INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

INA-RESPOND Secretariat

Badan Litbangkes, Kemenkes RI,
Building 4, 5th Floor,
Jl. Percetakan Negara No. 29,
Jakarta, 10560.
Phone: +62 21 42879189
Email: INA.Secretariat@ina-respond.net
Website: www.ina-respond.net

Newsletter
May 2017

In This Issue

Infectious Agents Can Contribute to Growth of Cancer; Can They Help to Cure As Well?

With 14.1 million of new cases and 8.2 million deaths in 2012, cancer remains a major health problem worldwide and is the second leading cause of death globally. Nearly 1 in 6 deaths is due to cancer, and approximately 70% of deaths from cancer occur in low and middle-income countries. In Indonesia, there are 299.700 new cases of cancer per year with194.500 deaths. Treatment and prevention strategies to manage this disease depend on our understanding of cancer cells and its development mechanism. Many research has discovered that carcinogenic viruses can play role at different steps of the cancer development, where its association is various from 15-100 %. Read more about the relation between infectious disease and cancer in this article series.

Page 6

The Burden That You Love – So Please Take Care of It!

What do we need when we want to proof our hypothesis? What do we need when we want to answer our research questions? Yes, GOOD DATA! Read this edition's Comic Corner to learn more about it

Save The Date

Important Events & Meetings

1 May	International Labor Day
11 May	Vesak Day
25 May	Ascension Day
24 May	HIV Protocol Development and Planning Meeting @Double Tree, Jakarta

May Birthday

2 May	dr. Dewi Muniarti	INA101 Site PI Site 540
5 May	Mr. Catur Endra Kurnia Ackri	INA102 Lab Tech Site 570
5 May	Ms. Ni Wayan Nilawati	INA101 Lab Tech Site 520
16 May	Ms. Nur Endartini	INA102 Research Nurse, Site 570
17 May	dr. Andra Pranata	INA102 RA Site 570
17 May	dr. Risna Halim Mubin	INA101 1st Co-PI Site 550
27 May	dr. Siswanto	Head of NIHRD
30 May	Ms. Dewa Ayu Nyoman Rustiati	INA102 Research Nurse, Site 520

Announcement

The month of Ramadan is coming soon. All over the world, people spend this whole month with full respect, dedication, devotion and by spreading love to others. It is a fact that this is not only a holy month but also a blessing for us to make us humble and peaceful, and this is the special month that helps us to keep ourselves a bit more near to Allah. Of course we get a valuable time to spend with our family as well. Wishing you happy Ramadan; may Allah shower His blessings on you and your family.

By:
dr. Nurhayati
dr. Anandika Pawitri

AFIRE Study (INA101) Updates

The sites Close-out Visits (SCV) have been conducted by the INA-RESPOND CRAs to all eight study sites. All queries have also been resolved and completed. Currently, we are waiting for approval from site PIs for the Self Evidence Correction Document. Once Site PIs approved and signed it, the INA101 database will be locked. The manuscripts will be finalized to be submitted to international journals.

For further information about this study please go to: http://www.ina-respond.net/afire-study/

