INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

August 2020

From Our Sponsors Laboratory Testing of SARS-COV-2

TRIPOD and INA-PROACTIVE Studies' Updates

Science Corner
World Hepatitis Day 2020: How much do we care about hepatitis B?

Data Management
PROACTIVE DATA CLEANING PHASES

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content

August 2020 Edition | issue #83

FEATURES

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INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

STUDY UPDATES

INA102

PARTICIPANT STATUS

Per 13 Aug 2020, the total ongoing participants in the TRIPOD study are 31 out of 490 enrolled participants. From those 31 ongoing participants, nine are still on TB treatment while 22 are waiting for a 6-month post-treatment visit. Two hundred and twenty-five participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 6.3% of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participant from site 520 and 570 have been completed the study. At the same time, there are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still need to be followed up, 17 participants from site 560 (RSUP dr. Kariadi Semarang), 6 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 6 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

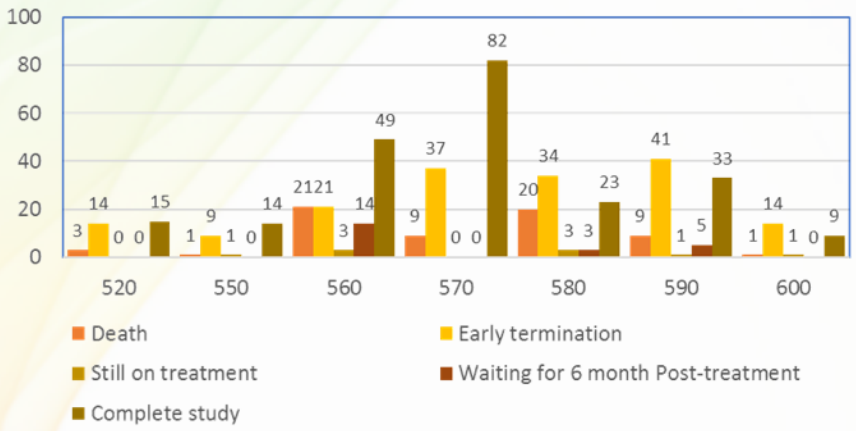

Figure 1.Participant status per site based on uploaded CRF per 13 August 2020

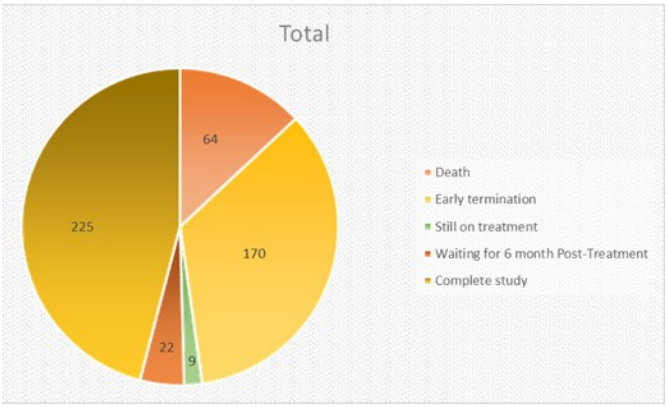

Figure 2. Total participant status based on uploaded CRF per 13 August

TRIPOD MANUSCRIPT

The authors for the TRIPOD manuscript have been selected. In the near future, a meeting with NIH will be performed to initiate the progress. The following are several manuscripts that being planned: a) focus on the baseline findings; b) treatment outcome and the related affected factors; c) related factors of TB and DM co-morbidity. The authors will be sorted according to enrolled participants. A discussion will be set up during the Clinical Research Protocol Writing Workshop.

Site number	Site name	Author
520	RS Sanglah Denpasar	dr. I Gede Ketut Sajinadiyasa, Sp.PD
550	RSUP dr. Wahidin Sudirohusodo	Dr. dr. Irawaty Djaharuddin, SpP(K)
560	RSUP dr. Kariadi	dr. Banteng Hanang Wibisono, Sp.PD-KP
570	RSUD dr. Soetomo	dr. Tutik Kusmiati, SpP (K)
580	RSUP dr. Sardjito	dr Bambang Sigit Riyanto, SpPD-KP, FINASIM
590	RSUP Persahabatan	dr. Diah Handayani, SpP
600	RSUP H Adam Malik	Dr. dr. Bintang YM Sinaga, M.Ked(Paru), Sp.P(K)

INA104

The screening and enrollment of all 19 INA-PROACTIVE sites ended on 30 Jun 2020. As of 30 Jun, a total of 4,336 subjects were enrolled, consisted of 4,148 adults and 188 pediatrics from a total of 7,364 subjects screened. Details are shown in Figure 1.

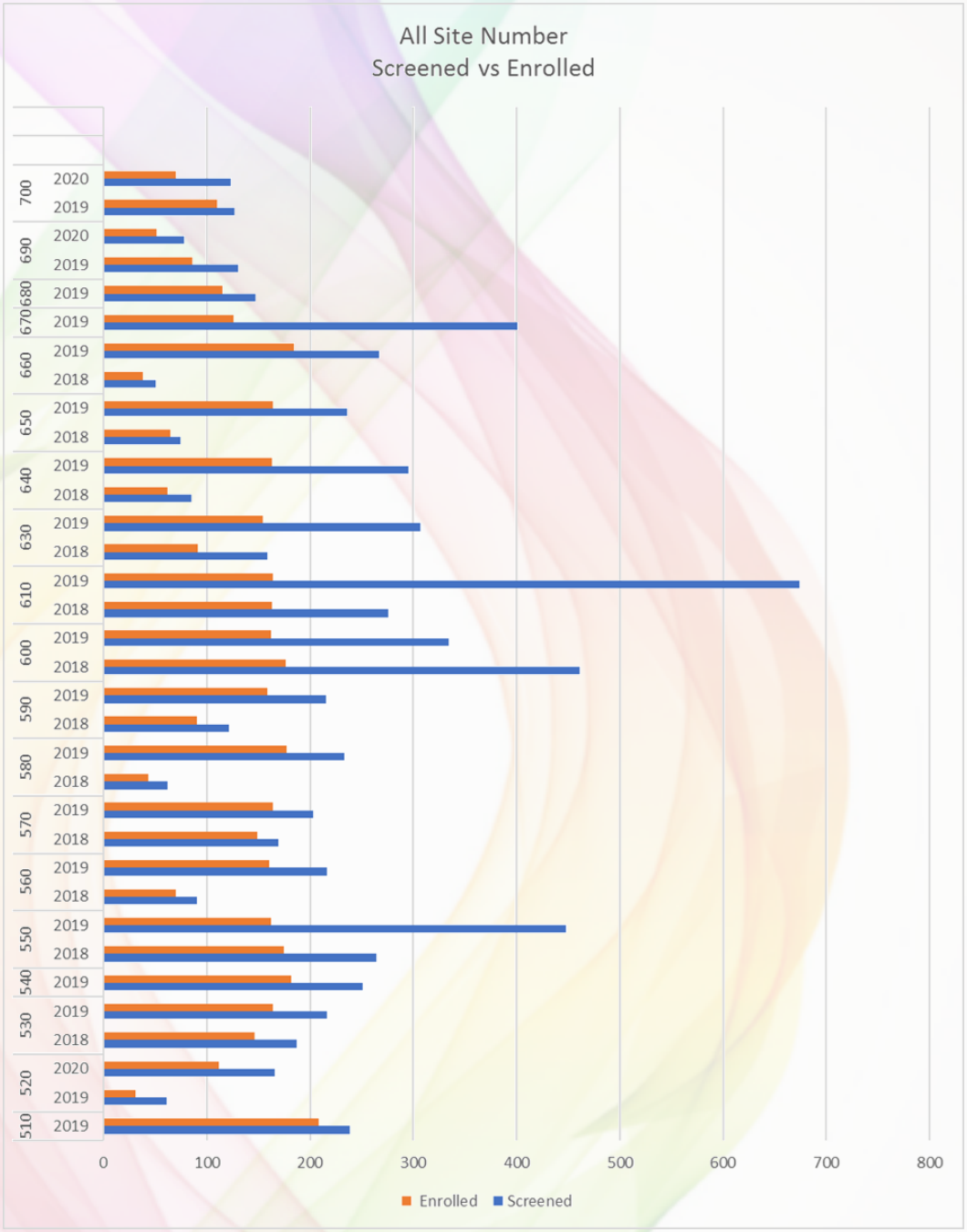

Figure 1. All Site Number Screened vs Enrolled

One hundred sixty-four participants ended the study because of various reasons such as death or moving to another city with no site or far from an INA-PROACTIVE study site hospital. There are 4.172 active participants of INA-PROACTIVE to date.

