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Name of the University, Hospital, Research Institute, Academy or Ministry

The Institute of Liver and Biliary Sciences

Name of the Division, Department, Unit, Section or Area

Hepatology

City New Delhi **Reference Number** IND-125

Title WHO Collaborating Centre on Viral Hepatitis and Liver Diseases

Report Year 12-2017 to 12-2018

1. Annual report on the agreed workplan

Describe progress made on the agreed workplan. For each activity, detail (1) the actions taken, (2) the outputs delivered, as well as (3) any difficulties that may have been encountered. Three responses are expected. [maximum 200 words per activity]. Indicate, if an activity has been completed previously, has not yet started or has been placed on hold.

Activity 1

Title: Cohort Studies

Description: ILBS will undertake hospital based cohort studies of HBV and/or HCV positive individuals to evaluate acceptable (invasive versus non-invasive) and cost-effective modalities for assessment and progression of hepatic fibrosis.

The facility of advanced biochemical testing, Fibroscan and Hepatic Venous Pressure Gradient measurement (HVPG) are available in the institute.

In the ILBS, nearly 40,000 liver disease related new and follow-up patients were seen in the past one year. Nearly 1,100 liver biopsies were done on patients undergoing evaluation and treatment for liver diseases. Hence, these cohort studies could be implemented in the facility itself.

The institute has a well structured Institutional Review Board (IRB), registered with the National Registry at the Drug Controller General's Office. The study protocols would be initiated only after due submission and approval by the IRB. The study protocol will also be submitted to the ERC in line with WHO rules and regulations.

Status: ongoing
Activities undertaken

The research proposal for a hospital based cohort study entitled “Cost effective non invasive diagnostic modalities and predictive model for development and progression of fibrosis among patients with Hepatitis B, Hepatitis C infection or non alcoholic fatty liver disease: A hospital based retrospective followed by prospective cohort study” was approved by the Institute’s Ethical Committee (IEC) on 9th Jan 2016. It was registered at ClinicalTrials.gov with the Identifier number as: NCT02658786 and the data collection was initiated.

A retrospective cohort of 3006 cases, who underwent biopsy during 2010-2015, was built up. This included 1685 HBV, 532 HCV and 789 NAFLD cases. The prospective phase of the study started from January 2016. A total of 640 cases have been enrolled till date. Out of these, 333 are Non-Alcoholic Fatty Liver Disease patients, 245 are cases of HBV and 62 are HCV cases. Total number of biopsies done for Hep B cases in last 4 years is 1050, The total number of biopsies done for Hep C cases in last 4 years is 375. Though we had initially proposed, but now due to the availability of an effective treatment, the need for biopsy has reduced in HCV infected cases and thus it would not be possible to enroll 1,000 cases of HCV.

Preliminary analysis of baseline data for NAFLD subjects had been done and the following results were obtained:

A total of 789 NAFLD (age 44.2 ± 11.8 years, 75.4% male, BMI- 24.4 ± 1.1 Kg/m²) cases were enrolled with 45.9% having diabetes. Mean controlled attenuation parameter (CAP) was 283.2 ± 51.2 dB/m. Distribution of cases as per METAVIR F-0,1, 2, 3, 4 was 141 (18.1%), 245 (31.5%), 164 (21.1%), 135 (17.3%) and 94 (12.1%), respectively.

The diagnostic accuracy for advanced fibrosis as per area under ROC curve was 75.4% (95%CI 71.5–79.4), 64.7% (95%CI 60.3–69.1), 79.6% (95%CI 76.0–83.2), 73.8% (95%CI 69.9–77.6), 80.2% (95%CI 76.6–83.7), and 90.1% (95%CI 87.5–92.7), respectively for AST/ALT ratio, APRI, NAFLD fibrosis score, BARD score, FIB-4 and TE.

Best cut-off for AST/ALT ratio was 0.8 (SN-70.4%, SP-70.3%), for APRI was 0.78 (SN-60.7%, SP-59.3%), for NAFLD fibrosis score was -1.65 (SN-73.8%, SP-73.2%), for BARD score was >1 (SN-80.3%, SP-63.3%), for FIB-4 score was 1.7 (SN-72.5%, SP-72.0%) and for TE was 9.5 (SN-82.5%, SP-81.1%) for diagnosing advanced fibrosis.