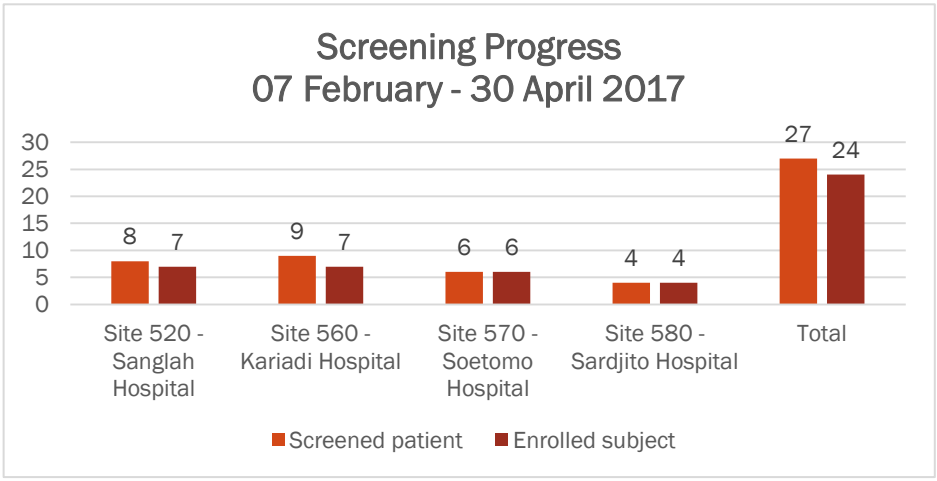
TRIPOD (INA102) Updates

Screening and Enrollment

Now that all 4 sites (520 – Sanglah Hospital, 560 – Kariadi Hospital, 570 – Soetomo Hospital, and 580 – Sardjito Hospital) are active, they are busy with screening and enrolling patient. Please refer to table 1 (right) for the screening report.

Site Activation

We are planning to activate two new sites, 550 – Wahidin Hospital and 590 – Persahabatan Hospital. Site 550 has been assessed by the Site Specialist to register the requirement they need for this study. Site 590's contract is currently being reviewed by the hospital's management team.



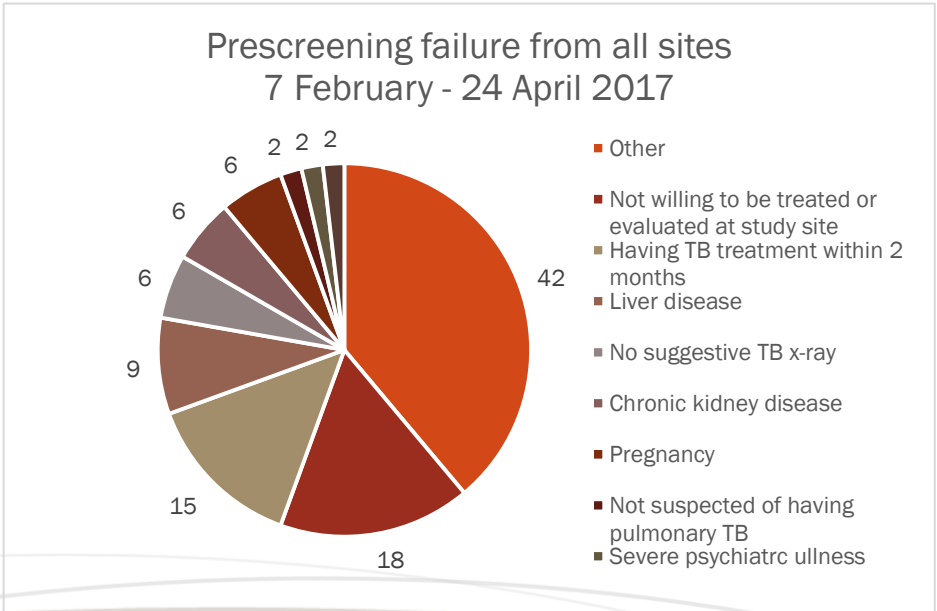


Chart 2 Reasons of prescreening failure. The reason "Other" has the highest number of all. This includes site 520 enrollment halt, weekly enrollment target achieved; patients refuse to join the study, etc.

The Burden That You Love – So Please Take Care of It

By:
dr. Aly Diana

What do we need when we want to proof our hypothesis? What do we need when we want to answer our research questions? What do we need if we want to publish something and let people know about our studies and hard work? What do we need if we want to compare or combine our results with other studies? Yes, GOOD DATA! It is not only data, but we need GOOD data. However, how many times do you ever think that it is very difficult to deal with your data: so many missing values, implausible values, outliers, wrong answers on wrong variables? And, how many times do you ever think that you get tired and almost give up after trying thousand times cleaning your data and they are still not behaving as well as you want them to be?

The best suggestion experts may recommend is we prevent these hassles from happening and cut the problems from the roots. Try to handle the issues later than sooner usually will create more difficulties than what we can handle with care. Data management plan (DMP) is a good solution. As we may notice, most of funders nowadays require sufficiently detailed DMP to be submitted as part of a research proposal and it will be used as one essential factor to determine the merit of our study.