The follow-up activities of the INA-PROACTIVE study are still on halted until further notice. INA-PROACTIVE sites may continue to arrange subject follow up with prioritizing safety for subjects who have reached maximum window period or who might have difficulties to go to the Site because of PSBB (large scale social restriction). However, several sites have notified the INA-RESPOND secretariat to continue routine follow-up activities, since their site hospitals are allowed to undergo outpatient services and clinical studies as long as they follow the coronavirus disease prevention and control protocol.

Due to the shipping restriction and the increased workload of the Reference lab team during the COVID-19 pandemic, the specimen shipping activity is limited up to 4 shipping per month. Furthermore, the monitoring for site 540 (Sulianti Saroso Hospital) was done remotely on 21-22 July 2020. No monitoring schedule is set for August 2020.

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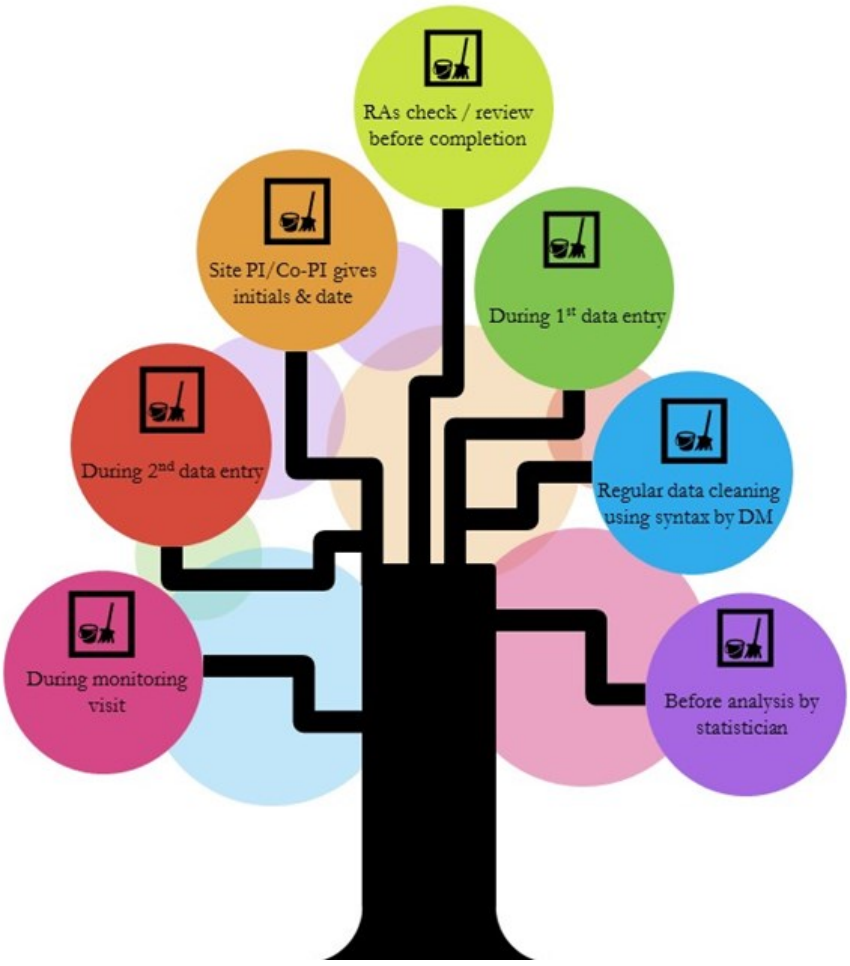
PROACTIVE DATA CLEANING PHASES

By: Silvera Erari, Kanti Laras, Santi Maulintania, Melinda Setiyaningrum



Data management (DM) in a clinical research study plays a crucial role. Data management activities may vary based on study phases. Before a study is implemented, the data management team is mainly responsible for preparing the CRF, developing the study database, training the site team, etc. Data management will continue to be an active element that makes sure the quality of study data during the study is maintained. However, the data management team is not the only member of the study team who is responsible for this. Every member of the study teams, whether at the site level or Secretariat level, plays a significant role in maintaining the quality of data. Data cleaning is one of the many ways to maintain the quality of the data. Following, we will discuss data cleaning phases in the PROACTIVE study.

During study implementation, there are approximately seven data cleaning phases starting from the site level to the secretariat level. These are the phases:

RAs check/review before completion (Site Level)

Research assistants (RAs) are strongly advised to review or check the Source Document Worksheet's (SDW) completeness and accuracy before requesting for site PI/Co-PI's initials and dates. RAs can check whether all required data have been entirely or accurately filled by thoroughly reading the SDW, as well as Data Entry Guideline (DEG), and comparing necessary variables. If discrepancies are found, RAs can directly revise the data based on appropriate data correction procedures. This action will significantly help to reduce the necessity to generate On-site Data Clarification Forms (ODCF).

Before site PI/Co-PIs give initials and dates (Site Level)

Before providing initials and dates on SDW, site PI/Co-PIs are encouraged to review SDW. This review can be based on completeness, accuracy, and medical perspectives. Site PI/Co-PIs can help to identify medical information that is significant for the study and make sure it is correctly captured in SDW. This action will provide a second layer cleaning advantage in addition to the one provided by RAs. If discrepancies are found, site PI/Co-PIs should request RAs to make some corrections.

During the 1st data entry (Site Level)

PROACTIVE study administers a double data entry method, where the first data entry is done at the site level, and the second data entry is done at the secretariat level. RAs can once again assure the cleanness of the data while entering the data into the OpenClinica system. If RAs find any discrepancy, RAs should directly issue ODCF for data correction. Please always remember that once SDW is completed with site PI/Co-PIs initials and date, any data correction only can be done by using ODCF. Rapidly issuing ODCF can prevent query generation; therefore, this action can help to reduce the number of queries generated for the site.

During the 2nd data entry (Secretariat Level)

During the second data entry process, Data Entry Specialists (DES) will check on or look for missing and inconsistent data. While doing second data entry, if discrepancies are found, DES will assign queries to appointed sites. Then, sites should directly respond to assigned queries, which are frequently in the forms of data correction or data confirmation, and they should be resolved within five working days. Any delays will affect the site's performance. Also, DES will replace any incorrect inputs that are done by RAs during the first data entry process.

Regular data cleaning using syntax (Secretariat Level)

The data manager regularly extracts data every month, which can further be used for data cleaning purposes. Extracted data will be run into the syntax system developed to clean the data deeply. Typically, this phase will catch any potential missing log pages, inconsistencies that require complicated calculations such as BMI, missing values, even incorrect inputs from RAs and DES. This process also can verify data accuracy across visits or pages, which is usually complicated to be done by second data entry. The results from this step will be generated in the form of a query inside OpenClinica.

During monitoring visit (Secretariat Level)

During the monitoring visit, either at the site or done remotely, monitor (CRA) will do the Source Document Verification (SDV), examining the precision between data written in SDW and various source documents. Unfortunately, since this visit is relatively short, not every SDW will be examined. Based on the Monitoring Plan, at least 20% of SDW will go through this process. Therefore, phase 1 and 2 are crucial because only RAs and site PI/Co-PI have access to source documents, in addition to monitors. Inaccuracies from this action will be addressed both in monitoring reports and queries.

Before routine and final analysis by statistician (Secretariat Level)

In preparation for routine and final data analysis, a statistician will further clean the data. However, in general, data cleaning is mostly done for interesting or crucial variables only. Therefore, the scope is slightly limited. If discrepancies are found, the statistician will send them to the data management team for queries generation. This cleaning usually will be more closely related to the purpose of the study or desired data analysis purposes.

Finally, one important note we should remember is that maintaining high-quality data, especially in the data cleaning process, is the responsibility of all study team members from the site level to the Secretariat level. This is not the responsibility of the data management team only. Therefore, to get good quality data, consistent collaboration from all study members is required.

