INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

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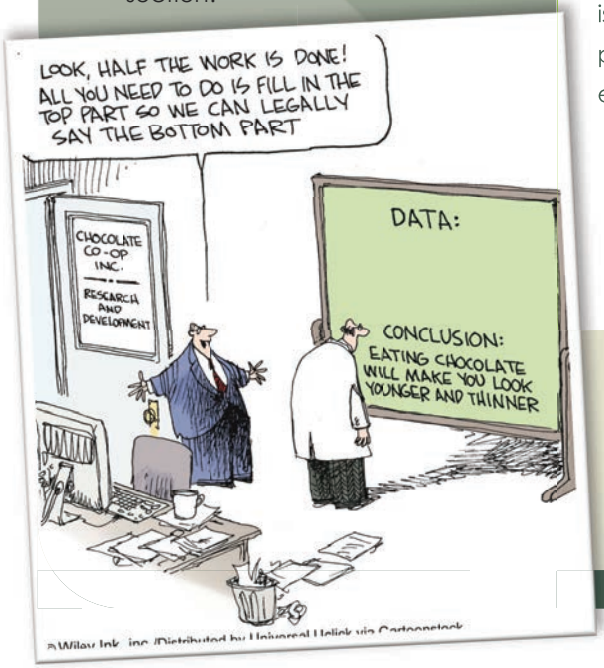
Newsletter December 2016

In This Issue



HIV Cure: Strategies and Recent Advances

The Indonesian government as part of the world community has committed to end the AIDS epidemic. Although we are winning against the AIDS epidemic as more and more countries try to reduce HIV transmission from mother to child, progress has not been made equally everywhere, with young women particularly at risk of becoming infected with HIV.

It is crucial that we take AIDS out of isolation if we want to make significant progress in battling HIV. The road is long before we can finally say that AIDS is over. However, it can be if we tailor the response to individual needs at particular times in life. Understanding this may be the key to end the epidemic.

The success we have achieved so far gives us hope for the future, but we must not become complacent; we cannot stop now. Let's work together to ensure a brighter future; a future free from HIV.

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Conflict of Interest: How Can We See You?

We have probably heard the term "conflict of interest" once or twice in our life. We may think that we would never have to deal with it, especially in our work life. Is it true, though? Can we recognize it when it is standing right in front of us? Find out more about it here!

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Save The Date

Important Events & Meetings

1 December	World HIV Day
5 – 19 December	IT Infrastructure Capacity Building
11 January	*AFIRE Protocol Core Team Meeting*

December Birthday

2 Dec	dr. Annisa Tridamayanti	RA SEA050 Site 43
5 Dec	dr. Dona Arlinda	NIHRD
6 Dec	dr. Bachti Alisjahbana	SC Member at Site 510
	dr. M. Karyana	Head of Steering Committee (SC)
7 Dec	dr. Nadia Iswandari	RA INA102 Site 510
8 Dec	dr. Banteng Hanang Wibisono	PI INA102 Site 560
14 Dec	Ms. Neneng Aini	Secretariat
16 Dec	dr. Delima	Core Team NIHRD
21 Dec	Mr. Dedy Hidayat S.	Secretariat
22 Dec	Ms. Umi Haryanti	LT INA101 Site 570
23 Dec	Dr. Desvita Sari	Co-PI INA102 Site 560
24 Dec	dr. Ketut Jaya Ningrat	RA INA101 Site 520
28 Dec	Prof. Ketut Tuti Merati	SC Member at Site 520
29 Dec	Prof. DR. dr. Ida Parwati	Site 520

Announcement

Christmas is such a delightful time, whether you are a Christian or not. It is always a time to cherish with your family and friends. It is also the perfect time to spare a moment from our life and show that you admire and respect your co-workers.

At the end of 2016, our network receives great news as the Implementing Arrangement (IA) has finally been signed. This is truly a wonderful way to start the new year.