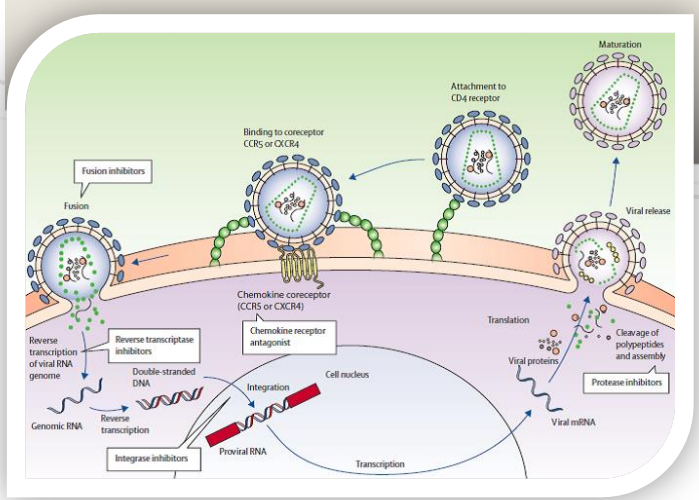
DMP must cover the plan during project and after the project ends; typically cover all or portions of the data life cycle—from data discovery, collection, and organization, through quality assurance/quality control, documentation and use of the data, data preservation and sharing (e.g., data policies and dissemination approaches). There are a lot of things to think about and the most important thing is to think about it ahead of time. As the famous quote by Benjamin Franklin says, "By failing to prepare, you are preparing to fail."

As there are a lot of templates of DMP to be followed, the next important step is not only to present a perfect DMP in the proposal, but also to execute the plan as wonderful as we proposed it. Here, I would like to highlight just several important steps, mostly to keep our data as GOOD DATA. Firstly, we must have a clear protocol. Collecting data without having a clear protocol and without making sure that everybody involved in data collection following the protocol is a recipe for real disaster. Types, sources, volume, and file formats of data should be clearly defined.

Secondly, we need to have metadata attach to our dataset. Metadata include descriptions of how data and files are named, physically structured, and stored as well as details about the experiments, analytical methods, and research context. The utility and longevity of data relate directly to how complete and comprehensive the metadata are. Accompanied by the good metadata, our data set should be able to speak for itself; means that people with certain expertise should be able to interpret the data as well as the data manager.

Thirdly, we need to do preventive measure by doing proper quality assurance and quality control, which may encompass training activities, instrument calibration and verification tests, double-blind data entry, and statistical and visualization approaches to error detection. Simple graphical data exploration approaches (e.g., scatterplots, mapping) can be invaluable for detecting anomalies and errors.

There are many more steps that should be carefully considered regarding our data. Nevertheless, following these three steps apparently will make our data closer to an ideal data set; and we may have what we really need: GOOD DATA. Congratulations!!!



Latest News:

Advances in Anti-HIV Drugs

By:
dr. Dona Arlinda

The pipeline of anti-HIV drugs has developed considerably over the past 20 years. New drug classes and newer generation of the existing antiretroviral offer more options to optimise antiretroviral therapy (ART) regimens, especially for treatment-experienced people with resistant viruses.

Currently, there are more than 25 anti-HIV drugs from six known classes based on their mechanism of action of blocking HIV replication (most are shown in Fig. 1), i.e. entry inhibitors, fusion inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (IIs), protease inhibitors (PIs), and pharmacokinetic enhancer/ booster. An ART regimen would generally use 2 NRTIs + 1 NNRTI or 2 NRTIs + 1 PI or 2 NRTIs + 1 IIs.

The Conference on Retroviruses and Opportunistic Infections (CROI) 2017 discussed several advances in the anti-HIV drug pipeline. Novel drug classes are being tested in various stage of clinical trials, including capsid inhibitors in early studies and monoclonal antibodies now in late-stage human trials. Newer-generation drug candidates of the existing antiretroviral classes are also being explored for long-action potential, such as elsulfavirine (NNRTI), MK-8591 and GS-9131 (NRTIs), cabotegravir (IIs), and GS-PI1 (PIs).

