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REVIEW ARTICLE

What's Hot in HIV in 2019—A Basic and Translational Science Summary for Clinicians From IDWeek 2019

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The field of HIV research is constantly evolving, and every year brings advances that draw us closer to ending the HIV epidemic. Here, we present a nonexhaustive overview of select notable studies in HIV prevention, cure, and treatment, published in the last year as presented at IDWeek 2019: What's Hot in HIV Basic Science. The past year brought interesting results on the use of broadly neutralizing antibodies for treatment and prevention, gene-editing approaches to HIV cure, and new ways to measure the HIV reservoir. We also saw encouraging results on novel HIV vaccine delivery strategies and how these may influence effective immune responses. Lastly, in the area of inflammation, some mechanistic insights were made into the contribution of cotrimoxazole prophylaxis and potential new targets to reduce HIV-associated chronic inflammation. The future from where we stand is bright for HIV research, with much more to look forward to in 2020.

Keywords. HIV; updates; translational research; clinicians.

Advances in HIV research paint an optimistic future for new strategies to combat HIV and AIDS. This review, targeted for clinicians, presents a nonexhaustive overview of selected HIV basic science studies spanning a 12-month period between October 2018 and October 2019. We highlight the research areas of HIV prevention, cure, and treatment adapted from a presentation delivered at IDWeek 2019: "What"s Hot in HIV Basic Science Research (featured studies summarized in Figure 1)." Of note, the articles included were subjectively selected based on their clinical relevance as determined by the authors.

HIV Prevention

A safe and efficacious vaccine to prevent HIV remains elusive. Traditional approaches to vaccine development have been ineffective, with the notable exception of the RV144 trial in Thailand, which showed modest prevention efficacy with a canary pox vector vaccine plus gp120 protein boost [1]. Follow-up studies of a similar vaccine regimen are ongoing in Sub-Saharan Africa (HVTN 702) [2]. Clinical trials and proof-of-concept studies in nonhuman primates (NHPs) have provided useful insights into a range of potential alternative approaches to protect against HIV infection. These include passive immunization with broadly neutralizing antibodies (bNAbs), non-neutralizing antibodies targeting the V1and V1 regions of the HIV envelope, polyfunctional HIV-specific antibodies [3], and the generation of envelope-specific T-cell responses (reviewed in [4]).

Early Human Trials of Engineered Monoclonal Antibody

Antibodies with longer half-life and broad neutralization capacity will be most practical for clinical implementation. Through bioengineering, scientists are making changes in the currently available bNAbs, cloned directly from HIV-positive individuals, to improve their effectiveness and practicality for clinical delivery. Gaudinski et al. reported on the first-in-human open-label trial assessing the safety of the VRC07-523LS engineered antibody, which has been genetically altered to prolong the half-life of the existing VRC07 antibody [5]. VRC07-523LS showed broader neutralization at lower serum concentrations and a half-life that was 4-fold longer than that of earlier-generation bNAbs, VRC01, and VRC01LS and maintained virologic suppression for 6–12 months in individuals harboring sensitive viruses. Infusions were safe, with participants reporting mild and moderate reactions with both intravenous (IV) and subcutaneous (SC) administration. The elimination half-life was 38 days for IV and 33 days for SC administration, suggesting that repeated dosing would be required. This study highlights the safety of engineered monoclonal antibodies targeting HIV-1 in humans and supports the development of engineered bNAbs with prolonged dosing and improved breadth.

Adeno-Associated Virus Vectors for Delivering HIV-Specific Antibodies to Prevent Infection

Gardner et al. designed an entry inhibitor, eCD4-Ig, which they tested in an NHP model as a preventative strategy against

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SIV infection [6]. This entry inhibitor is a fusion protein that incorporates domains 1 and 2 of human CD4 with a sulfated CCR5 mimicking protein. As a result, the fusion protein is capable of binding both the CD4 and co-receptor binding sites on the HIV-1 and SIV-1 envelope, thus preventing infection. In this study, a recombinant adeno-associated virus vector (AAV) was used to enable long-term expression and systemic delivery of eCD4-Ig. Using AAV can bypass the need for repeated bNAb infusions as the inoculated transgene persists as an unintegrated episome and continues to express the protein of interest (ie, eCD4-Ig) for years. The authors were able to show complete protection against SIVmac239 challenge in rhesus macaques with this approach. Macaques challenged with escalating inoculums of virus eventually succumbed to infection, and eCD4-Ig provided selective pressure for mutations in the virus envelope protein. Nonetheless, safety concerns associated with using adenovirus vectors for delivery included the lack of an "off-switch" and the development of antidrug antibodies over time [7].