We wish you a very Happy Holiday season and a peaceful and prosperous New Year.

INA-RESPOND Study Updates

INA101 (AFIRE) Study Updates

Several manuscripts related to the AFIRE study are currently being prepared. The first manuscript that will be published is the description of all 1,492 enrolled subjects. To elaborate this first manuscript and also to discuss progress of laboratory tests, a meeting will be held in January 2017. The meeting will be attended by Protocol Investigators. Currently, all laboratory specimens are being investigated for etiology of fever by reference Lab.

All sites are now being prepared for Close Out Visit which is planned to be held in March 2017. This visit is to ensure that there will be no activities after Close Out Visit and will be attended by site team and monitor.

Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.net/EdmFile/getfile/797233
For further information about this study please go to: http://www.ina-respond.net/afire-study/

INA102 (Tripod) Study Updates

Before sites are activated to recruit patients, there are several things we need to do. First, Site Preparation Visits (SPV) are conducted to introduce the TRIPOD study. Second, Monitors will execute Site Initiation Visit to check sites' readiness. Third, we will conduct the Site Activation Visits (SIV) when all pending documents have been completed.

Site	Remarks
510	Under preparation for site preparation visit
520	Site Preparation Visit and Site Initiation Visit done, being prepared for Site Activation
530	Under preparation for site preparation visit
540	Under preparation for site preparation visit
550	Under preparation for site preparation visit
560	Site Preparation Visit, refresher training before activation
570	Site Preparation Visit done, being prepared for Site Activation
580	Site Preparation Visit done, will have site Initiation Visit in mid of January

Tripod Study Preparation Status

On 21-22 December 2016, the INA-RESPOND Secretariat team [dr. Dewi Lokida (Head of Lab), dr. Anandika (Site Specialist/SS), Ms. Maria Intan (SS), dr. Retna (Protocol Specialist), and Ms. Kanti (Data Management)] went to RSUP Sardjito, Yogjakarta for SPV. On the first day, they had a meeting with dr. Abu Tholib Aman, MSc, PhD, SpMK (K) as the Steering Committee at site and several hospital departments' representatives, as well as the TRIPOD study team members. On the second day, the meeting was attended only by the study team members: dr. Bambang Sigit Riyanto, SpPD K-P, FINASIM (PI), dr. Riat el Kahr and dr Titik Nuryastuti, Msi, PhD, SpMK (Co-PI), dr. Friska Faradina (RA), Ms. Linda Oktabriana and Ms. Clara (LabTech) to discuss more about the study and documents used.

The INA-RESPOND Secretariat team highly appreciated the enthusiasm of site team members during the SPV. Several questions arose and were well-answered during the discussion sessions. Pending documents will be completed immediately since the SIV will be held mid-January 2017.

Latest News:

Not Double, but Triple Threats: Is It True Zika, Dengue, and Chikungunya can come from one bite?

By:

Ms. Maria Intan Josi

A recent study published in 2016 revealed that out of 346 samples, 6 of them had triple infections of Zika, Dengue, and Chikungunya. This fact attracted interest since these viral infections shared almost similar common clinical symptoms (Fig.1).

The viruses are transmitted by *Aedes* mosquitos and co-circulate in many geographical regions. *Aedes aegypti* are well-known for transmitting Zika, Dengue and Chikungunya, whilst *Aedes albopictus* can take part in Zika's spread. Zika and Dengue are closely related flaviviruses, while Chikungunya is an alphavirus from the family of Togaviridae.

The study demonstrated that out of 263 positive subjects, there were 192 cases of mono infection and 71 cases of co-infections of 2 or 3 viruses. (Fig.2). Quantitation of viremia with rRT-PCR were performed in each of those cases. The mean quantifiable viremia in mono infections are significantly higher than the viremia of the same virus in the coinfections group. In some cases of Dengue and Chikungunya co-infections, high level viremias were interfered with the detection of low level Zika viremia. This suggest that triple infections cannot be ruled out and might have been missed in Dengue and Chikungunya coinfections.

