**Introduction**

Hepatitis B and C are common causes of viral hepatitis in Pakistan. Meta analysis from the previous studies showed that the prevalence of hepatitis B was between 3-4% \(^1\) and for hepatitis C it was between 4-6%, \(^2\) giving an overall 10% prevalence of the two viral diseases. \(^3\) A recent survey showed the prevalence of hepatitis B (HBV) and C (HCV) as 2.5% and 5% \(^4\) respectively with an estimated total of 12 million cases being exposed to these viruses. Higher prevalence of hepatitis C has been reported from Punjab \(^5\) and Sindh, \(^6\) while Sindh and Balochistan \(^7,8\) have shown very high prevalence of hepatitis B. \(^9\)

Genotype of hepatitis C vary worldwide and the type and duration of treatment vary according to the genotype. Since genotype 3 is the most prevalent (80%) followed by genotype 2 in Pakistan, \(^3,10\) a treatment protocol of 3 million unit interferon, three times a week subcutaneously is recommended for 6 months along with antiviral ribarvin twice a day (weight <70 kg). For all other genotypes either pegylated or conventional interferon is recommended for 12 months. A stringent selection criteria lead to achieving best treatment response which rarely cross beyond 70% for viral clearance, \(^11\) while 30% do not respond or relapse following cessation of therapy. \(^12\)

Treatment of hepatitis B is more difficult as inclusion criteria and followup is dependent on sophisticated tests which are difficult to interpret by many general practitioners. Only naive cases of hepatitis B (wild type and pre-core/core mutants) with raised alanine amino-transferase (ALT) are likely to respond with nucleoside analogue-lamivudine. \(^13,14\) The drug is to be given orally before breakfast as it is absorbed in acidic medium and treatment is to be continued till seroconversion in the wild type and almost for life in mutants, while the drug has no therapeutic role in carriers and delta infected cases. \(^15\)

The Prime Minister’s Programme for the Prevention and Control of Hepatitis Viral Infections was launched for 5 years from 2005 to 2010 to support treatment of hepatitis B and C for patients who could not afford the treatment due to high cost of medicines and diagnostics along with promoting preventive interventions. Medicines along
with diagnostics were supplied to 61 treatment sites across the country along with training of the doctors and laboratory staff on the subject and development of clear guidelines about who to treat and with what drug and dose, and how to follow them up to see response.

The present study was undertaken to evaluate how well the developed guidelines for treatment were followed and if the targets were achieved post-treatment in terms of money and workforce spent.

**Patients and Methods**
A total of 61 sites were providing diagnostic and treatment facilities to the patients in the four provinces of Pakistan and the federal capital. Out of these 12 sites for HCV and 8 for HBV were selected through computer-generated numbers, giving equal representation to all the regions, using provincial population figures. There were 3 sites each from Sindh and Punjab, 2 each from Balochistan and NWFP and the Federal Capital area. For confidentiality, the name of treatment sites were coded alphabetically. The consent of the programme manger and all selected site managers was taken before the start of the study. The case records of all patients treated at those sites were photocopied and brought to Pakistan Medical Research Centre (PMRC) at the Jinnah Postgraduate Medical Centre (JPMC) in Karachi for data entry and analysis in 2011. For those centers that gave a soft copy of the record, the hard copy was checked before accepting the soft copy.

The inclusion and exclusion criteria and the treatment protocols developed and printed by the programme management were taken from the programme manager for reference while evaluating the inclusion of cases and their management.

For inclusion in the treatment programme, a letter or endorsement form was required to be issued by the local government, stating that that the patient is technically recognised as eligible for treatment support and is economically poor and unable to afford the treatment cost. For hepatitis C, only patients between 18 to 50 years of age were considered eligible, provided they had a reactive anti-HCV on Enzyme-linked immunosorbent assay (ELISA) along with raised ALT levels of over 1.5 times the upper limit of normal on two occasions 6 months apart with Hepatitis B ‘s’ antigen (HBsAg) reactive and HBV-DNA detected were included in the study. Both groups were eligible for treatment i.e wild type (HBeAg reactive) and core or pre-core mutant (HBeAg non-reactive). The treatment was one tablet of lamivudine (100mg) to be taken orally before breakfast and if the targets were achieved post-treatment in terms of money and workforce spent.

Special data entry programme was developed for data entry and analysis. Although it was the site manager's responsibility to hand over the complete data, but still PMRC personnel were trained to understand what data to look for before photocopying it and how to check for the missing data. All efforts were made to retrieve as much data as possible without causing much inconvenience to the record holder. All data was photocopied at the treatment site and once photocopied, it was counter-checked and signed by the on-site manager before being taken by the PMRC person.