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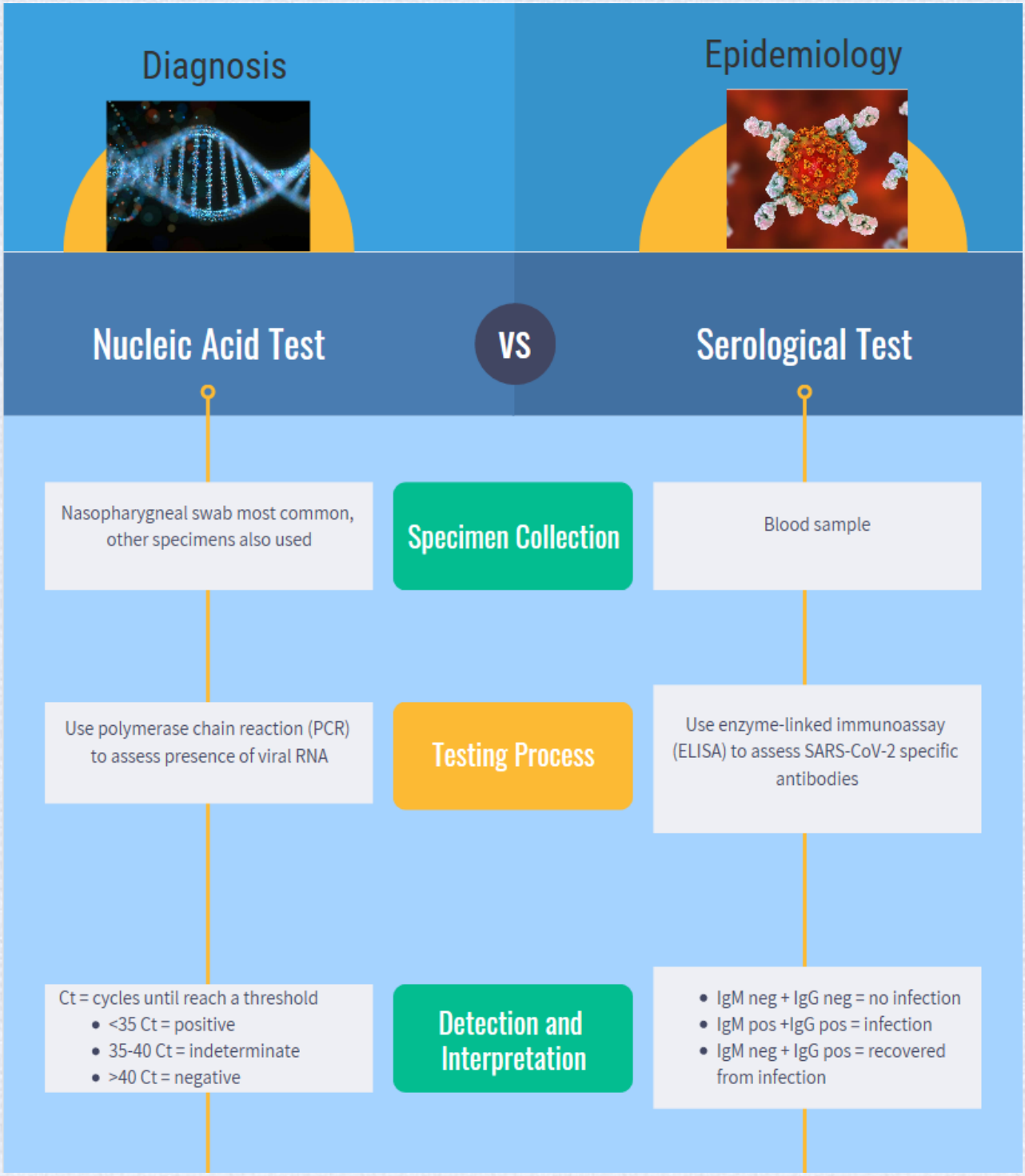
LABORATORY TESTING OF SARS-COV-2

By: William Yang



• Sensitivity: Varies on specimen, can be as high as ~95% • Specificity: ~100%	**Sensitivity and Specificity**	• Sensitivity: Varies by assay used • Specificity: ~95%
• Direct pathogen detection: asymptomatic and early disease • Relatively easy to conduct • Guides immediate management of patients	**Pros**	• Alternative when nucleic acid test unavailable • May reveal timing of infection • May inform public health decisions
• Only detect viral RNA, virus may not be viable • Alternative specimens can require invasive procedure	**Cons**	• Not approved for acute infection diagnosis • Correlate of protection and durability unknown • More prone to false positives

Five Facts for Fighting Infection

1. Person it takes to spread infection to a loved one
2. Negative PCR tests 24 hours apart (with symptom improvement) = end of isolation
3. Weeks after symptom onset is when seroconversion typically occurs
4. Fold increase in antibody titer suggests recent infection
5. and a half days after onset, ELISA IgM detection efficiency > PCR

Bottom Line

The Covid-19 pandemic is a critical public health issue that must be taken seriously by all. By selecting the most appropriate type of test in each given setting, we can get ever closer to defeating the curve and returning to normalcy.

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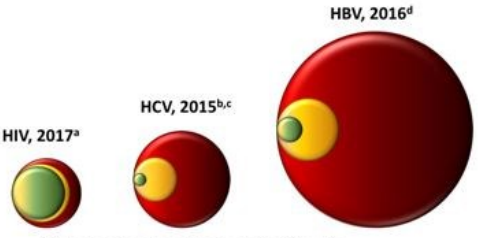
SCIENCE CORNER

WORLD HEPATITIS DAY 2020; HOW MUCH DO WE CARE ABOUT HEPATITIS B?

By: Yan Mardian

World Hepatitis Day is commemorated each year on 28 July to enhance awareness of viral hepatitis, an inflammation of the liver that causes a range of health problems, including liver cancer. There are five main strains of the hepatitis virus – A, B, C, D, and E. Above those five, Hepatitis B Virus (HBV) is the most common cause of deaths, with almost 900.000 lives lost globally each year. Amid the COVID-19 pandemic, HBV continues to claim thousands of lives every day. However, how much do we know in detail about HBV as health care personnel and/or health scientist?



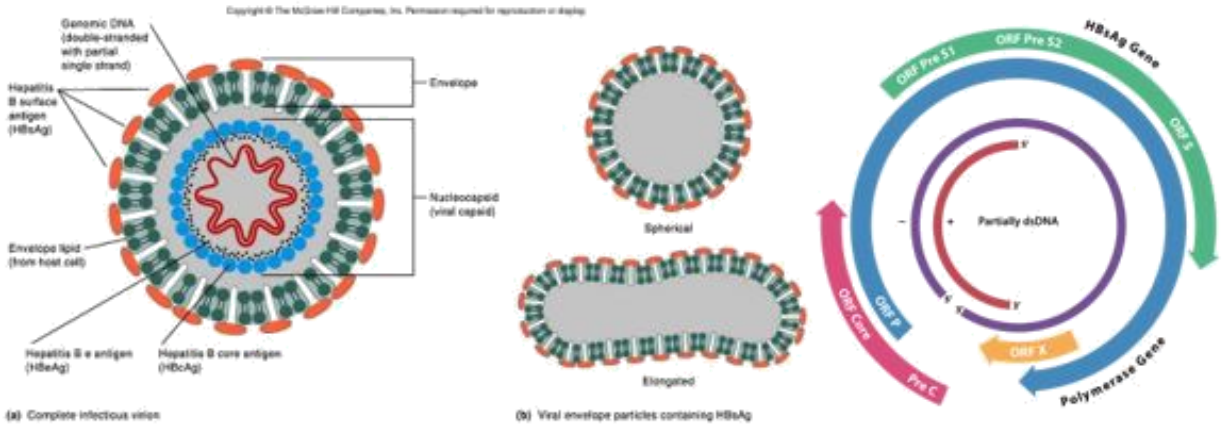
Global estimates of patients (millions)

Prevalence	36.9	71.1	292.0
Diagnosed	27.7	14.2	28.8
Treated	21.7	1.1	4.8

As we can see from this data, the global burden and awareness for Hepatitis Virus Infection is still an iceberg tip phenomenon, as we can measure from the magnitude of the problem, the proportion between diagnosed and receiving treatment group between each disease. If we compare the problem with HIV, in 2017 (the latest data available), 36.9 million people globally were living with HIV, while 21.7 million of them million people were accessing antiretroviral therapy in the year. So more than half of the people living with HIV aware of their disease and seeking treatment. However, in 2015, WHO estimates 257 million persons (3.5% of the world population) were living with chronic HBV infection, and around 71 million persons were living with HCV infection in the world, accounting for 1% of the community. The African and Western Pacific regions accounted for 68% of those infected with HBV. Compared with HBV, the prevalence of HCV infection is lower, but more heterogeneously distributed, with differences across and within WHO regions and countries. Among them, just about 10% (for HBV) and 20% (for HCV) were diagnosed correctly and a much lower percentage among them who received treatment. This phenomenon might have resulted from limited public knowledge about this disease, lack of access to examinations for the lower middle class, or lack of access to hepatitis treatment.