An intriguing work by scientists from Colorado State University tested what happens in *Aedes* mosquitoes if they encountered more than one viruses at the same time. In the experiment, the scientists allowed mosquitoes to feed on blood that contained Dengue, Chikungunya, and Zika, either alone or in combination. The tests showed strong evidence that the mosquitoes can pick up and transmit Zika and Chikungunya simultaneously. Previous laboratory study also found that *Aedes* mosquitoes can carry Dengue and Chikungunya simultaneously. However, it is still not clear whether the mosquitoes can carry all three viruses at the same time.

The chances for mosquitoes to encounter more than one of these viruses seem to be increasing as a study in Nicaragua found out that one in five patients, tested positive for Dengue, Chikungunya, or Zika,

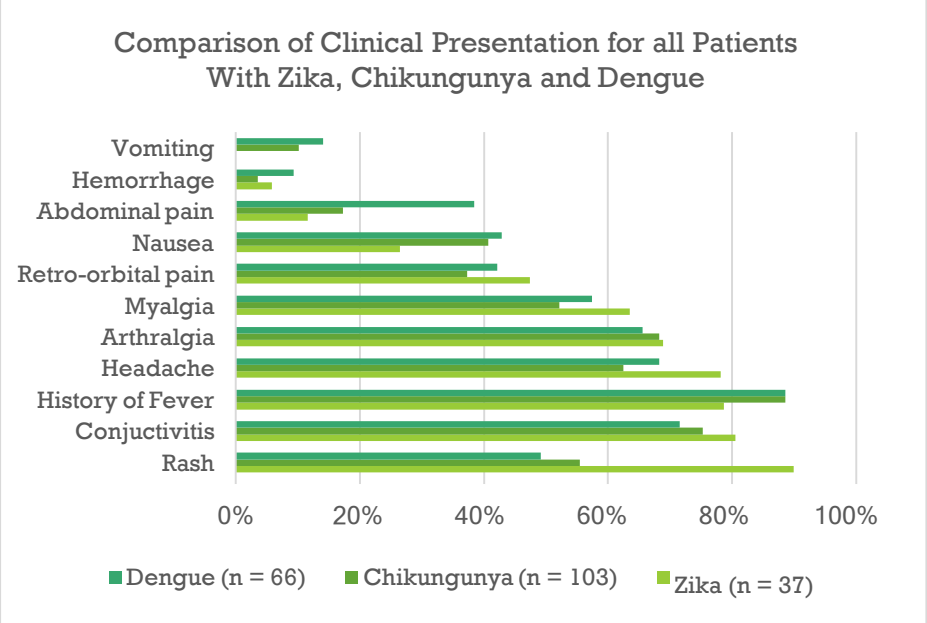

Fig. 1 Comparison of Clinical Presentation for All Patients with Zika, Chikungunya, and Dengue

also had a co-infection with at least one of the other two diseases. Some even tested positive for all three.

Scientists are preparing the tools for diagnosing the three viruses simultaneously. They developed and evaluated a single reaction, multiplex real-time reverse transcription PCR for these viruses in patient's samples from Nicaragua. By using this assay, the viruses can be detected and differentiated during the acute phase of illness. They run the assay for molecular and quantification tests for all 3 viruses. This could be a good news since