All data from these 12 sites was brought to PMRC head office from where it was sent to PMRC research centre at the JPMC, Karachi, where data entry and analysis was performed.
Results
The number of patients treated at the selected sites were 7752 for HCV (Table-1) and 454 for HBV (Table-2). A pre-requisite for treatment support was endorsement from the member of the local government, like the Union counselor or Nazim. This letter was missing from most of the sites and only a national identity card (NIC) photocopy was attached in the file. For hepatitis C, the adherence to inclusion and exclusion criteria and the treatment response was evaluated in all those cases who received the treatment. Out of 7752 patients who received treatment, adherence to protocol was followed in 7572 (97.6%) patients, while the remaining 180 (2.3%) cases had insufficient or missing information to justify inclusion. All patients were treated with 3 million international units (MIU) interferon thrice a week along with ribavirin.

Out of 7572 patients who received treatment, only 3440 (45.4%) cases completed 6-month interferon therapy, while the rest were lost to followup and were excluded from the final analyses. Adequate information at the end of 6 months was available at only 2 out of 12 (16.66%) sites. At 6 months, tests like ALT and PCR were available for 1686 (49%) cases and these were finally used to calculate the ETR.

As seen on normalisation of ALT and non-detected PCR at 6 months, ETR was seen in 1133/1686 (67%) cases, while the remaining 553 (33%) cases showed persistence of virus and thus were labelled as non-responders. For hepatitis B, treatment was given to 454 cases at 8 selected sites. Adherence to inclusion criteria was met in 85 (18.72%) cases only. Using the given criteria, 54 (63.52%) cases were of wild type, and 31 (36.47%) cases core/pre-core mutant group. Followup was poor and only 9 (10.58%) cases completed treatment and 3 (3.52%) cases showed seroconversion i.e. HBeAg clearance and appearance of anti-HBe.

The records showed that drug was supplied to the patients on a monthly basis as this information was entered in the file, but reports for blood CP and ALT, PCR

Table-1: Evaluation for Hepatitis C virus.

<table>
<thead>
<tr>
<th>HCV - sites</th>
<th>Overall</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>7752</td>
<td>987</td>
<td>746</td>
<td>260</td>
<td>900</td>
<td>320</td>
<td>635</td>
<td>360</td>
<td>329</td>
<td>15</td>
<td>223</td>
<td>2050</td>
<td>927</td>
</tr>
<tr>
<td>Nos. Fulfilling inclusion criteria</td>
<td>7572</td>
<td>982</td>
<td>727</td>
<td>244</td>
<td>871</td>
<td>320</td>
<td>538</td>
<td>360</td>
<td>329</td>
<td>6</td>
<td>222</td>
<td>2046</td>
<td>927</td>
</tr>
<tr>
<td>HCV &amp; PCR +ve</td>
<td>(97%)</td>
<td>(99%)</td>
<td>97%</td>
<td>94%</td>
<td>97%</td>
<td>100%</td>
<td>85%</td>
<td>100%</td>
<td>100%</td>
<td>40%</td>
<td>99%</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment: Completed</td>
<td>3440</td>
<td>133</td>
<td>278</td>
<td>216</td>
<td>871</td>
<td>320</td>
<td>14</td>
<td>354</td>
<td>329</td>
<td>5</td>
<td>114</td>
<td>-</td>
<td>806</td>
</tr>
<tr>
<td>End Point - End of 6 months ETR</td>
<td>1686</td>
<td>100</td>
<td>3</td>
<td>50</td>
<td>602</td>
<td>311</td>
<td>14</td>
<td>71</td>
<td>115</td>
<td>-</td>
<td>16</td>
<td>-</td>
<td>404</td>
</tr>
<tr>
<td>PCR Done at 6 months.</td>
<td>553</td>
<td>52</td>
<td>1</td>
<td>3</td>
<td>164</td>
<td>72</td>
<td>14</td>
<td>12</td>
<td>32</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>201</td>
</tr>
<tr>
<td>Non Responder : (PCR positive)</td>
<td>(32.7%)</td>
<td>(67%)</td>
<td>48%</td>
<td>67%</td>
<td>82%</td>
<td>73%</td>
<td>74%</td>
<td>83%</td>
<td>72%</td>
<td>75%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders: (PCR negative)</td>
<td>1133</td>
<td>48</td>
<td>2</td>
<td>47</td>
<td>438</td>
<td>229</td>
<td>-</td>
<td>59</td>
<td>83</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>232</td>
</tr>
</tbody>
</table>

| HCV: Hepatitis C virus. PCR: Polymerase chain reaction. |

Table-2: Evaluation for Hepatitis B virus.

<table>
<thead>
<tr>
<th>HBV - sites</th>
<th>Overall</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>454</td>
<td>35</td>
<td>175</td>
<td>30</td>
<td>12</td>
<td>37</td>
<td>16</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>Fulfilling inclusion criteria</td>
<td>85</td>
<td>22</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>(19%)</td>
<td>(63%)</td>
<td>(7%)</td>
<td>(7%)</td>
<td>(25%)</td>
<td>(19%)</td>
<td>-</td>
<td>(28%)</td>
<td>(23%)</td>
<td></td>
</tr>
<tr>
<td>Group I (Wild type) HBeAg +ve HBV DNA +ve</td>
<td>54</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>-</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Group II (Pre_core mutant) HBeAg -ve, HBV DNA +ve</td>
<td>31</td>
<td>11</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Treatment: Completed (ETR)</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>HBV DNA negative, ALT normal at 1 year</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

and other viral markers were missing during the therapy in most of the cases.