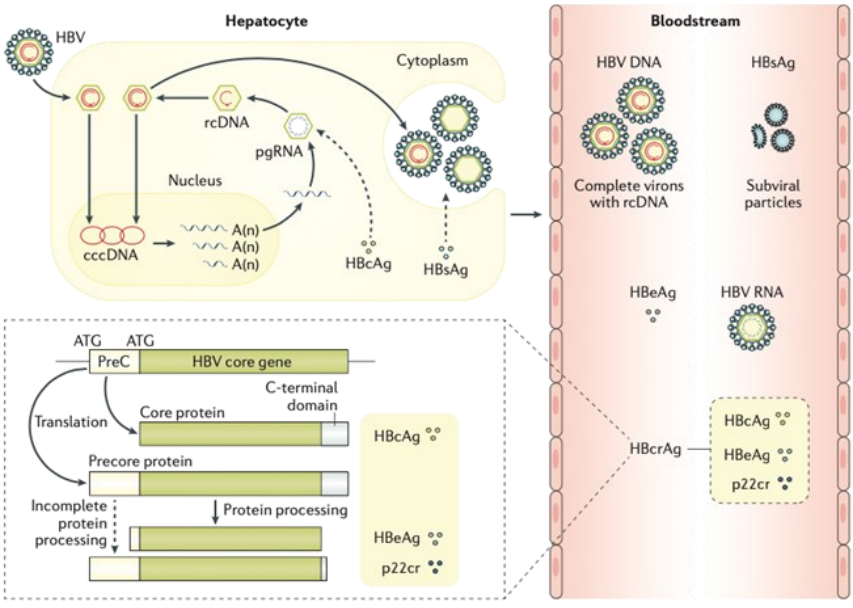
HBV Virology

Hepatitis B virus (HBV), a partially double-stranded hepatotropic DNA virus, is the etiological agent of acute and chronic hepatitis B in humans. The Intact hepatitis B virion, also known as the Dane Particle, is a sphere that is approximately 42 nm in diameter containing about 3200 bp. The HBV genome is organized in a circular form with the positive-strand DNA (with variable base length) forming the inner circle and the negative-strand DNA (completely circular) forming the outer circle. The four overlapping genes are P for translating polymerase, PreS1/PreS/S for hepatitis B surface antigen (HBsAg), PreC/C for core protein, and X for HBx protein. The P protein has reverse transcriptase activity. The C and S open reading frames (ORFs) have extensions at their 5′ ends termed pre-C and pre-S. The pre-S region is divided into pre-S1 and pre-S2 domains, and translation of the S ORF leads to the production of the large (L), medium (M), and small (S) HBsAg. Translation of the pre-C ORF results in a secretory protein, hepatitis B e antigen (HBeAg), which is an accessory protein required establishing chronicity, whereas the C ORF results in the capsid protein. HBx is required for the establishment of infection and maintenance of ac-



tive replication by inhibiting the host nuclear restriction factor, sister chromatid cohesion 5/6 (SMC 5/6).

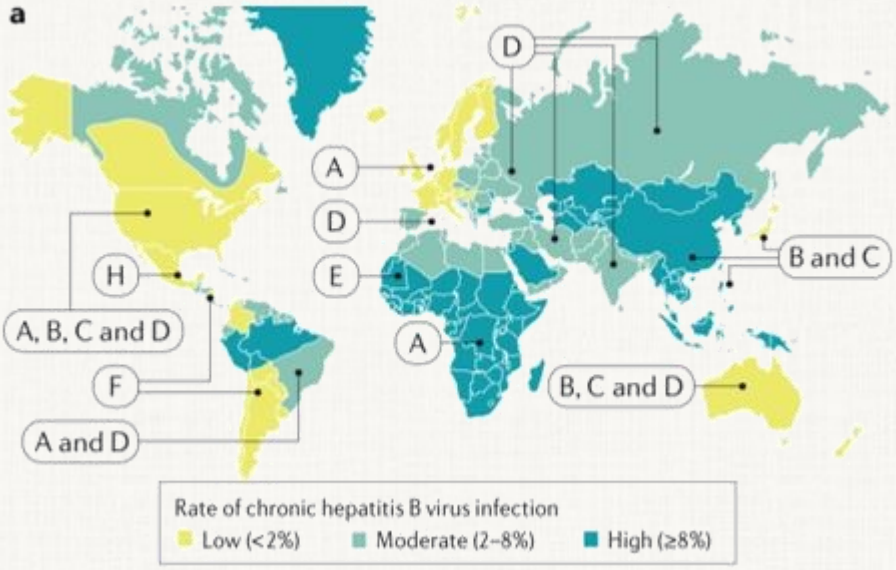
After viral entry into hepatocytes via the high-affinity receptor sodium taurocholate co-transporting polypeptide (picture below, left upper diagram), hepatitis B virus (HBV) relaxed circular DNA (rcDNA) enters the nucleus and is converted into covalently closed circular DNA (cccDNA) in the form of a minichromosome — the major transcriptional template of the virus. The transcription products are exported from the nucleus, with the larger pregenomic RNA (pgRNA) incorporated into replication complexes in the cytoplasm comprising the viral polymerase and core protein. Within these replication complexes, pgRNA is reverse-transcribed into HBV DNA, which can replenish cccDNA or undergo further packaging. The HBV DNA containing capsid binds to the HBV surface proteins on the endoplasmic reticulum, is translocated into the lumen before exiting the hepatocytes through the secretory pathway, and is then released as mature virus particles. mRNAs transcribed from cccDNA also produce various viral antigens. Except for cccDNA, all the other viral products (HBV rcDNA, HBV RNA, hepatitis B e antigen (HBeAg), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg) and 22 kDa precore protein (p22cr)) are easily measurable in the blood (right diagram). The lower left part of the diagram illustrates the three antigens, HBcAg, HBeAg and p22cr (collectively known as hepatitis B core-related antigen (HBcrAg)), produced from the translation of different starting codons of the preC core gene and differential protein processing afterward. A (n), polyadenosine at the end of mRNAs. The reverse transcriptase lacks proofreading activity; thus, mutations of the viral genome are frequent and result in the coexistence of genetically distinct viral species in infected individuals (quasispecies).



Geographical Distribution

In countries where HBV prevalence is high, infection usually occurs early in life, leading to lifelong chronic infection and carriage of the virus, whereas infection later in life usually leads to an acute, self-resolving illness followed by viral clearance or, in rare fulminant cases, liver failure. Chronic hepatitis B infection is defined as the detection of serum hepatitis B surface antigen

(HBsAg; the viral glycoprotein) after 6 months of infection. The transmission route of HBV is primarily through blood and bodily fluids and includes perinatal and early infant transmission (mother to child transmission (MTCT)) as well as sexual and parenteral modes. Chronic HBV infection is a major public health problem. In chronic HBV infection, there may be ongoing low-grade liver inflammation, with episodes of transient high-grade liver inflammation and activation of fibrogenic processes, leading to liver fibrosis and cirrhosis, which may culminate in decompensated (symptomatic) liver disease and/or the development of hepatocellular carcinoma (HCC) in 25–40% of HBV carriers. In addition, HBV infection has further oncogenic potential after HBV integration into the host genome, which is an additional pathway contributing to HCC.