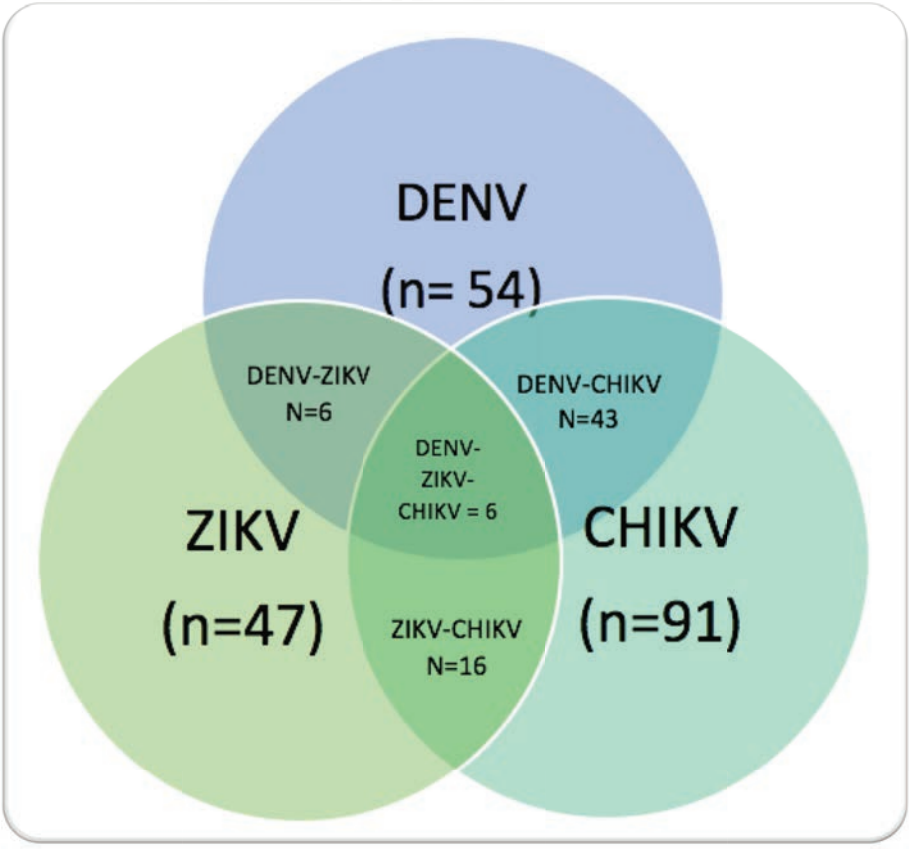

Fig. 2 Assay Results for 346 patients with suspected Zika (ZIKV) Virus. Chikungunya (CHIKV) Virus and/or Dengue (DENV) Virus Infections

"Their saliva is clearly testing positive for both, which could mean that people bitten by this type of mosquito could be infected by both viruses at once. Yet, we need to understand more about what happens in both mosquitoes and people when all the viruses are circulating in close proximity. "

(Claudia Ruckert, PhD-presented at ASTMH meeting)

we know that triple-virus co-infections cases can emerge in the future.

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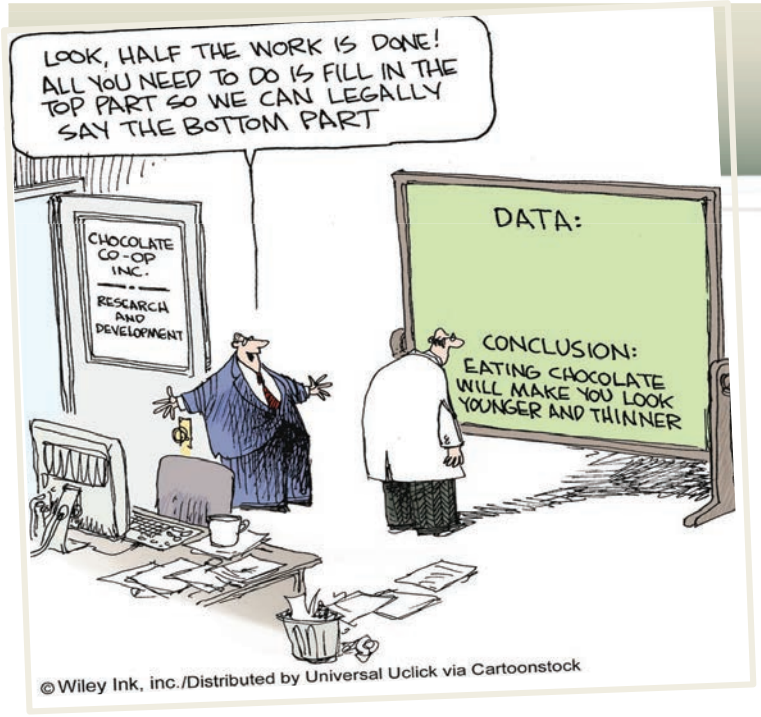