Capsid Inhibitors with Long Action Potential

Capsid encloses HIV genetic materials. Capsid inhibitors are a novel mechanism of anti-HIV drugs that impaired capsid function at multiple point during HIV core assembly, disassembly, and nuclear translocation of pre-integration complex. Dr. Winston Tse from Gilead Sciences presented GS-CA1 as the selected candidate of capsid inhibitors to enter pre-clinical studies. GS-CA1 binds to a highly conversed site resulting in high barrier to resistance. It showed highly potent EC50 of 140 picomolar in peripheral blood mononuclear cells and has high metabolic stability resulting in low efficacious dose of once a month. Toxicology studies and phase 1 clinical trials are projected in 2018.

Long acting monoclonal antibodies

Long acting monoclonal antibodies (Ibalizumab and PRO 140) offer new treatment options for people with highly resistant virus and limited treatment options. A phase 3 trial evaluating 2000 mg Ibalizumab intravenous infusions every two weeks in combination with optimised background ART in 40 heavily treatment-experienced participants, which most had exhausted all available drugs in at least three classes, showed modest antiviral activity and was generally safe and well tolerated.

PRO 140 blocks CCR5, one of the two co-receptors HIV uses to enter cells. In 42 HIV-positive adults with exclusively CCR5-tropic HIV on a stable ART with undetectable viral load (<40 copies/ml), weekly 350 mg subcutaneous injections of PRO 140 maintained viral suppression for more than two years in a majority of responders and was generally safe and well-tolerated.

Selected references

Tse WC et al. *Discovery of novel potent HIV capsid inhibitors with long-acting potential*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 38, 2017.

Lewis S et al. *Long-acting ibalizumab in patients with multi-drug resistant HIV-1: a 24-week study*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 449LB, 2017.

Lalezari J et al. (Dhody K presenting) *PRO140 single-agent maintenance therapy for HIV-1 infection: a 2-year update*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 437, 2017.

Infectious Agents Can Contribute to Growth of Cancer; Can They Help Cure As Well?

By:
dr. Venty Muliana Sari

With 14.1 million of new cases and 8.2 million deaths in 2012, cancer remains a major health problem worldwide and is the second leading cause of death globally. Nearly 1 in 6 deaths is due to cancer and approximately 70% of deaths from cancer occur in low and middle-income countries. In Indonesia, there are 299,700 new cases of cancer per year with 194,500 deaths. Treatment and prevention strategies to manage this disease depend on our understanding of cancer cells and its development mechanism.

Recently, some infections are known as risk factors for cancer. It is estimated that carcinogenic infectious agents, especially viral infections contribute to 2.2 million or 15.4% of cancers diagnosed in 2012 and two-thirds of them occurred in less developed countries. Many research has discovered that carcinogenic viruses can play role at different steps of the cancer development, where its association is various from 15-100%.

International Agency for Research on Cancer (IARC) has classified the carcinogenic infectious agents based on evidence of human exposure and carcinogenicity. Group 1 agent is classified as proven carcinogenic to human being and there are 11 agents of infection among this group. : *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV type 1 (HIV-1), human papillomavirus (HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), Epstein-Barr virus (EBV), human herpesvirus type 8 (HHV-8; also, known as Kaposi's sarcoma herpesvirus), human T-cell lymphotropic virus type 1 (HTLV-1), *Opisthorchis viverrini, Clonorchis sinensis*, and *Schistosoma haematobium*.