Comment:

The research tool for the collection of data is available with the WHO CC ILBS and ILBS shall support similar studies in other countries in SE Asia region as per its mandate as WHO CC.

Activity 2

Title: Training for clinicians in clinical management of viral hepatitis and its complications

Description: i. The team of expert hepatologists, clinical nutritionists and intervention radiologists at the ILBS would develop and/or improvise curricula for the clinical diagnosis and management of viral hepatitis, cirrhosis and liver cancer using current guidelines from Liver Associations, Global Advisory boards, WHO, and recent scientific evidences.

ii. The training program would be of two broad categories

a) Hepatitis Induction Program (HIP) - This will be a dedicated program for different level of health care workers (as mentioned below).

b) Hepatitis UpDate Program (HUP) - This will provide a continuous ongoing e-learning opportunity. The participants of the HIP will be entitled and encouraged to undertake the HUP- continuous self learning program. The scientific and policy related material for the HUP would be context dependent and will be constantly updated based on new data, evidence based analysis, and guidelines.

iii. The training curricula for the HIP will be ready for review within 9 months of designation of the CC. The quality and the usefulness of the contents will be assessed by a 3 tier peer review process before implementation; a) internal committee of experts, b) external reviewers, and , c) interaction and inputs from WHO officials.

iv) The HIP is aimed to deliver well organized and monitored training courses with defined outcomes, which will be termed as certificate courses. These will be available for different levels of health care workers and officials (as detailed below). ILBS being a Deemed-to-be- University for Liver and Biliary Sciences, the course material would be placed before the Academic Council of the University for consideration before certification.

v). WHO will arrange for clinicians and other operational staff from other countries to be sent to ILBS for training.

vi). The interactions with participants from different countries would help learn more about cost-effective screening and early detection strategies for liver diseases, cirrhosis and liver cancer.

Status: ongoing
Activities undertaken

These activities were undertaken at 3 levels

1. Medical Colleges across India
2. Primary care physicians
3. Health care workers (Nurses and paramedics)

- Project Prakash (PRogrammed Approach to Knowledge and Sensitization on Hepatitis) was initiated to train 1000 physicians and 1000 nurses in the country. We received a letter of support from Delhi Government Directorate of Health Services to nominate physicians and nurses from the state. This training includes both HIP and HUP components. HIP (Hepatitis Induction Programme) & HUP (Hepatitis Update Programme) were initiated for the Physicians & Nurses, more than 800 Nurses participants have so far been trained from approximate 63 hospitals, dispensaries and clinics across 5 states of India (Delhi NCR, Haryana, Nagaland, Rajasthan and Uttar Pradesh). More than 200 physicians participants have attended the program from approximately 30 different hospitals, dispensaries and clinics across 3 states of India (Delhi NCR, Haryana and Uttar Pradesh) and there is plan to accelerate these training sessions in the coming year.
- All the training modules for both HIP and HUP activities for physicians, nurses as well as laboratory persons are available with WHO CC and would be used for the capacity building in other states of India as well in the region.
- WHO CC ILBS supported the development of the operational guidelines for Viral hepatitis management in India, which is now being used by the country under the National Viral Hepatitis Control Program. ILBS also provided technical assistance in formulation of Guidelines for management of hepatitis C in India
- WHO CC ILBS provided technical support to the WHO SEARO in reviewing the National Viral Hepatitis operational and management guidelines developed by Nepal.
- The WHOCC at ILBS supported WHO SEARO in developing a report of progress in hepatitis action plans in SEARO by collating the information from all the 11-member states in the SERAO region regarding the progress towards Elimination of Viral Hepatitis in 2018. A model data extraction proforma was created and sent to all member states in SE Asia region and the following information were obtained from all member states: 1) Prevalence of viral hepatitis in general population and specific high-risk groups; 2) Formulation and Implementation of a National Action Plan / National health program for Viral Hepatitis; 3) Status regarding key strategies for elimination of viral hepatitis like a) Birth dose Vaccine for Hep B, b) Universal use of Autodisable / ReUse Prevention Syringes to ensure safe injection practices, c) Safe Blood for elimination of Hep B / C Transmission and d) Scale up testing and treatment for Hepatitis B & C. The finalized report is under review and publication by SEARO.