Comic Corner

Hiding Behind the Shadow: Conflict of Interest –How Can We See You?

By:

dr. Aly Diana

I think the cartoon above is funny. Yes.., I am hopeful that chocolate can make me look younger and thinner – who doesn't?

We have to admit that sometimes we believe, often without any doubts, that our hypothesis will apparently become our conclusion. This practice is very common, but the common thing does not always mean the right one. Research should be opened to the options of accepting or rejecting the hypothesis (if the study has one), despite of our preference/belief. So, all studies have their own rights to be proven wrong (rejected) or correct (accepted). This is the nature of research.

A minute later, I saw the writing on the door: "Chocolate Co-Op Inc. – Research and Development". Apparently, this is not only about bad researchers who jump into conclusion but also about conflict of interest, which by definition, "… *is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.*" Although the definition seems quite simple, the application is actually quite complicated. To give you an idea about how complicated the issue is, Institute of Medicine (IOM) has published a book, 436 pages in total, to discuss about "Conflict of Interest in Medical Research, Education, and Practice". Considering the complexity, however, most of us maybe spend less than 5 minutes to make this strong statement in our article: "Potential Conflict Of Interest**:** The authors have indicated they have no potential conflicts of interest to disclose."

Is it true that there isn't any conflict of interests? Are we being honest or are we bending the truth with our unknowledgeable mind? Financial issues usually become the most sensitive and obvious conflicts; for example, when the researcher conduct research following request from companies/industries, obtain financial advantages highly related to the results of study, or delay/restrict negative results to be published because of commercial reasons. Also, there are many other forms of conflicts, such as scientific integrity, patient safety, and investigator objectivity. Here, bias might creep in not only to influence the research questions and the methods, but also to affect the collection, statistical analysis, interpretation, and reporting of the data. It is in the clinical setting that bias and loss of objectivity not only can damage the entire research, but can also lead to injury and harm to study participants.

Although we try our best to avoid it, conflict of interest may still exist. Generally, the policies were made not to prevent authors with significant conflicts from publishing a paper, but mainly to provide readers with information to make their own judgments. However, whether a specific journal takes into account the declaration about conflict of interests in its review process depends on the journal's policies, yet declaring conflict of interests is a must and it is a part of our moral obligations.

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HIV Cure: Strategies and Recent Advances

By

dr. Dona Arlinda

Since it was first discovered over three decades ago, more than 70 million people worldwide have been infected with HIV. Although antiretroviral therapy (ART) showed great effectiveness in keeping the virus from multiplying, people living with HIV are deemed to take life-long medications and withstand the adverse effects. Is it possible to end or to cure HIV? This question has intrigued scientists for many years. Broadly, researches addressing this issue are either going towards sterilising cure or functional cure. A sterilising cure or viral eradication is complete elimination of the virus as well as clearing HIV cellular and anatomical reservoirs in the body. Functional cure or sustained viral remission is a state of long-term undetectable viral load (HIV RNA <50 copies/mL plasma) without use of ART.[1]

