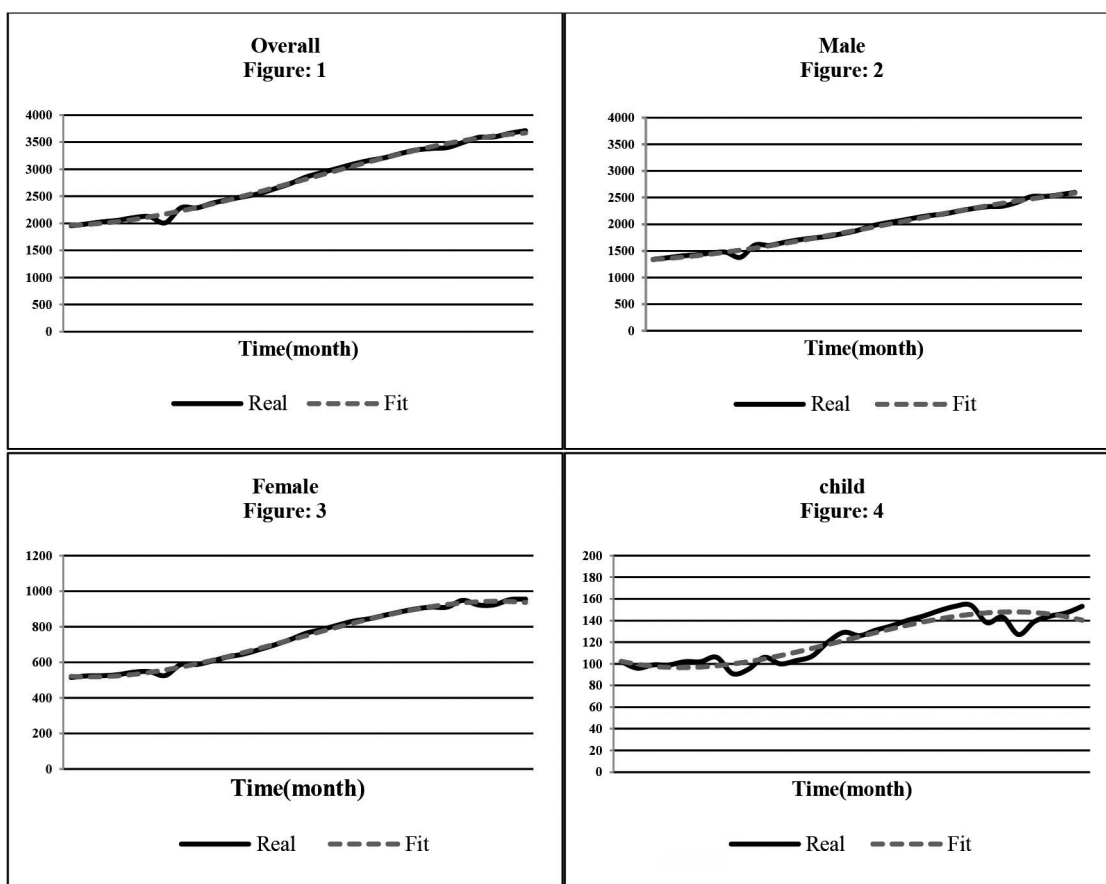
Cases	July2012 to June13 (Observed)	July2013 to June14 (Predicted)	% change
Overall	40930	42207	3
Male	28269	32097	14
female	10842	9042	-17
Child	1731	998	-42

Table-II. Forecast summary for various cases under cubic model along with expected % change

	Linear	Logarithmic	Inverse	Quadratic	*Cubic	Compound	Power	s-curve	Growth	Exponential	Logistic
Overall											
R ²	0.986	0.79	0.35	0.98	0.99	0.98	0.83	0.39	0.98	0.98	0.93
MSE	4571.8	69043.79	217001.8	4412.92	1644.14	6595.35	46039.91	200849.3	6595.35	6595.35	12761.94
MAD	54.23	221.26	416.04	53.7	27.14	61.58	187.58	401.21	61.58	61.58	87.69
MAPE	2.18	8.67	15.85	2.09	1.05	2.15	7.12	14.85	2.15	2.15	3.67
Male											
R ²	0.989	0.797	0.362	0.99	0.993	0.985	0.842	0.41	0.985	0.985	0.989
MSE	1805.01	32742.51	102818.4	1566.65	1080.2	2185.3	21840.22	95017.01	2185.3	2185.3	6349.96
MAD	29.89	149.88	282.38	28.65	20.75	32.8	125.16	271.55	32.8	32.8	68.13
MAPE	1.81	8.44	15.5	1.63	1.17	1.7	6.82	14.47	1.7	1.7	3.97
Female											
R ²	0.971	0.79	0.35	0.972	0.995	0.965	0.824	0.385	0.965	0.965	0.958
MSE	715.12	5239.59	16231.18	706.45	122.5	1095.87	3509.57	15028.65	1095.87	1095.87	1533.1
MAD	23.72	61.44	115.36	23.61	8.5	26.6	52.77	111.83	26.6	26.6	29.27
MAPE	3.36	9.3	16.9	3.4	1.2	3.47	7.72	15.89	3.47	3.47	4.76
Child											
R ²	0.806	0.628	0.245	0.807	0.882	0.807	0.637	0.25	0.807	0.807	0.732
MSE	84.97	162.62	329.94	84.53	51.73	89.21	142.37	319.2	89.21	89.21	95.41
MAD	7.42	10.18	16.11	7.34	5.86	7.73	9.71	15.99	7.73	7.73	7.8
MAPE	6.17	8.88	13.81	6.17	4.81	6.28	8.3	13.48	6.28	6.28	6.86

Table-III. A detail summary of models along with coefficient of determination and accuracy measures

**Lowest values of accuracy measures and higher value of R-Square*



CONCLUSIONS

The overall HIV affected patients taking anti-retroviral therapy are expected to increase in Pakistan. Men are expected to be at greater risk as compared to female and children in Pakistan. These statistical models will serve as a guide to the policy maker to adopt the optimum strategies, and source allocations and timely intervention so that the maximum life could be saved.

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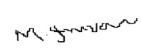
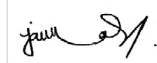
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