Translating bNAb-based prevention strategies to broad clinical use presents several challenges that will need to be considered in order to clearly define their utility in the prevention and treatment space. Suboptimal efficacy of bNabs in blocking cell-to-cell virus transmission has been described [8], their impact on the viral reservoir is not fully understood, frequent emergence of resistance and rebound viremia have been reported in treatment studies [9], and cost-effectiveness of these interventions could limit their scalability.

Alternative Immunization Strategies

Mucosal transmission is the predominant mode of HIV-1 acquisition; thus vaccination strategies that elicit robust immune responses at the mucosal interface are highly attractive for HIV prevention. Jones et al. explored needle-free sublingual (SL) and buccal (B) delivery of a modified vaccinia ankara (MVA) and recombinant gp120–based HIV vaccine with mucosal adjuvant dmLT to protect rhesus macaques from SHIV rectal challenge [10].

Mucosal vaccination generated strong vaccine-specific IgG and IgA responses in serum, rectal, vaginal, and salivary secretions, as well as comparably robust vaccine-specific CD8/CD4 cellular responses. This immune response was broadly neutralizing against several HIV-1 clades, a feature that is highly desirable for any vaccine candidate against a highly diverse HIV-1. They further showed that this immune response provided some degree of protection against SHIV in rhesus macaques with rectal challenge given 19 weeks after administration of the second booster. Needle-free mucosal vaccination, but not topical vaccination, led to a significant delay in the acquisition of infection with SHIV in vaccinated animals compared with unvaccinated controls.

This study provides proof of concept that needle-free mucosal delivery of an HIV-1 vaccine candidate can generate protective systemic and mucosal vaccine-specific immune responses. The mechanisms by which this approach elicits such responses remain incompletely understood. The authors used a fairly intense vaccination protocol including immunization at 2 separate time points as well as 2 boosters, raising the issue of the practicality and acceptability of this approach in humans. Further studies to improve the durability of the mucosal response to elicit long-term protection are needed.

In a preclinical NHP model, Cirelli et al. compared 3 immunization strategies to deliver a soluble native-like Env trimer vaccine (BG505 Olio6$_{CD4ko}$ protein) in a saponin adjuvant [11]. A traditional bolus subcutaneous dosing approach was compared with 2 slow delivery approaches: (1) slow release via an implantable nonmechanical osmotic pump and (2) an incremental subcutaneous dosing approach. The slow release strategies led to improved B-cell germinal center and T-follicular helper cell responses as well as enhanced nAb responses. The significant differences in immune responses with different vaccine delivery strategies suggest that how the immune system sees the antigen is an important consideration in its ability to mount an effective response. The slow vaccine delivery kept B cells activated for longer and extended the window for these cells to interact with T-follicular helper cells, resulting in generation of antibodies with improved binding and neutralizing qualities.

Osmotic pumps have been used effectively for medication delivery in clinical practice [12] but are impractical for large-scale vaccination. Multiple SC injections also present logistical challenges that need to be addressed before moving to human trials. It is important to note that while slow delivery enhanced and improved the diversity of the immune response, the immune responses in "slow-immunized" animals were still targeted toward non-neutralizing HIV epitopes. Additional work to optimize immunogens and focus the response toward neutralizing epitopes is needed.

HIV Cure

Through the years, we have gained considerable understanding of how HIV establishes latent reservoirs within the host and persists in the presence of suppressive antiretroviral therapy (ART). HIV latency is the integration of replication-competent intact virus into the host genome in the absence of virus production [13]. Attempts to perturb and eliminate the viral reservoir to effect cure or durable remission have been unsuccessful. Current approaches in HIV cure research (reviewed in [13]) focus on 3 main areas—targeting HIV replication, enhancing the HIV-specific immune response, and immune modulation. These strategies face considerable barriers such as fully defining and adequately measuring all tissue reservoirs of virus, proliferation of latently infected cells, and residual viral replication in sanctuary sites [13]. In HIV cure research, proof-of-concept studies using novel combination strategies to reduce

and eliminate the viral reservoir are emerging, as are methods of accurately quantifying the virus reservoir.

Gene Editing and Enhanced Drug Delivery

Using a humanized mouse model, Dash et al. combined long-acting slow effective release antiretroviral therapy, termed LASER-ART, with excision of HIV-1 proviral DNA using the Clustered Regularly Interspaced Short Palindromic Repeats–associated protein 9 (CRISPSR-Cas9) gene-editing system delivered by AAV_9 [14] as a cure approach. LASER-ART is a delivery strategy for ART that enhances durable suppression of viral replication by slow delivery of long-acting lipophilic antiviral nano-particles, thus significantly reducing integrated proviral DNA [15].

In 2/7 infected mice treated with combined LASER-ART and CRISPR-Cas9, no virologic rebound was observed and HIV was not detected in any of the animal tissues. No off-target effects were noted in this study, an important barrier to the success of gene-editing interventions, providing support for the potential safety of this approach. Although useful for research purposes, the applicability of results from humanized mouse models to human biology is unclear. Furthermore, editing a highly diverse HIV proviral reservoir, as seen in chronic HIV infection in humans, using a CRISPR-cas9 approach presents a challenge that is not fully captured by the animal model of early infection and treatment used in this study.