The frequency of infection and patterns of transmission varies in different parts of the world. It was estimated that around 250 million people worldwide are chronic HBsAg carriers. If left untreated, up to 40% will develop into cirrhosis, liver failure, HCC, and death. As estimated in 2015, 887 000 deaths were attributed to HBV-related liver disease and HCC. Regions with a different population prevalence of chronic hepatitis B infection, categorized as high (>8%), moderate (2–8%), and low (<2%), is depicted in the picture above. A high prevalence of chronic hepatitis B infection is found in the Western Pacific and Africa. Prevailing genotypes of HBV (letters) in different countries are also depicted above. >80% of the world population lives in intermediate-high countries. In China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon Basin, 8% to l5% of the population carry the virus. The lifetime risk of HBV infection is higher than 60%, and most infections are acquired at birth or during early childhood when the risk of developing chronic infections is most elevated. In these areas, because most infections are asymptomatic, minimal acute disease related to HBV occurs, but rates of chronic liver disease and liver cancer among adults are very high. While in the United States, Western Europe, and Australia, HBV infection is a disease of low endemicity. Infection occurs primarily during adulthood, and only 0.1% to 0.5% of the population are chronic carriers. The lifetime risk of HBV infection is less than 20% in low prevalence areas. It is of particular concern that Indonesia is the third-highest prevalence of HBV infection worldwide, with a moderate-to-high incidence of hepatitis B endemicity that affects 242 million people.

Modes of Transmission

In highly endemic areas, hepatitis B is most commonly spread from mother to child at birth (perinatal transmission), or through horizontal transmission (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life. Hepatitis B is also spread by needlestick injury, tattooing, piercing, and exposure to infected blood and body fluids, such as saliva and, menstrual, vaginal, and seminal fluids. Sexual transmission of hepatitis B may occur, particularly in unvaccinated men who have sex with men and heterosexual persons with multiple sex partners or contact with sex workers. Transmission of the virus may also occur through the reuse of needles and syringes either in

health-care settings or among persons who inject drugs. In addition, the infection can occur during medical, surgical, and dental procedures, through tattooing, or through the use of razors and similar objects that are contaminated with infected blood. The hepatitis B virus can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine. The incubation period of the hepatitis B virus is 75 days on average but can vary from 30 to 180 days. The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B.

Natural History and Diagnosis

Most people do not experience any symptoms when newly infected. However, some people have acute illnesses with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting, and abdominal pain. A small subset of persons with acute hepatitis can develop acute liver failure, which can lead to death. In some people, the hepatitis B virus can also cause a chronic liver infection that can later develop into cirrhosis (a scarring of the liver) or liver cancer. The likelihood that infection becomes chronic depends on the age at which a person becomes infected. Children less than 6 years of age who become infected with the hepatitis B virus are the most likely to develop chronic infections. In infants and children: 80–90% of infants infected during the first year of life develop chronic infections; and 30–50% of children infected before the age of 6 years develop chronic infections. While in adults: less than 5% of otherwise healthy persons who are infected as adults will develop chronic infections; and 20–30% of adults who are chronically infected will develop cirrhosis and/or liver cancer.

It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents, hence, laboratory confirmation of the diagnosis is essential. A number of blood tests are available to diagnose and monitor people with hepatitis B. They can be used to distinguish acute and chronic infections. Laboratory diagnosis of hepatitis B infection focuses on the detection of the hepatitis B surface antigen HBsAg. WHO recommends that all blood donations be tested for hepatitis B to ensure blood safety and avoid accidental transmission to people who receive blood products. Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to the core antigen, HBcAg. During the initial phase of infection, patients are also seropositive for hepatitis B e antigen (HBeAg). HBeAg is usually a marker of high levels of replication of the virus. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly infectious. While chronic infection is characterized by the persistence of HBsAg

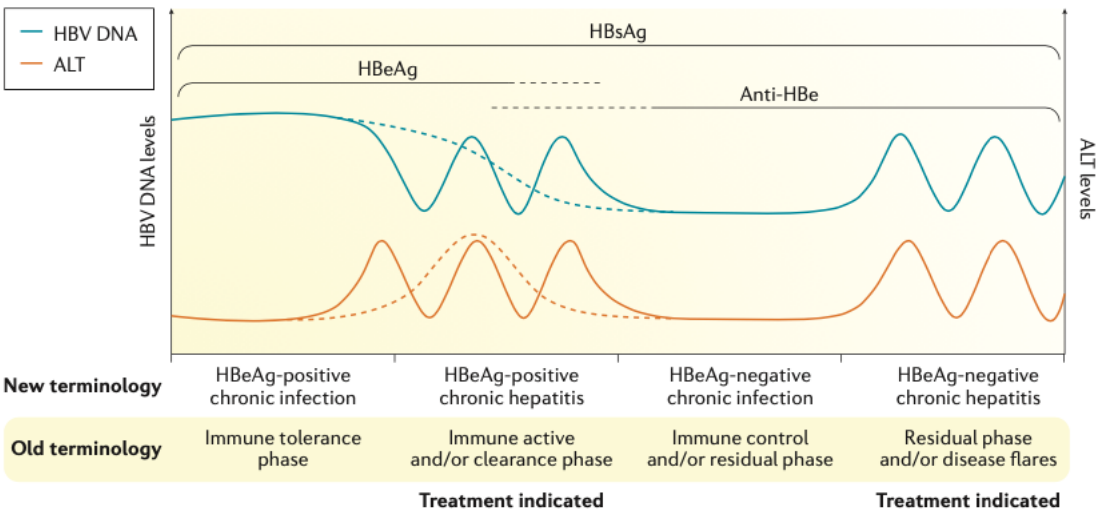


Figure 6 | **Hepatitis B disease phases and treatment indications.** Diagram showing the relationship between hepatitis B virus (HBV) DNA and alanine transaminase (ALT) levels and the relation of these levels to different phases of chronic HBV infection using new and old terminology. Some patients (solid lines) experience intermittent flares in HBV DNA and ALT levels before achieving HBeAg seroconversion, whereas other patients (dashed line) may have a less frequent flares. Treatment is indicated when the HBV DNA levels are >2,000 or >20,000 international units (IU) per litre and ALT levels are higher than one or two times the upper limit of normal according to different regional guidelines. anti-HBe, antibodies against HBeAG; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

for at least 6 months (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and liver cancer (hepatocellular carcinoma) later in life.

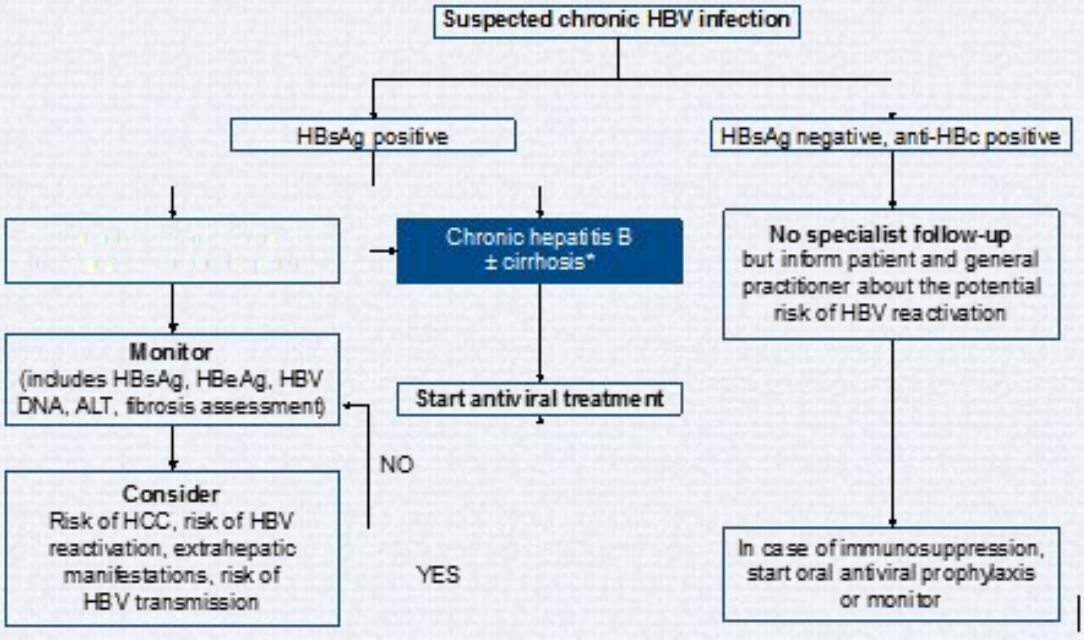
The above diagram showing the relationship between hepatitis B virus (HBV) DNA and alanine transaminase (ALT) levels and the relation of these levels to different phases of chronic HBV infection using new and old terminology. Some patients (solid lines) experience intermittent flares in HBV DNA and ALT levels before achieving HBeAg seroconversion, whereas other patients (dashed line) may have less frequent flares. Anti-HBe, antibodies against HBeAg; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Treatment

HBV treatment is typically aimed to achieve profound virological suppression, which in turn will lead to biochemical remission (return of ALT values to the normal range), histological improvement and prevention of the complications of liver disease, such as cirrhosis, liver failure, and HCC. There is no specific treatment for acute hepatitis; more than 95% of adults with acute HBV hepatitis do not require specific treatment. Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with antiviral agents and considered for liver transplantation. However, chronic hepatitis B infection can be treated with medicines, including oral antiviral agents. Treatment can slow the progression of cirrhosis, reduce the incidence of liver cancer, and improve long term survival. Only a proportion (estimates vary from 10% to 40% depending on setting and eligibility criteria) of people with chronic hepatitis B infection will require treatment.