The Berlin patient was a remarkable example of sterilising cure documented in 2008. A 40-year-old male with ten years' history of HIV-1 infection and four years course of highly active antiretroviral therapy (HAART) without any AIDS-associated illnesses. The man was newly diagnosed with acute myeloid leukemia and underwent total ablative chemotherapy, radiation therapy, and stem-cell transplantation from a donor with a homozygous defect in CCR5, a CD4+ T cells coreceptor greatly needed for HIV entry. The defect essentially provides protection against HIV-1 acquisition, or in other words, CD4+ T cells are somewhat "resistant" to HIV infection. The patient was virus-free 20 months after the transplantation and discontinuation of HAART. RNA and proviral DNA PCR assays failed to detect HIV-1 virus in his peripheral blood, bone marrow, or rectal mucosa. Five years after, he remained off-ART with no detectable viremia using standard assays. He also has waning HIV antibody levels, limited to undetectable HIV-specific T-cell responses, and has no evidence of HIV-related immunologic progression.[2,3]

The second case was an example of functional cure reported in 2013. In 2010, a woman with HIV-1 infection without history of prenatal care had a spontaneous vaginal delivery at 35 weeks of gestation before antiretroviral prophylaxis was given. The infant was considered at high risk of exposure. A positive HIV-1 DNA in peripheral-blood mononuclear cells at 30 hours after birth and HIV-1 RNA (19,812 copies/mL) at 31 hours confirmed in-utero infection. Antiretroviral therapy was initiated 30 hours after birth and was discontinued when she reached 18 months of age. Plasma level of HIV-1 RNA was undetected during follow up at 23 and 24 months of age. A repeated HIV-1 DNA PCR assay and HIV-1 antibody test at aged 24 months revealed negative results. At 30 months of age, plasma level of HIV-1 RNA remained undetected with standard assays. Circulating HIV-1 antibodies was also undetected and positive CD4 T-cell percentages were within or exceeded normal range for age at all time points tested. Sadly, in 2014, her remission period ended and she was declared of having detectable levels of HIV.[4]

Cellular and anatomical reservoirs hold major contribution to the mechanism of HIV persistence. Looking at the dynamics of viremia in HIV positive individuals on ART (Fig. 1), patients are able to reach undetectable viral load (HIV RNA <50 copies/mL plasma) after more than two years of ART. However, on that constant third phase of viremia, a low-level residual viral replication (HIV RNA 1-5 copies/mL plasma) is consistently detected with ultrasensitive RT-PCR assays in most patients despite years of ART. This phenomenon has been extensively studied and several theories have been imposed. It seemed that low level residual viremia is the result from a low degree of ongoing cycles of viral replication (either in the presence of ART or in anatomical reservoirs where drug penetration is hindered such as the central nervous

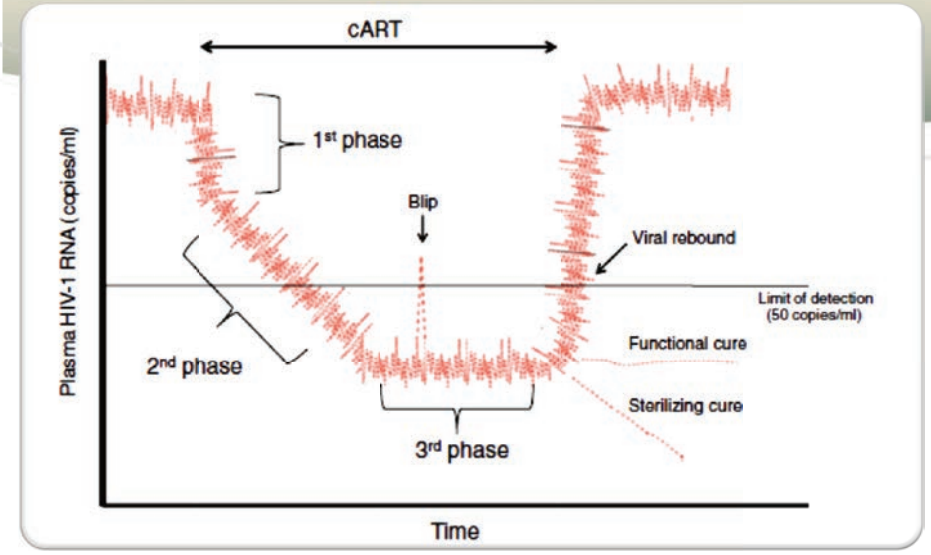

Fig 3. The dynamics of viremia in HIV positive individuals on ART (Source: Retrovirology, 2013)