Besides that, other research study also found some pathogens that

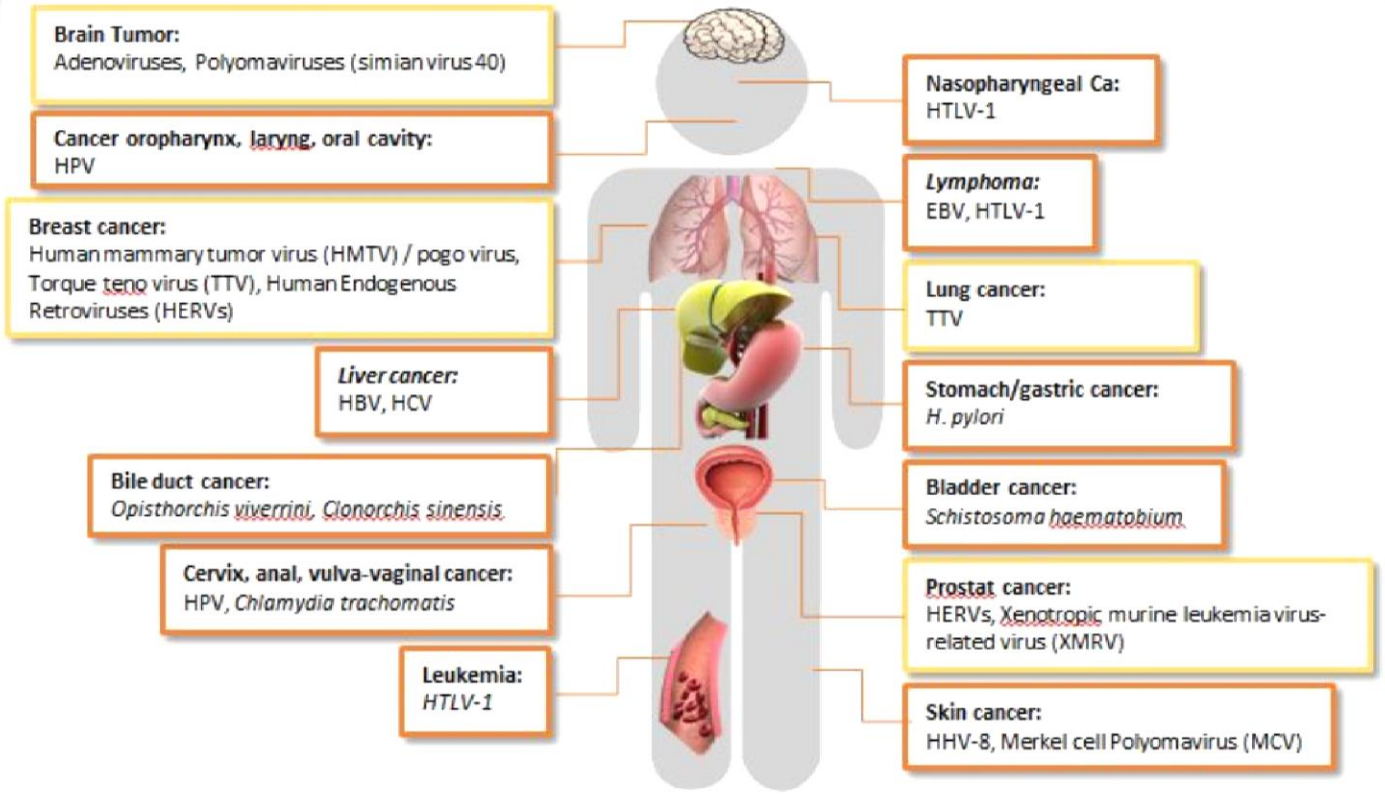


Fig. 1 Infectious agents that have correlation with cancer

might be involved in cancer development, such as polyomaviruses (simian virus 40 and Merkel cell polyomavirus), adenoviruses, human endogenous retroviruses (HERVs), human mammary tumor virus (HTMV) / pogo virus, xenotropic murine leukemia virus-related virus (XMRV), Torque teno virus (TTV) and *Chlamydia trachomatis*. Summary of infectious agents and the associated cancer is shown in figure 1.

Of the 11 infectious agents in group 1 IARC, HIV is the one which have a unique attributable risk's calculation because the cancer risk increases only in combination with other carcinogenic agents. Thus, the research of Plummer et al in 2016 which assess the contribution of infectious agents to cancer burden did not include HIV to the calculation.

Plummer's study found that from the 10 carcinogenic agents, the main infectious agents contributing to the cancer burden were *Helicobacter pylori* (35,40%), HPV (29,50%), HBV (19,2%), and HCV (7,8%), which together accounted for 92% of all infection-attributable cancers worldwide in 2012, and *H. pylori* has the higher percentage of contribution.