Recommendations		
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
• Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	■	2
Can be treated		
• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	■	2

Recommendations		
Follow-up at least every 3–6 months		
• HBeAg-positive chronic HBV infection, <30 years old	II-2	1
Follow-up at least every 6–12 months		
• HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml	II-2	1
Follow-up every 3 months for the first year and every 6 months thereafter		
• HBeAg-negative chronic HBV infection, serum HBV DNA ≥2,000 IU/ml	■	1



HBV infection is managed with reverse transcriptase inhibitors, which are nucleoside or nucleotide analogues (NUCs/NA), and, less commonly interferon (IFN) therapy. The total elimination of HBV from patients (HBV cure) remains a remote treatment goal, but a more practical goal is the achievement of HBsAg seroclearance (functional cure) as early as possible after infection. Although HBsAg seroclearance occurs in only a small proportion of patients who have undergone

treatment with NUCs/NA, it is associated with a low rate of clinical complications and a high chance of disease remission after treatment cessation.

As seen in the figure above, newer NA (ATV, TDF, TAF) gives a higher barrier to resistance than previous drugs and generally more preferred than PegIFNalpha due to its lower side effects compared with the later, and is a choice of monotherapy for treatment-naïve patients.

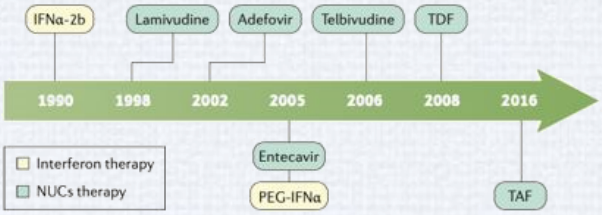
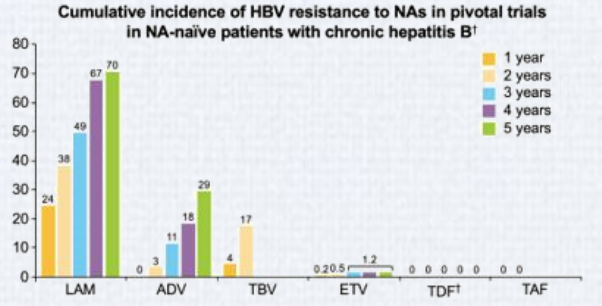


Figure 7 | **Approved treatment agents for chronic HBV infection.** A timeline that shows the year of US FDA approval for individual hepatitis B virus (HBV) treatment agents. All the treatment agents have also been approved by the European Medicines Agency and in various Asian countries. The boxes in green refer to nucleoside or nucleotide analogues (NUCs), and the pale yellow boxes refer to interferon-based therapy. In 2018, the recommended first-line agents are pegylated interferon α-2a (PEG-IFNα), entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).



Unresolved issues and the future of HBV treatment

In most people, however, the treatment does not cure hepatitis B infection, but only suppresses the replication of the virus. Therefore, most people who start hepatitis B treatment using NA must continue it for life. In addition, there is still limited access to diagnosis and treatment of hepatitis B in many resource-constrained settings. In 2016, of the more than 250 million people living with HBV infection, 10.5% (27 million) were aware of their infection. Of those diagnosed, global treatment coverage is 16.7% (4.5 million). Many people are diagnosed only when they already have advanced liver disease. Moreover, with the current treatment, still many issues keep unresolved, such as:

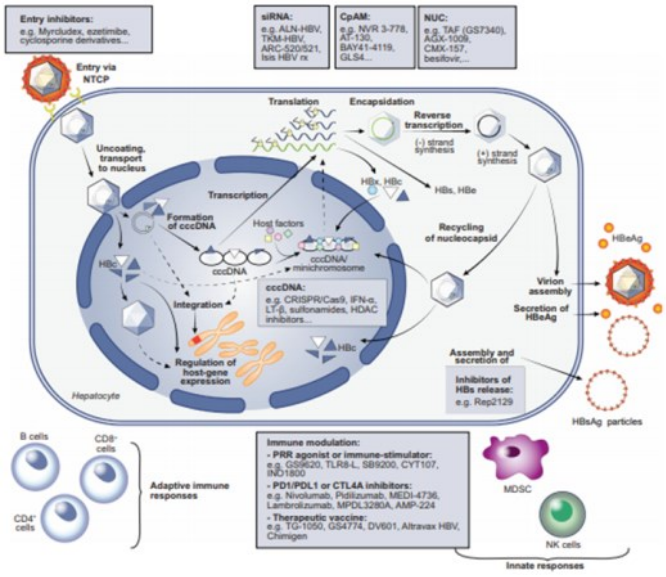
- When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
- Stopping rules for HBeAg-negative patients treated with an NA
- Retreatment criteria after NA discontinuation
- How to accelerate HBsAg decline in long-term NA-treated patients

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs†	Probably not‡
Contraindications	Many‖	None‖
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate¶	Low in first year, moderate over long term
Effect on HBsAg levels	Variable¶	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none††

Responses	NA therapy	PegIFNα-therapy
Virological (on-treatment)	**Response:** HBV DNA <10 IU/ml **Primary non-response:** <1 $\log_{10}$ decrease in HBV DNA after 3 months of therapy **Partial response:** HBV DNA decreased by >1 $\log_{10}$ but still detectable after ≥12 months of therapy in compliant patients **Breakthrough:** confirmed HBV DNA increase of >1 $\log_{10}$ above on-therapy nadir	**Response:** HBV DNA <2,000 IU/ml
Virological (off-treatment)	**Sustained response:** HBV DNA <2,000 IU/ml for ≥12 months after end of therapy	
Serological	HBeAg loss and development of anti-HBe* HBsAg loss and development of anti-HBs	
Biochemical	ALT normalization† (confirmed by ALT determination at least every 3 months for at least 1 year post-treatment)	
Histological	Decrease in necroinflammatory activity‡ without worsening in fibrosis compared with pre-treatment histological findings	

- Better baseline or on-treatment predictors of sustained response in patients treated with PegIFNa
- Definition of the residual risk of HCC in patients on long-term NA therapy and impact on surveillance
- Requirement for new treatments with finite duration and high cure rates
- Novel endpoints to define a cure of HBV infection
- Biomarkers for the cure of infection and for the cure of liver disease

As of 2016, a universal hepatitis B vaccination program has been implemented in 186 countries worldwide. Global coverage with three doses of HBV vaccine is estimated to be 84% (>90% in the Western Pacific, regions of the Americas, and the South–East Asia region). Vaccination remains the most effective tool to prevent HBV infection. HBsAg produced in yeast has been engineered as an effective recombinant vaccine for HBV and was licensed for use in the United States in 1986. An updated generation of HBV vaccines has been developed that consists of genetically engineered viral proteins, which can achieve a primary neutralizing antibody response after vaccination in >95% of individuals. In addition, strategic planning is emerging for antiviral prophylaxis in pregnant HBV-infected women, which effectively decreases MTCT. As a result of these efforts, the global prevalence of HBV infection and also the incidence of HBV-associated liver decompensation and HCC are expected to decline. However, it may take at least 30 years for this favorable outcome to emerge. Until then, we should improve awareness of the disease, case finding, surveillance strategies, and treatment optimization for the existing 257 million HBV chronically infected people. These challenging steps should be implemented without delay in all countries to reach the goal set in May 2016 by the WHO: the elimination of viral hepatitis as a public threat, with a 90% reduction of new hepatitis infections and a 65% reduction in mortality by 2030. Although health-care workers, health-related statutory personnel, paramedics, and patient groups are actively involved in the first three aspects, HBV disease clinicians and researchers are the key persons to improve the treatment for HBV disease.



