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 deceases; HIV; lifesaving therapies; Mathematical and statistical models; Pakistan

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 counties⁴. In Pakistan, people who inject drugs are on top²,⁵. 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 transfusion⁶⁷. 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 medications\textsuperscript{9}. 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 death\textsuperscript{10-13}. 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 tuberculosis\textsuperscript{12}. Various studies suggest that the use of ART may reduce the HIV incidence among people who inject drugs\textsuperscript{14}. 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/\(\mu\)L\textsuperscript{1}. The results suggested in a collaborative analysis of eighteen HIV cohorts concluded that 350 cells/\(\mu\)L should be the minimum threshold for start of antiretroviral therapy\textsuperscript{16}.

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 2012\textsuperscript{1}. 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 males\textsuperscript{2}.

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 significance 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 incidence\textsuperscript{16}. Hontelez et al. (2013) investigated the prospects for elimination of HIV in South Africa through expanded access to antiretroviral therapy using a micro-simulation model\textsuperscript{17}. Rao (2003) used mathematical modelling of AIDS epidemic in India\textsuperscript{18}. UNAIDS reference group on estimates, modelling and projections (2002) gives improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact\textsuperscript{19} Alkema et al. (2007) used a Bayesian modelling approach to project the HIV prevalence in Uganda\textsuperscript{20}. Modelling has also been applied to highly active antiretroviral therapy\textsuperscript{21}.

Different statistical models are used for forecasting the HIV/AIDS data. Curve fitting models give the better results as compared to other models\textsuperscript{22}. 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 models\textsuperscript{22-23}.

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 \(\beta_0\), \(\beta_1\), \(\beta_2\) and \(\beta_3\) are the regression’s coefficient, “\(e\)” represents regression residual.
Linear Trend Model  
This model is defined by the following equation:  
\[ y = \beta_0 + \beta_1 t + e \]

Quadratic Trend Model  
This model is defined by the following equation:  
\[ y = \beta_0 + \beta_1 t + \beta_2 t^2 + e \]

Cubic model  
This model is defined by the following equation:  
\[ y = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 t^3 + e \]

Growth model  
This model is defined by the following equation:  
\[ y = e^{(\beta_0 + \beta_1 t)} + e \]

Compound model  
This model is defined by the following equation:  
\[ y = \beta_0 e^{\beta_1 t} + e \]

S-curve trend model  
This model is defined by the following equation:  
\[ y = \frac{y_{U}}{\beta_0 + \beta_1 t} \]

Power model  
This model is defined by the following equation:  
\[ y = \beta_0 t^{\beta_1} + e \]

Inverse model  
This model is defined by the following equation:  
\[ y = \beta_0 + \frac{1}{(\beta_1 t)} + e \]

Exponential Model  
This model is defined by the following equation:  
\[ y = \beta_0 e^{\beta_1 t} + e \]

Logistic model  
This model is defined by the following equation:  
\[ y = \frac{1}{\left[ \frac{e^{(\beta_0 + \beta_1 t)}}{U} \right]} \]

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 defined 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  
\[ \text{Mean absolute deviation} = \frac{1}{n} \sum |e| \]  
\[ \text{Mean absolute percentage error} = \frac{1}{n} \left( \frac{\sum |e|}{\sum y} \right) \times 100 \]  
\[ \text{Mean square error} = \frac{1}{n} \left( \frac{\sum (y - f_t)^2}{\sum y^2} \right) \]  
Where “e=\(y_t - f_t\)” is a forecast error.

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. A 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 Overalls**
\[ y = 1960.998 - 0.09t + 5.021t^2 - 0.104t^3 \] ……… (1)

**For Male**
\[ y = 1326.09 + 13.44t + 2.25t^2 - 0.04t^3 \] …………… (2)

**For Female**
\[ y = 527.29 - 8.62t + 2.17t^2 - 0.048t^3 \] ……………… (3)

**For Children**
\[ y = 105.93 - 4.1t + 0.516t^2 - 0.011t^3 \] …………….... (4)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1954.0</td>
<td>3711.0</td>
<td>2792.90</td>
<td>590.82</td>
</tr>
<tr>
<td>Male</td>
<td>1338.0</td>
<td>2595.0</td>
<td>1931.70</td>
<td>408.42</td>
</tr>
<tr>
<td>Female</td>
<td>514.0</td>
<td>955.0</td>
<td>735.27</td>
<td>160.68</td>
</tr>
<tr>
<td>Children</td>
<td>91.0</td>
<td>154.0</td>
<td>122.67</td>
<td>21.27</td>
</tr>
</tbody>
</table>

**Table-I. Descriptive statistic**

<table>
<thead>
<tr>
<th>Cases</th>
<th>July2012 to June13 (Observed)</th>
<th>July2013 to June14 (Predicted)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>40930</td>
<td>42207</td>
<td>3</td>
</tr>
<tr>
<td>Male</td>
<td>28269</td>
<td>32097</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>10842</td>
<td>9042</td>
<td>-17</td>
</tr>
<tr>
<td>Child</td>
<td>1731</td>
<td>998</td>
<td>-42</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Linear</th>
<th>Logarithmic</th>
<th>Inverse</th>
<th>Quadratic</th>
<th>*Cubic</th>
<th>Compound</th>
<th>Power</th>
<th>s-curve</th>
<th>Growth</th>
<th>Exponential</th>
<th>Logistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>0.986</td>
<td>0.79</td>
<td>0.35</td>
<td>0.98</td>
<td>0.99</td>
<td>0.98</td>
<td>0.83</td>
<td>0.39</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>MSE</td>
<td>4571.8</td>
<td>69043.79</td>
<td>217001.8</td>
<td>4412.92</td>
<td>1644.14</td>
<td>6595.35</td>
<td>46039.91</td>
<td>200849.3</td>
<td>6595.35</td>
<td>6595.35</td>
</tr>
<tr>
<td>MAD</td>
<td>54.23</td>
<td>221.26</td>
<td>416.04</td>
<td>53.7</td>
<td>27.14</td>
<td>61.58</td>
<td>187.58</td>
<td>401.21</td>
<td>61.58</td>
<td>61.58</td>
</tr>
<tr>
<td>MAPE</td>
<td>2.18</td>
<td>8.67</td>
<td>15.85</td>
<td>2.09</td>
<td>1.05</td>
<td>2.15</td>
<td>7.12</td>
<td>14.85</td>
<td>2.15</td>
<td>2.15</td>
</tr>
</tbody>
</table>

| R²     | 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    |

| R²     | 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    |

| R²     | 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     |

**Table-III. A detail summery 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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**AUTHORSHIP AND CONTRIBUTION DECLARATION**

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