Since its emergence in 1981, the HIV/AIDS pandemic has exerted a major toll on humanity with 39 million deaths worldwide. In 2016, 39.7 million people were infected with HIV, 1 million died and about 1.8 million were newly infected. Despite decades of research, there is no cure or vaccine; anti-retroviral therapy (ART) that suppresses viral replication remains the only option to prevent the outbreak of AIDS and death.

HIV poses a considerable challenge for developing a cure or vaccine as the virus inscribes its genome into the DNA of immune cells where it can stay quiescent for months or years. This reservoir of infected cells—that are invisible to the immune system—causes persistent infection that slowly depletes the immune system to cause AIDS and eventually death. A major focus of research is therefore on developing vaccines to prevent infection and on destroying the reservoir to cure the disease.

In his keynote talk, Nelson Michael reviewed the results from vaccine trials including the Ad26/MVA vaccine to treat both acute and latent infection. Animal studies showed that early treatment with this vaccine in combination with ART can drastically reduce acute infection. Ad26/MVA is now being tested for so-called ‘kick and kill’ latency reversal therapies that awaken and destroy quiescent reservoir cells.

Louis Picker’s presentation focused on the role of CD8+ immune cells in controlling cells infected with SIV (simian immunodeficiency virus, the animal precursor of HIV) and the efficacy of a RhCMV...
vaccine to treat acute and latent infection in nonhuman primates. Animal experiments showed that the vaccine creates a strong CD8+ immune response during early treatment, which is not enough, however, to destroy infected cells during latent infection.

Some patients develop broad neutralizing antibodies (bnAbs) that protect against a wide variety of viral strains and mutations. William Schief’s group attempts to generate such bnAbs through sequential vaccination with engineered forms of the viral envelope protein.

Michael Farzan presented their work on engineered proteins that block HIV from entering its target cells. They use a viral vector to transfer the gene encoding the engineered protein into muscle cells to enable its sustained production.

David Margolis described the results of kick and kill approaches by which quiescent infected cells are repeatedly activated with the aim of reducing the viral reservoir. Studies in patients showed promising results, but it will require new approaches to better stimulate immune cells to attack active, infected cells.

Olivier Schwartz’s group found that antibodies against CD32, a surface marker of infected cells, are able to bind to latently infected cells and could be used for latency reversal therapy.

Christine Kunze described the use of CRISPR/Cas to inactivate the viral genome in astrocytes, a main reservoir cells in the brain. While it keeps infected cells alive and reduces HIV expression, it is not sufficient to fully block the virus from reactivating.

To improve latency reversal therapies, it is necessary to better understand how and where the virus persists. In patients treated with ART, lymph nodes are the major reservoir of infected cells as the drugs cannot penetrate the nodes in sufficient concentration to completely suppress viral replication. In his keynote presentation, Steven Wolinsky presented genomic analysis and computational modeling of HIV evolution during ART, demonstrating that while ART eliminates HIV replication in the
blood, it does not fully arrest viral replication and mutation in lymphoid tissue. This rate of replication, however, is insufficient to develop resistance to ART.

Victor Garcia’s group developed a humanized mouse model of HIV infection to study the efficacy of therapies and viral persistence in different tissues and cell types. It revealed that macrophages are a main reservoir of HIV in the brain. Another important locus of HIV persistence are lymph nodes in the gut. John Thornhill showed that viral replication and immune responses in gut tissues are distinct at different sites in the intestinal tract.

Mathias Lichterfeld studies how HIV evolves from primary infection to latent persistence using full-genome sequencing. While the viral reservoir remains relatively stable during ART, proteomic analysis revealed that drugs stimulating viral reactivation can improve survival and proliferation of latently infected cells, complementing shock and kill strategies against the viral reservoir.

Nicolas Huot’s research on monkeys that are naturally able to tolerate infection with SIV, without developing AIDS, showed that immune cells known as NK cells migrate into reservoir tissues where they suppress SIV replication. Therapies to treat latent infection require reliable methods to quantify the size of the reservoir. Christine Rouzioux and Bonnie Howell described assays to measure viral DNA and protein respectively to determine viral load in patients and predict disease progression.

Studying early acute infection to understand how HIV infects its target cells and the immune system’s countermeasures could help to improve first-line therapies to prevent infection. Persephone Borrow discussed the role of interferon (IFN)-mediated immune response to HIV infection, which only few viral strains survive. After infecting its target cells, the virus rapidly loses its IFN resistance, but slowly regains it during latent infection.

The first target of HIV are pathogen-sensing dendritic cells; upon infection, the virus suppresses their ability to trigger an immune response. In contrast, Langerhans cells—a subset of dendritic cells—
efficiently destroy the virus. Teunis Geijtenbeek explained the mechanism of dendritic cells’ vulnerability to HIV and how the unique Langerin receptor protects Langerhans cells.

Shariq Usmani uses intravital microscopy in a mouse model of HIV to study the balance between viral infectivity and dissemination. He showed that the viral protein Nef is needed to establish latent infection, but first encumbers dissemination by slowing down the movement of infected cells.

Frank Kirchhoff described the evolution of SIV to HIV as it moved from monkeys to great apes and to humans. Most of the viral countermeasures against the human immune system were already fully evolved when SIV jumped from monkeys to gorillas and orangutans, even before it was able to infect humans.

Understanding the immune system’s role in HIV persistence—particularly in patients who are able to suppress the virus without ART—can also inspire novel therapeutic strategies. Eli Boritz presented his results studying these controllers, which show that the virus replicates and evolves only in the lymph nodes; infected cells that escape into the blood stream remain quiescent.

Marcus Altfeld’s research identified specific surface markers by which NK immune cells recognize HIV-infected cells. These insights could help to improve the efficiency of latency reversal therapies to kill reactivated infected cells.

While ART efficiently suppresses the virus, there are concerns about the long-term safety of these drugs. Hendrik Streeck presented findings from patient cohorts from Germany and the USA indicating that two cause T lymphocyte loss over time by damaging their mitochondria. Since these drugs are commonly used in ART, this could have severe consequences for long-term therapy.

ART requires ‘analytical treatment interruption’ (ATI) to let the virus rebound so as to optimize treatment. Brenda Salantes studied viral diversity before and after ATI to assess whether it increases the risk of resistance; her results show that although the number of viruses increases, the probability of resistance to ART does not.
Epidemiological and clinical studies can also inform preventive and therapeutic strategies. **Penny Moore** analyzes patients who became infected more than once, whether they are more likely to generate bNAbs. Her research shows that superinfection triggers de novo responses by the immune system rather than boosting existing Abs to evolve into bnAbs. This has implications for serial vaccination as a possible strategy to generate bNAbs.

**Anne Goldfeld** presented her work in Cambodia with AIDS patients who were co-infected with tuberculosis, the major cause of death due to AIDS. Starting ART early during anti-tuberculosis treatment restored their immune response and drastically reduced mortality.

**Jo-Ann Passmore’s** studies in South Africa show that genital tract infection drastically increases the risk of HIV infection in young women. Bacterial infections not only attract HIV’s target cells to the vaginal mucosa but also diminish the efficiency of vaginal microbicides used to protect against the virus during intercourse.

Given the lack of efficient vaccines or a cure, further research into HIV biology and epidemiology, and the immune response in monkeys and humans is sorely needed to improve existing therapies and inspire novel therapeutic and preventive approaches.

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