Therefore, some efforts had been made to fill the unmet needs of currents HBV management, including finding new HBV biomarkers, including:

- cccDNA (the template for viral gene expression, associated with viral persistence in HBV-infected hepatocytes, but limited use in research due to the need for liver biopsy)
- HBcrAg (may demonstrate the persistence of intrahepatic cccDNA and differentiate HBeAg-negative from HBeAg-positive disease, also may be used to predict HBeAg seroconversion, sustained response to NUCs treatment, the presence of necroinflammatory disease, the risk of reactivation of hepatitis B with immunosuppression and the risk of HCC development), and
- HBV RNA (which has a strong correlation with intrahepatic cccDNA, possible utility in predicting viral rebound after discontinuation of NAs).

Moreover, future treatment options for HBV are being developed, such as several novel direct-acting antivirals and immunotherapeutic agents and combinations of antiviral and immunomodulatory therapy, targeting multiple steps in the HBV lifecycle, that will likely be needed to achieve an HBV 'cure' in the future.

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INA-RESPOND Newsletter

FIGHT OBESITY WITH EXERCISE DURING PANDEMIC COVID-19

By: Dr. Monica Surjanto, Sp.K.O

Working From Home (WFH) over the past few months has caused many people to gain weight and waist circumference. This can be caused by the higher frequency of eating, snacking, and decreasing physical activity and exercise. Finally, many of them become overweight, even obese, and can be related to other diseases. The measurement of overweight and obesity is commonly assessed by using Body Mass Index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

Table 1. Classification of obesity as recommended by the Asia-Pacific Task Force[1]

		Risk of Comorbidities	
Classification	**BMI (kg/m²)**	**Waist Circumference**	
		<90 cm (men)	**≥90 cm (men)**
		<80 (women)	**≥80 (women)**
Underweight	<18.5	Low*	Average
Normal	18.5-22.9	Average	Increased
Overweight:	≥23		
At risk	23.0-24.9	Increased	Moderate
Obese I	25.0-29.9	Moderate	Severe
Obese II	≥30	Severe	Very severe

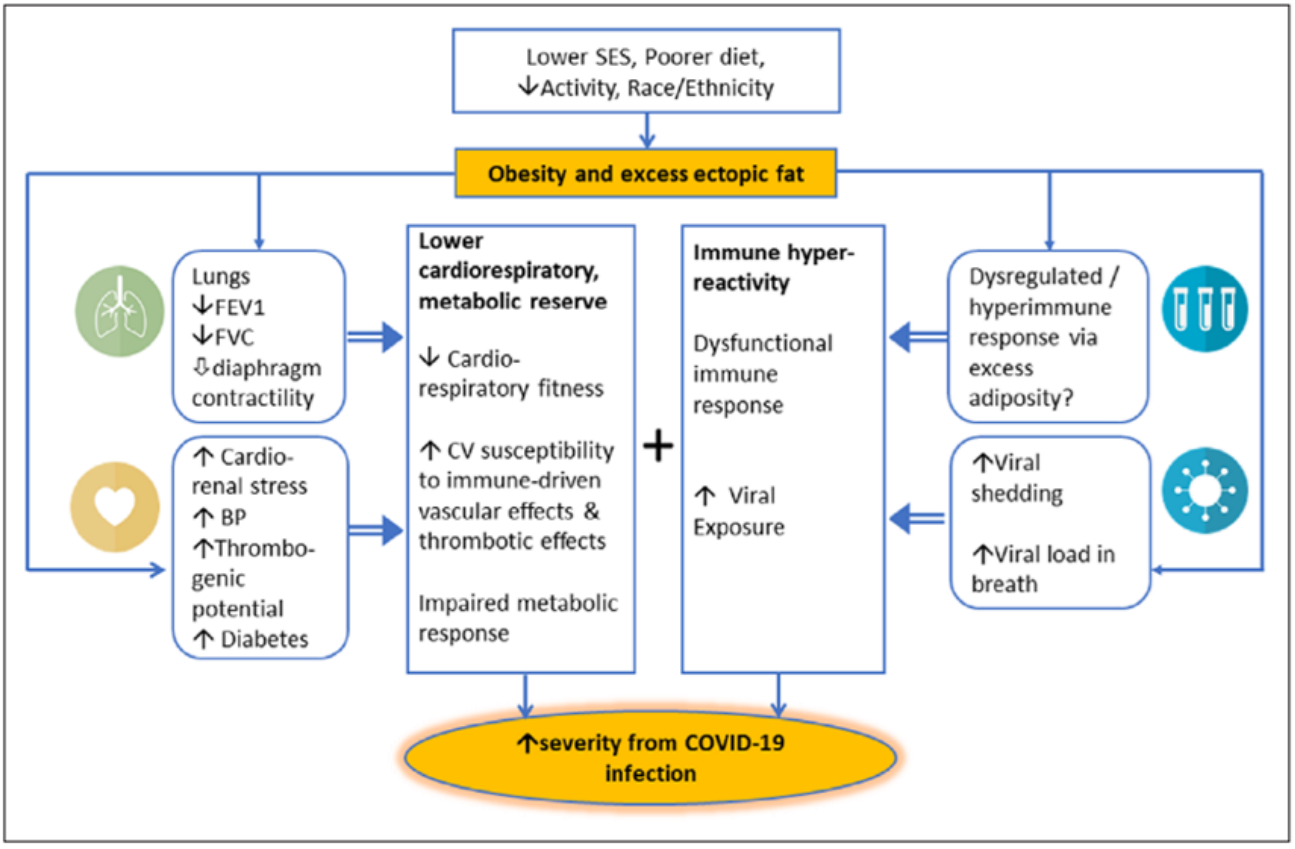
* but increased risk of other clinical problems

The causes of obesity are complex and multifactorial and are a mixture of genetic, behavioral, physiological, geographical, economic, and social factors. A healthy diet and regular physical activity or exercise are critical for attaining or maintaining a healthy weight. Weight management is dependent on energy balance: energy intake (the number of calories consumed) and energy expenditure (the number of calories expended). Energy expenditure must exceed energy intake in reducing body weight, referred to as a negative energy balance.[2]

Obesity is an important emerging risk factor for severe COVID-19 infection that deserves the attention of individuals, physicians, and public health professionals during the present pandemic. Obese individuals should be more careful about preventive measures during the pandemic.

Obesity Is a Risk Factor for Severe COVID-19 Infection

Obesity or excess ectopic fat deposition may be a unifying risk factor for severe COVID-19 infection, reducing protective cardiorespiratory reserve as well as potentiating the immune dysregulation that appears, at least in part, to mediate the progression to critical illness and organ failure in a proportion of patients with COVID-19.[3]



A study of more than 5,200 hospitalized patients with COVID-19 reported a strong association between obesity and critical illness. Patients under age 60 years who were overweight were twice as likely to be hospitalized as their leaner counterparts, while those with obesity were three times as likely to need intensive care. These findings contribute to the growing body of evidence that obesity and other chronic conditions likely predispose an individual to increased risks associated with infectious diseases.[4]

The Importance of Physical Activity to Attenuate the Impact of COVID-19

Similar to obesity, physical inactivity increases the severity of symptoms and the risk of mortality in those with chronic diseases or acute respiratory infections. The inhibited immune response and blunting of macrophage activation appears to be associated with the diminished insulin sensitivity that occurs with reduced physical activity. Exercise increases a person's physiologic reserve, thereby lowering the risk of mortality from cardiovascular and metabolic diseases. Exercise also provides immunological benefits that are mediated by enhanced immuno-surveillance via augmented macrophage responses, increased circulation of immunoglobulins and anti-inflammatory cytokines, and an attenuation of inflammation. Therefore, it is important to encourage physical activity or exercise to assist with disease management and increase physiologic reserve beyond the immediate SARS-CoV-2 pandemic especially for individuals with overweight and obesity.[4]

Treatment of Obesity through Exercise

Exercise is defined as a physical activity that is structured and repetitive, uses large muscle groups, and has the intent of changing one or more fitness components. Exercise promotes increased levels of energy expenditure and should be done at a moderate to vigorous intensity. Regarding weight loss, the combination of diet and exercise produces the largest weight loss compared with diet or physical activity only. Depending on the amount of excess body weight and the aerobic fitness of the client, the FITT principle can be adjusted to meet the needs of individuals.