Discussion

The data of 7752 cases of HCV and 454 cases of HBV was retrieved who received treatment. For hepatitis C, the overall response at the end of 6 months was seen in 1133/1686 (67%) with 553 showing no response. Overall, there was non-adherence to the set criteria of inclusion, exclusion, treatment and followup. SVR was not checked as this was not the part of the project.

Studies have shown that despite picking the best cases for treatment of hepatitis C, the response rate is around 60-70%.\textsuperscript{16-20} It is reported that patients who fail to clear the virus with the conventional interferon have only 10-15% chance of viral clearance with the pegylated interferon\textsuperscript{15} which is 3-4 times more expensive. Therefore, every effort should be made to choose the eligible cases, treat them adequately and ensure good compliance. The response rate achieved in the present study clearly points towards a compliance issue and not the quality-of-drug issue.

Despite its modest financial resource allocations to the health sector, the Pakistan government had made a genuine and commendable effort to respond to the treatment needs of chronic HCV and HBV patients, recognising the potential high ambulatory and hospital costs and related economic burden to the national exchequer.\textsuperscript{21} The intervention aimed also to mitigate the catastrophic out-of-pocket expenditures that the underprivileged patients and their families would have faced through the high cost of prescription drugs. The results of the present study show that proper planning, monitoring and evaluation were lacking after the project was implemented. There is a need to hold accountable those who failed to follow the guidelines.

Calculating the cost of treatment is difficult as the drugs and diagnostics were purchased in bulk, therefore their cost was substantially low. Presuming the cost of treatment to be a quarter of the standard market rates, interferon plus ribavirin cost would be Rs1500/month/patient. The cost for 6 months would be Rs9000. When multiplied by the number of patients (7572) who received treatment, it comes to Rs68 million. For HBV, the cost of one tablet daily was Rs25; so for one month the cost would be Rs1050, and for one year it would be Rs12600/patient. When multiplied by the number (454) of cases who were treated, the cost comes to Rs5.7 million. Adding these, the money spent on treatment cost comes to Rs74 million. With a few more millions for the diagnostic tests, the cost would escalate to approximately Rs100 million. The government thus spent about Rs100 million on the treatment of about 8000 cases with an ultimate response in only 1135 cases.

The ability of 2 sites to vigilantly follow the cases was able to give us the numerical figures to play with the data. It also clearly shows the commitment of these two site managers. However, the loss of over 50% recruited patients raises serious concerns and lack of commitment of the managers at the other treatment sites. The reasons of failure, like managerial issues, bad patient selection and poor compliance should have been timely assessed and rectified. Such an action would have induced significant improvements in the programme implementation and would have prevented the unjustified discontinuation of therapy, and enhance the desired good treatment response and followup to verify its sustainability.

Hepatitis B treatment through nucleoside analogues-lamivudine is recommended in a selected patient population with markers showing viral activity.\textsuperscript{22} Response is, therefore, dependent on the right selection of cases, treatment duration and therapy compliance, as a high level of resistance is reported with this drug after one year of therapy.\textsuperscript{23} In the present study, many cases were treated for a year without supporting markers for viral replication, thus defaulting the inclusion criteria and probably also adding to the pool of drug-resistant cases. In future, treatment of hepatitis B should be given to specialised centres to avoid the misuse of drugs that could accelerate the development of more resistant cases.

The timely treatment of chronic HBV and HCV hepatitis patients before their progression to liver cirrhosis and hepatocellular carcinoma would result in long-term cost savings for Pakistan, a country with an infection pool of about 12 million, where public health services system constitute the only source of care available for the poor. The programme for the prevention and control of hepatitis should work more and spend more on preventive interventions that would yield substantive gains to population’s health with nominal to be spent on treatment. The sheer pressure from the communities and policymakers at national, provincial and district level on the highly demanded treatment component has overshadowed the wider preventive and control measures against these viral infections. In the socio-economic context of Pakistan, a nationwide intervention for the control of hepatitis viral infections would require a robust anti-viral therapy component along with proper propagation of knowledge, attitude and practices that are relevant to the prevention of these viral infections. These interventions are essential and necessary to halt the
escalating trend of HBV and HCV transmission in the country, the most effective being the promotion of safe injection practices and universal vaccination against hepatitis B.

Conclusion
To enhance its effectiveness, the HCV and HBV treatment component should be combined with other national poverty reduction, social safety activities along with strict treatment eligibility, identification and approval criteria.

Acknowledgements
We are grateful to the WHO for financial support, and, indeed, to consultants/physicians and their supporting staff at the 12 selected sites for cooperation. Mr Mahmood Ahmed and other PMRC personnel who visited the sites and collected data and those who analysed it also deserve our acknowledgement.

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