Activity 3

Title: Viral Hepatitis Diagnostic Laboratory Support Program

Description: 1. ILBS will help develop SOPs and provide support to existing national virology and immunology laboratories in the country/region with the capacity to diagnose, monitor and assess outcome of all types of viral hepatitis infections by providing guidance on quality assurance of viral hepatitis testing; serological, NAT based and molecular testing.

2. The training program would be of two levels

- a) For microbiologists, virologists, immunologists - short duration programs of 7-14 days
- b) For technicians - hands on training, wet-lab exposure, for 4-8 weeks on molecular diagnostics.

The ILBS laboratories are accredited by the National Accreditation Board for Laboratories (NABL) and follow the external quality control procedures.

Status: ongoing

One day "Laboratory Technician Training Program" was initiated in the year 2016.

- Delhi State AIDS Control Society (DSACS) nominated laboratory technicians for the training.
- 5 trainings were organized in 2016, 3 in 2017 and about 160 lab technicians posted at either blood banks or integrated counselling and testing centres (ICTCs) of DSACS in Delhi were trained.
- Dedicated session under "PRAKASH" and ECHO program on Viral Hepatitis Laboratory diagnosis is routinely done and all the primary care physicians, nurses, paramedics are trained on laboratory diagnosis of Viral hepatitis, biosafety and injection safety. Dedicated lectures are taken as well as a part of visit to the functional laboratory they are demonstrated to various types of testing methodologies like Rapid card tests, EIA, PCRs etc.
- Regularly provided training to laboratory physicians and technicians as one day hands on training program. More than 100 doctors and laboratory technicians attended his one day wet lab training program. In this program doctors and technicians were actually made to perform various Hepatitis serological assays.
- Department of Clinical Virology conducted PG assembly on "Clinical Virology made easy" under the aegis of IAMM-DC at Institute of Liver And Biliary Sciences on 16th and 17th Aug 2018. 60 Microbiologists from various medical colleges of North India were trained in this program.
- Under project PRAKASH technician training program is also added and 2 trainings are already done in this year 1 in October and 1 in the month of November.
- WHO CC ILBS also contributed in the formulation of National Viral Hepatitis Testing guidelines and is actively involved in imparting training to microbiologist across the Nation who would be involved in starting the testing of viral hepatitis under the National program.

Comment:

Under decentralizing the diagnostic services along with Delhi Govt and with the support of Foundation for Innovative New Diagnostics (FIND) WHO CC ILBS has initiated a HEAD-start (Hepatitis C Elimination through Access to Diagnostics) project. This will screen 50,000 population of Delhi for HCV and complete treatment till cure will be offered to all who would be found infected with the virus. WHO CC ILBS will capacitate peripheral hospitals of Delhi in diagnosis of HCV and will help them in developing molecular testing facilities at these sites.

WHO CC at ILBS plans to provide similar support to other countries in the region in 2019.

Activity 4

Title: Operational models for delivery of viral hepatitis treatment at lower income levels

Description: ILBS would do operational research to see how viral hepatitis treatment could be expanded to lower levels of healthcare within a healthcare delivery system and help prepare working modules likely to suit different geographical regions.

It could also help in evaluating bio-similars in different countries for their comparative antiviral efficacy so as to improve affordability and reach of antiviral drugs.

The institute has a well structured Institutional Review Board (IRB), registered with the National Registry at the Drug Controller General's Office. The study protocols would be initiated only after due submission and approval by the IRB. The study protocol will also be submitted to the ERC in line with WHO rules and regulations.