Table 2. FITT Recommendation for Individuals with Overweight and Obesity[5]

	Aerobic	Resistance	Flexibility
Frequency	≥ 5 days/week	2-3 days/ week	≥ 2-3 days/week
Intensity	Moderate intensity (64-76% HR max); progress to vigorous (>76% HR max) for greater health benefits	60-70% of 1 RM; gradually increase to enhance strength and muscle mass	Stretch to the point of feeling tightness
Time	30 min/day (150 min/week) increase to 60 min/day or more (250-300 min/week)	2-4 sets of 8-12 repetitions for each of the major muscle groups	Hold the static stretch for 10-30 secs, 2-4 repetitions of each exercise
Type	Prolonged, rhythmic activities using large muscle group (walking, cycling, swimming)	Resistance machines and/or free weights	Static, dynamic stretching

Target a minimal reduction in body weight of at least 3% -10% of initial body weight over 3-6 months. A decrease of 500-1000 kcal/day is adequate to elicit a weight loss (0,5-0,9 kg/week). This should be combined with a reduction in dietary fat intake.[5]

Conclusion

During the COVID-19 pandemic, it is even more important for all people, especially individuals with overweight and obesity, to be physically active, even if it is only a short break from sitting at your desk to do some walking or stretching. Being physically active will be a challenge for all of us, but we must find and plan ways to be active and reduce our sedentary time. As we have known that obesity is a comorbidity and risk factor for COVID-19 infection, therefore they need to stay physically active and do some exercises during the pandemic. The current situation should be a concern for all those who want to perform exercises. Everyone needs to practice proper physical distancing and to employ aggressive personal hygiene and also sanitation protocol during the training.

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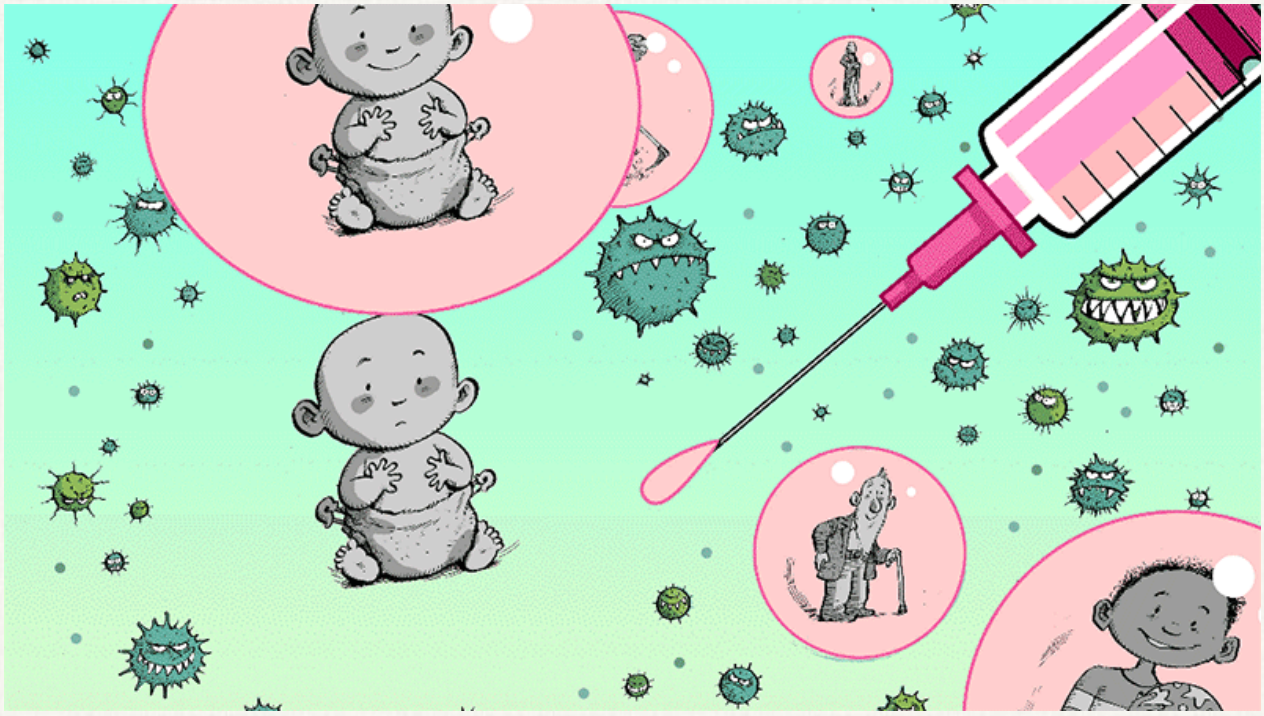
INA-RESPOND Newsletter

COVID-19 VACCINES: MAGIC BULLETS FOR US ALL?

By: Aly Diana



COMIC CORNER

The whole world is crying right now, and I guess it is chanting the same words: "Coronavirus, please go away!". However, as it seems that it is not going to happen soon, and good hygiene, as well as quarantine which have been implemented on a very sporadic basis, are showing varying outcomes, most people turn their hopes into the development of vaccines. On average, it takes 12-15 years or more to develop a vaccine. With the COVID-19 crisis looming, everyone is hoping that this time will be different.

The good news is several COVID-19 vaccines have shown promising results in the early stages of development. These few months, several vaccines will enter Phase III clinical trials to determine their efficacy and safety. On 13 August 2020, WHO just launched the latest landscape of COVID-19 candidate vaccines. There are 29 candidate vaccines in the clinical phase, with six leading candidates already entering phase 3.

A striking feature of the vaccine development landscape for COVID-19 is the range of technology platforms being evaluated, including nucleic acid (DNA and mRNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus, and inactivated virus approaches. Many of these platforms are not currently the basis for licensed vaccines. The novel platforms based on DNA or mRNA offer great flexibility in terms of antigen manipulation and potential for speed. In super brief, this is the summary of the vaccine technology with their upside and downside; and some examples:

Live, weakened virus vaccines use the virus itself, but weaken so that it does not cause disease. Licensed vaccines have used this technology, and a single dose may be possible. However, these vaccines are very slow to produce and require extensive safety testing. Example: Codagenix.

Inactivated virus vaccines inactivate the virus so that it is not infectious. Licensed vaccines have used this technology. However, this technology poses the risk of enhancement of an infection, which is what happened with the SARS vaccine. As a result, this vaccine requires extensive safety testing. Example: Sinovac, Wuhan- and Beijing Institute of Biological Products.

Viral vector vaccines use a different virus, such as the adenovirus, to carry COVID-19 protein spikes that provoke an immune response. The vector virus is weakened and can be either replicating or non-replicating within cells. The replicating types use technology that licensed vaccines use, such as the measles and Ebola vaccines. Production of these vaccines can be scaled quickly, and a single dose may be possible. However, non-replicating types use technology that no licensed vaccine has used. Also, pre-existing immunity to the vector virus could reduce its effectiveness. Example: Oxford University/ AstraZeneca, Johnson & Johnson, and Merck.

Protein vaccines use a protein fragment of the virus to provoke an immune response. Several licensed vaccines use this technology, such as Hepatitis B, Influenza, and HPV vaccines. The production of these vaccines can be scaled quickly. However, they may require adjuvants and multiple doses. Example: GlaxoSmithKline, Sanofi Pasteur, Novavax, and Baylor College of Medicine.

Nucleic acid vaccines use genetic DNA or RNA to program replication of the protein spike, which provokes an immune response. Production of these vaccines can be scaled quickly because no culture or fermentation is required. However, this technology is unproven; no licensed vaccine uses it. Example: Moderna, Pfizer, and Inovio.

We keep our fingers crossed that soon, in 6 months or so, we will hear some more good news with vaccines' progress. One important thing, most experts believe at least 70 percent of the population must be vaccinated, so enough part of the community is immune, which will help to stop the spread of the virus. It will not be a fast process, but let's be positive. There is still light in front of us.

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