system, gut mucosa, genital tract, and lymph nodes), and/or reactivation of viral expression from latently infected resting CD4+ T cells which produce replication-competent proviruses), and/or the release of virus from other stable reservoirs. Latently infected resting memory CD4+ T cells are the most studied HIV cellular reservoir that are able to produce replication-competent viruses. Activation of these cells could also responsible for the inevitable and abrupt viral rebound or relapse after ART cessation.[5,6]

It is generally agreed that multiple agents and approaches are needed to attain HIV cure. The concept of research toward sterilising cure is to eradicate HIV reservoir by inducing viral replication in latently infected cells so they may express HIV proteins, and then an enhanced-immune system or other agents can identify and destroy those cells. Whilst in functional cure, the main idea is to control viral rebound after ART cessation or prolonging the state of viral suppression with the absence of, or at least lesser use of ART.

Studies on reversing latency and destroying HIV reservoirs has been difficult because latently infected cells are rare (1 per million resting CD4+ T cells) and assays measuring the size of latent reservoirs have limitations. In addition, it is very difficult to distinguish latently infected cells from normal uninfected cells. Some promising reversing agents such as disulfiram and histone deacetylase inhibitors (vorinostat and romidepsin) are being investigated in several studies. After reactivation, infected resting CD4+ T cells should be killed efficiently to ensure reservoir eradication. In 2015, a bispecific T-cell engager (BITE) called VRC07-aCD3 was developed at the NIAID. This protein attaches one arm to an infected CD4+ T-cell and prompting that cell to express HIV proteins. The other arm of VRC07-aCD3 then binds to these proteins and present it to a killer T-cell to do its job. Stem cell transplantation and gene therapy such that employed in the Berlin patient is a promising strategy but the procedure is very aggressive and may not easily work on other patients. Gene editing therapy to modify CCR5, a CD4+ T cells coreceptor needed for HIV entry, is another promising strategy to make T-cells somewhat "resistant" to HIV but still need further evaluation on its safety.[7-10]

There has been much breakthrough on methods controlling viral rebound after ART cessation. Optimizing ART by adding long-acting agents is a great strategy, in addition to initiation of early ART (hopefully before latent infection and HIV reservoir are established) such that employed to the infant in 2010. Immunotherapies with passive transfer of broadly neutralizing antibodies is the direction pursued by scientists at the NIAID. In 2016, they found that a CD4-binding site (CD4bs) antibody called N6 was able to neutralize 98% of HIV isolates tested, including 16 of 20 strains resistant to other antibodies of the same class. N6 and the other members of CD4bs antibody such as VRC01, VRC27, 3BNC117, and VRC07-523-LS are being investigated thoroughly on their tolerance to HIV mutations, so far N6 showed great potency. Another promising pathway is through directing monoclonal antibody against gut-homing integrin, called α4β7, which is a homing molecule on CD4+ T cells that allow them to go to or remain in the gut. Interestingly in animal study, infusion of antibody against α4β7 leads to decreased plasma and gastrointestinal tissue viral loads.[11-13]

In summary, studies on HIV cure demonstrate remarkable progress over the last few years. Functional cure or sustained viral remission is a more feasible and realistic goal of researches on HIV cure. Several promising proofs of concept are available, but none is ready for widespread clinical application. Multiple combined approaches will be needed, as well as multidisciplinary approach that includes basic virologists, immunologists, clinicians, pharmacologists and the infected community.

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INA-RESPOND Newsletter

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Thanks to : INA-RESPOND Network and Partners

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