Status: ongoing

ILBS WHO CC geared up the momentum in the country towards development of National Viral Hepatitis Control Program in India

- Four consultative meets were organised by ILBS WHO CC along with WHO and Govt of India to advocate the initiation of this process.
- 1st GOI-WHO-ILBS National Technical Consultation on viral hepatitis was held at ILBS on 28th July 2014, with the theme of "Towards comprehensive National Hepatitis Prevention and Control Program, India"
- 2nd GOI-WHO-ILBS National Technical Consultation on viral hepatitis was held at ILBS on 28th July 2015, theme of this meeting was "Prevent hepatitis. Act now."
- 3rd GOI-WHO-ILBS National Technical Consultation on viral hepatitis was held at ILBS on 29th July 2016,

theme of this meeting was “Towards a National Action Plan for Viral Hepatitis (NAP-VH)”

- 4th GOI-WHO-ILBS National Technical Consultation on viral hepatitis was held at ILBS on 28th July 2017, theme of this meeting was Framework of National Program on Viral Hepatitis (NAP-VH) in India
- After 4 years of strong advocacy by WHO CC ILBS together with other representatives, finally on 28th July 2018, Govt of India launched in the country “National program for control of Viral Hepatitis”.
- ILBS WHO CC has contributed immensely in the draft of the National Policy, national guidelines for the management and treatment and National guidelines for the laboratory diagnosis of Viral Hepatitis. ILBS WHOCC is actively involved in the trainings that are being provided to various Hepatitis centres both treatment as well as testing centres that are being identified by Gol for the implementation of this National Program.
- Together with Gol, ILBS WHO CC will ensure smooth rolling out of this National Program for the country.
- Under the Surveillance plan, we have initiated hospital-based registries for Cirrhosis and Hepatocellular carcinoma patients in 13 centers of excellence in Hepatology from the country. Out of 13, 6 centers have already taken ethical clearance and started data collection. Others are in the process of seeking ethical clearance. The status of subjects enrolled till date is as follows:

S No Name of the centre of excellence No of subjects enrolled

1	ILBS 2017-270 2018-231	
2	Bombay Hospital	165
3	CMC Vellore	6
4	PGI Chandigarh	39
5	DMCH Ludhiana	27
6	LTMMC	27

Key findings of sequelae surveillance:

- 81% of the subjects were men
 - 52.8% belonged to Child’s B and another 46.3% to Child’s C
 - Attributable fraction of HBV for Cirrhosis: 14.8%
 - Attributable fraction of HBV for HCC: 15.9%
 - Attributable fraction of HCV for Cirrhosis: 7.7%
 - Attributable fraction of HCV for HCC: 10.9%
- With Foundation for Innovative New Diagnostics (FIND) as already mentioned above, we have planned a Hepatitis C: Delhi Demonstration Project. This project is funded from Unitaid (Geneva, Switzerland), which has now been funded as the HEAD-Start project (“HEAD” for Hepatitis C Elimination through Access to Diagnostics; the “Project”). The Project intends to contribute to the WHO targets on HCV for 2030: 90% reduction in incidence/ 65% reduction in mortality/ 80% of patients receiving treatment. The key intended outcome is a change in global normative guidelines and national policies that are conducive to scaling up HCV management.
- Under this activity 50,000 residents of Delhi from these 25 peripheral sites will be screened for HCV and complete treatment will be offered to all those who will be found to be infected.
 - Various modalities for HCV diagnosis like DBS cards evaluation, HCV core antigen evaluation will also be done through this project.
 - ILBS launched a “Liver screening mobile van” on the occasion of the 20th Hepatitis Day on December 4, 2017, This program is an initiative under the “Healthy liver and Healthy Delhi” project to screen, diagnose and refer to care of Hepatitis B and C infected patients and those with fatty liver. Already approximately 5382 persons in Delhi have been screened under this activity and we target to screen around 10,000 people in the coming year.