Xu and colleagues demonstrated promising clinical feasibility for another CRISPR-Cas9 gene-editing approach to HIV cure in a single patient [16]. They reported on a 27-year-old man with acute lymphoblastic leukemia (ALL) and HIV-1 infection who was treated with 6 rounds of ALL-targeted chemotherapy and allogeneic human stem cell transplant (HSCT) with CRISPR-edited stem cells to disrupt the CCR5 gene. CRISPR-edited human primary stem cells (HPSCs) successfully engrafted and differentiated into multiple lineages, leading to disease-free remission from ALL for 19 months. After infusion and engraftment, CCR5 disruption was detected in 5.2%–8.28% of bone marrow cells and persisted during remission. No gene-editing-related adverse or off-target events were identified. This report demonstrates that transplantation and long-term engraftment of CRISPR-edited allogeneic HPSCs can be achieved; however, the efficiency and durability of the CCR5-edited cells were not sufficient to cure HIV-1 infection. Most importantly, it demonstrates that improved gene editing could be a viable approach for HIV cure. The scalability and potential toxicities of CRISPR-Cas9 and stem cell transplant–based therapies in humans present important cost and ethical considerations, which may limit their applicability for broad clinical use.

CAR-T Cell Therapy

Chimeric antigen receptor T (CAR-T) cells have revolutionized treatment of some B-cell malignancies [17]. In cancer therapy, T cells are derived from the patient and genetically altered ex vivo to give them new properties. The technique involves introducing a gene for a type of receptor that binds only to proteins found in cancer cells, thereby allowing the T cells to specifically target these cancer cells once re-infused into the patient. Anti-HIV CAR T cells have been studied for HIV-1 treatment and cure, with limited success. In some instances, the CAR-T cells themselves were noted to have enhanced susceptibility to HIV infection with limited efficiency in their ability to control viremia and eradicate infection (reviewed in [18]).

Anthony-Gonda et al. took an updated approach to designing anti-HIV CAR T cells by engineering the chimeric cells to express 2 receptors (duo-CAR-T) [19]. Instead of altering the T cells to use the CD4 receptor as a CAR-targeting site, this approach allows multiple sites on the HIV envelope to be targeted. The 2 molecules used were identified by developing >40 lentiviral vectors and screening them to choose the most effective ones. Duo-CAR T cells eliminated 99% of 11 strains of HIV-infected human immune cells, and in a humanized mouse model of infection, they suppressed virus replication by 97% after 1 week of therapy [19]. Duo-CAR T cells were resistant to infection with HIV, improving on earlier generations of anti-HIV CAR T therapies. Although a promising concept, additional animal data and, eventually, clinical trials in humans will be necessary to confirm the CAR-T approach as a viable strategy to cure HIV.

Rituximab for Reducing the HIV Reservoir

Serra-Peinado et al. investigated the utility of the anti-CD20 antibody rituximab in reducing the HIV reservoir [20]. The authors showed that a significant minority subset of HIV RNA + CD4 T cells express the CD20 marker, which is a typical B-cell marker not classically thought to be expressed on T cells. Rituximab was able to deplete these cells from PMBCs derived from HIV-positive donors. They also studied 3 HIV-positive individuals receiving rituximab therapy for non-malignancy-related indications and found that in these persons rituximab led to significant reductions in HIV RNA [20]. The CD20+ subset of T cells also expanded with latency-reactivating agents (LRAs), such as romidepsin. These findings suggest that rituximab could be a useful intervention in combination with other LRAs, as the ability of rituximab to deplete HIV-1 RNA in CD4 cells was directly correlated with HIV reactivation [20]. Rituximab use is associated with increased risk for infections [21], a non-negligible factor that needs to be considered if it is to be considered for broad use in future cure strategies.

Measuring the HIV Virus Reservoir

To appropriately evaluate HIV cure interventions, the development of scalable assays to accurately quantify the viral reservoir and its depletion is critical. The HIV reservoir has an estimated half-life of 44 months and has previously been defined

by quantitative viral outgrowth assays (QVOAs) for cells that release infectious virus after 1 round of T-cell activation [22]. These assays tend to underestimate the size of the reservoir, as 1 round of activation may not induce all latent proviruses. Simpler polymerase chain reaction (PCR)–based methods that quantify all of the proviral DNA regardless of transcriptional status have also been used, but their clinical relevance is limited, as a vast majority of integrated proviruses detected by DNA PCR are defective [23].