H. pylori, as the most attributable pathogen, are associated with stomach cancer such as gastric carcinoma and gastric non-Hodgkin lymphoma. Hepatitis B virus and hepatitis C virus have correlation to liver carcinoma, while Human papilloma virus (HPV) has a strong correlation to the cervix uteri carcinoma. Moreover, HPV is also related to anal carcinoma, penile carcinoma in men, vulva-vaginal carcinoma, carcinoma of oropharynx, larynx and oral cavity. Each infectious agent has various attributable fractions (AF) to their associated cancer (Figure 2).

As expected, the burden of cancers related to infections was dominated by cancers of the stomach, liver, and cervix. Which are the fifth, sixth, and seventh most common cancers worldwide respectively. This incidence is in accordance with the burden of infectious agent related to cancer as we discussed above.

How do infectious agents attribute to cancer?

According to Hanahan and Weinberg (2011), infection can

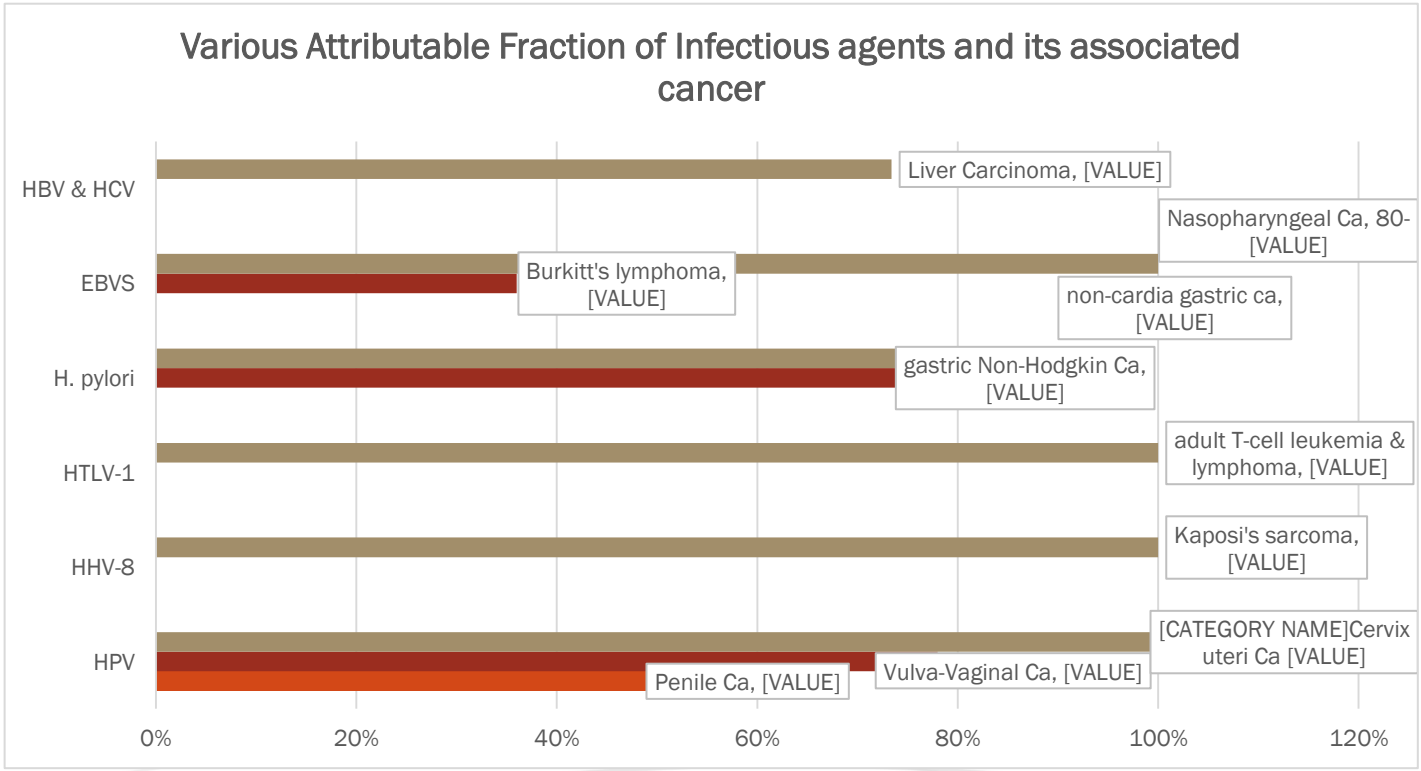
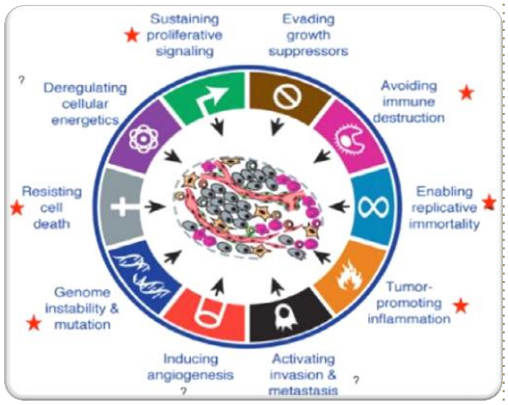