Based on the interim analysis, some of the key findings were:

- Proportion of subjects screened positive for Hepatitis B: 1.2%
- Proportion of screened positive for Hepatitis C: 0.5%

- Proportion of subjects with raised ALT levels: 21.3%
- Proportion of subjects with raised liver stiffness measure (LSM): 12.1%
- Mobile App: WHO CC ILBS has developed a mobile application namely, “Hepcare” for the general population. This app was launched on 28th July, 2018 and is available for free download on google play store. This application has two interfaces; one interface provides detailed information on viral hepatitis in simplified language and the other interface is hepatitis risk assessment tool, which any individual can use at their convenience in a confidential manner, and based on responses, the application guides the individual on the need for getting tested for Hepatitis B & C.
- This app can be used by any centre in the region.
- Project Empathy: WHO CC ILBS, is undertaking a 4 year campaign with the goal to de-stigmatize Hepatitis and create an enabling environment for individuals with hepatitis and their families in India for social participation and care seeking. A comprehensive campaign with the goal to destigmatize Hepatitis and create an enabling environment for individuals with hepatitis and their families in India for social participation and care seeking.
- The specific objectives of this campaign will be to: Generate awareness on Hepatitis B and C across India through sustained advocacy and tailored behavior change communication for developing and promoting positive behavior at individual, community and societal levels for people with hepatitis and their families and to create a conducive policy environment at sub-national level to encourage dialogue on hepatitis between policy makers, program managers, care providers, civil society and the patients and their families
- This initiative is funded by Airports Authority of India under their corporate social responsibility. The campaign aims to ‘generate awareness on Hepatitis B and C across India through sustained advocacy and tailored behaviour change communication for developing and promoting positive behaviours at individual, community and societal levels for people with hepatitis and their families’ and ‘creating a conducive policy environment at sub-national level to encourage dialogue on hepatitis between policy makers, program managers, care providers, civil society and the patients and their families’
- All the modules made under this activity are available with WHO CC and can be used for extending this activity in the South East Asia region.

2. Annual report on other activities requested

Should WHO have requested activities in addition to the agreed workplan, please describe related actions taken by your institution [maximum 200 words]. Please do not include in this report any activity done by your institution that was not requested by and agreed with WHO.

- WHO CC ILBS provided technical support to the WHO SEARO in reviewing the National Viral Hepatitis operational and management guidelines developed by Nepal.
- The WHOCC at ILBS supported WHO SEARO in developing a report of progress in hepatitis action plans in SEARO by collating the information from all the 11-member states in the SERAO region regarding the progress towards Elimination of Viral Hepatitis in 2018. A model data extraction proforma was created and sent to all member states in SE Asia region and the following information were obtained from all member states: 1) Prevalence of viral hepatitis in general population and specific high-risk groups; 2) Formulation and Implementation of a National Action Plan / National health program for Viral Hepatitis; 3) Status regarding key strategies for elimination of viral hepatitis like a) Birth dose Vaccine for Hep B, b) Universal use of Autodisable / ReUse Prevention Syringes to ensure safe injection practices, c) Safe Blood for elimination of Hep B / C Transmission and d) Scale up testing and treatment for Hepatitis B & C.

The finalized report is under review and publication by SEARO.

3. Resources

Indicate staff time spent on the implementation of activities agreed with WHO (i.e. those mentioned in questions no. 1 and no. 2 above). Do not include any data related to other activities done by your institution without the agreement of WHO. Please indicate staff time using the number of “full-day equivalents” – a day of work comprising 8 hours (e.g. 4 hours work per day for 7 days should be recorded as 3.5 full-day equivalents).

Number of staff involved (either partially or fully)

Senior staff	Mid-career staff	Junior staff, PhD students
7	3	0

Number of full-day equivalents, total for all staff involved

Senior staff	Mid-career staff	Junior staff, PhD students
70	42	42

Implementation of the agreed workplan activities (i.e. those mentioned in questions no. 1 and no. 2 above) normally require resources beyond staff-time, such as the use of laboratory facilities, purchasing of materials, travel, etc. Please estimate the costs of these other resources as a percentage of the total costs incurred (e.g. if you incurred costs of USD 100 and the value of your staff time was USD 50 which makes the total of USD 150, please report 33.3% and 66.7%).

Percentage of costs associated with staff time	Percentage of costs associated with other resources	Total
40.00	60.00	100.00

4. Networking

Describe any interactions or collaboration with other WHO Collaborating Centres in the context of the implementation of the agreed activities. If you are part of a network of WHO Collaborating Centres, please also mention the name of the network and describe your involvement in that network [maximum 200 words].

There were not many interactions with other WHO CC apart from WHO CC at SGPGI, India. WHO CC ILBS worked in close collaboration with SEARO office.