Figure 2 Various AF of infectious agents and its associated cancer. AF (Attributable Fraction) is the proportion of new cancer cases that would have been prevented in a population if all infections had been avoided or successfully treated before they caused cancer (Plummer et al, 2016).

raise the risk of cancer in many different ways. Some of the studies have revealed that viruses directly affect the genes inside cells that control their growth. These viruses express the viral oncogene that causing the cell to grow out of control. Viruses also integrate with cell gene and alter the signal transduction pathways and causing genome instability and mutation. As consequence, they sustain proliferative signaling or evading growth suppressors.

Some infectious agents such as HBV and HCV cause a chronic inflammation that can change the habit of infected cells and avoiding immune destruction by nearby immune cells. Subsequently it can induce a massive cell proliferation, which leads to oxidative DNA damage, but in the same time it inhibits DNA repair and apoptosis. This results in cell death resistance and eventually enabling replicative immortality of a cancer.



The Hallmark of Cancer (Hanahan and Weinberg, 2011)

Albeit infections can increase a person's risk of certain types of cancer, in some people with evidence of these infections, cancer never develop. It is well known that several factors play a role in the development of cancer. For example, infection with *H. pylori* bacteria might increase your risk of stomach cancer, but what your diet, your smoking habit and other factors also affect your risk.

How is infectious agent, especially virus can cure cancer?

To be continued in the next newsletter…..

References:

McLaughlin-Drubin ME, Munger K. Viruses associated with Human Cancer. *Biochim Biophys Acta.* 2008. 1782(3):127-50

American Cancer Society. Infection that Can Leads to Cancer. 2016. https://www.cancer.org/cancer/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer.html (accessed Jan 3, 2017)

Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health.* 2016. 4: e609-16

Ford C. How do viruses cause cancer. University of New South Wales. 2016. https://www.rcpa.edu.au/getattachment/8b3fba52-ecb5-4a6b-9788-62b6bc5e7536/How-do-Viruses-Cause-Cancer.aspx (accessed Jan 3, 2017)

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase no. 11. 2013. Lyon: International Agency for Research on Cancer. http://GLOBOCAN.iarc.fr (accessed Mar 21, 2017).

IARC. List of Classification, volume 1-117. *IARC Monogr Eval Carcinog Risks Hum*. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf (accessed Mar 21, 2017)

INA-RESPOND Newsletter

Advisors : dr. M. Karyana, M.Kes, dr. Herman Kosasih
Editors : Dedy Hidayat S, S.Kom, Dona Arlinda, MD
Columnists : dr. Aly Diana, dr. Anandika Pawitri, Dona Arlinda, MD, Ms. Venty Muliana Sari, dr. Nurhayati.
Thanks to : INA-RESPOND Network and Partners

We would like to hear from you. Go ahead and send us your scientific articles, team profile, or feedback to INA.Secretariat@ina-respond.net