Bruner et al. analyzed 431 near full-genome sequences (nFGS) of HIV-1 DNA derived from 28 adults with HIV-1 infection and mapped out deletions and lethal mutations. They then developed an intact proviral DNA assay (IPDA) algorithm using strategically placed DNA probes that distinguished proviruses with deletions or multiple mutations from intact proviruses. The authors showed that there was a difference in the decay dynamics of defective proviruses compared with intact proviruses capable of causing virologic rebound. IPDA relies on amplification of 2 subgenomic regions that together sample only about 2% of the HIV-1 genome. As a result, this method is also likely to incorrectly categorize a significant fraction of proviruses as intact, thus overestimating the reservoir. Nonetheless, this method has the significant benefit of being scalable for use in large clinical trials.

Goebler et al. described another method to quantify the HIV reservoir: combined quantitative PCR (qPCR) and next-generation sequencing (NGS) methods for a more accurate estimation of the viral reservoir [24]. In their approach, they utilized 4 different qPCR probes covering the packaging signal (PS), group-specific antigen (gag), polymerase (pol), and envelope (env) to screen for intact proviruses followed by NGS to verify the replication competence of these proviruses. Combining qPCR and NGS allows for more sensitive and specific detection of the reservoir. However, this approach is more labor-intensive and less scalable to large studies compared with the IPDA described above [19]. Other notable reservoir studies provided evidence that HIV-1 in lymph nodes is maintained by cellular proliferation [25] and demonstrated preferential accumulation of intact HIV-1 proviruses in distinct chromosomal positions during ART [26].

HIV Treatment

Currently available ART is effective, safe, and better tolerated than ever before. The pipeline for new ART interventions remains rich, as the focus has shifted to designing long-acting agents with reduced frequency of dosing [27], antibody-based treatments, early treatment, and reducing chronic inflammation [28]. bNAbs directed against HIV-1 are being pursued for both HIV prevention and treatment (reviewed in [28]). The characteristics of the bNAbs developed so far greatly differ in terms of the breadth of HIV-1 viruses that they are able to neutralize, their half-life, and other pharmacokinetic properties, which could lead to important differences in clinical outcomes, side effects, and implementation in clinical settings.

Monoclonal and Broadly Neutralizing Antibody Therapies

The humanized monoclonal IgG4 antibody ibalizumab binds to the CD4-extracellular domain 2 and is currently approved for use in highly multidrug-resistant HIV-1 infection [29]. Wang et al. investigated monotherapy with the IgG1 monoclonal antibody UB-421, which competitively binds to CD4 domain 1, blocking virus entry. In an open-label nonrandomized trial including 29 participants who received either 10-mg/kg infusions weekly or 25-mg/kg infusions every 2 weeks for a total of 8 infusions of UB-241, they measured time to viral rebound following analytic treatment interruption (ATI) for up to 16 weeks off ART. UB-421 suppressed viremia in all participants during ATI, with only intermittent viral blips and no plasma virus rebound >400 copeies/mL. Treatment was well tolerated with few adverse events, and CD4 T-cell counts remained stable for the duration of the study [30].

Treating individuals with HIV-1 with infusions of a single bNab delays viral rebound when ART is stopped, but also rapidly selects for resistance to the bNAb [28]. Mendoza et al. evaluated combining 2 bNAbs as a treatment for maintaining long-term virus suppression. They included 11 participants on ART with undetectable HIV viremia [9]. Participants received 3 infusions, spaced 3 weeks apart, of 3BNC117 (binds CD4 binding site on the HIV envelope) and 10–1074 (binds HIV envelope V3 loop and glycans). ART was stopped 2 days after the first infusion. During ATI, dual bNAb therapy maintained long-term virus suppression (>30 weeks) in 2 individuals who had bNAb-sensitive reservoirs. Nine individuals maintained viral suppression for >15 weeks, so long as the concentration of both antibodies in the serum remained above 10 μg/mL. The 2 individuals who had early rebound within 7 weeks were noted to have preexisting resistance to 1 of the bNAbs in the combination. The median time to rebound was 21 weeks, compared with 6–10 weeks noted with bNAb monotherapy in previous studies. HIV resistance rapidly emerged to 10–1074 when serum levels of either antibody declined, though none of the participants who had sensitive reservoirs before the infusions developed resistance to both bNAbs. This study supports combination therapy with bNAbs as a viable strategy for maintaining long-term viral suppression in individuals harboring sensitive viruses.

These 2 studies show that monoclonal and neutralizing antibody-based therapies can durably suppress virus replication; however, delivery requires intravenous infusions or subcutaneous injections. This presents logistical challenges for scalability, especially in resource-limited settings. Development of resistance over time is still a concern, and the ease and tolerability of current oral dosing ART regimens (eg, single-tablet regimens) may remain preferable to many patients and clinicians.

Hyperacute Treatment and T-Cell Function

A study from from the FRESH cohort showed the impact of treating hyperacute HIV infection on anti-HIV T-cell responses

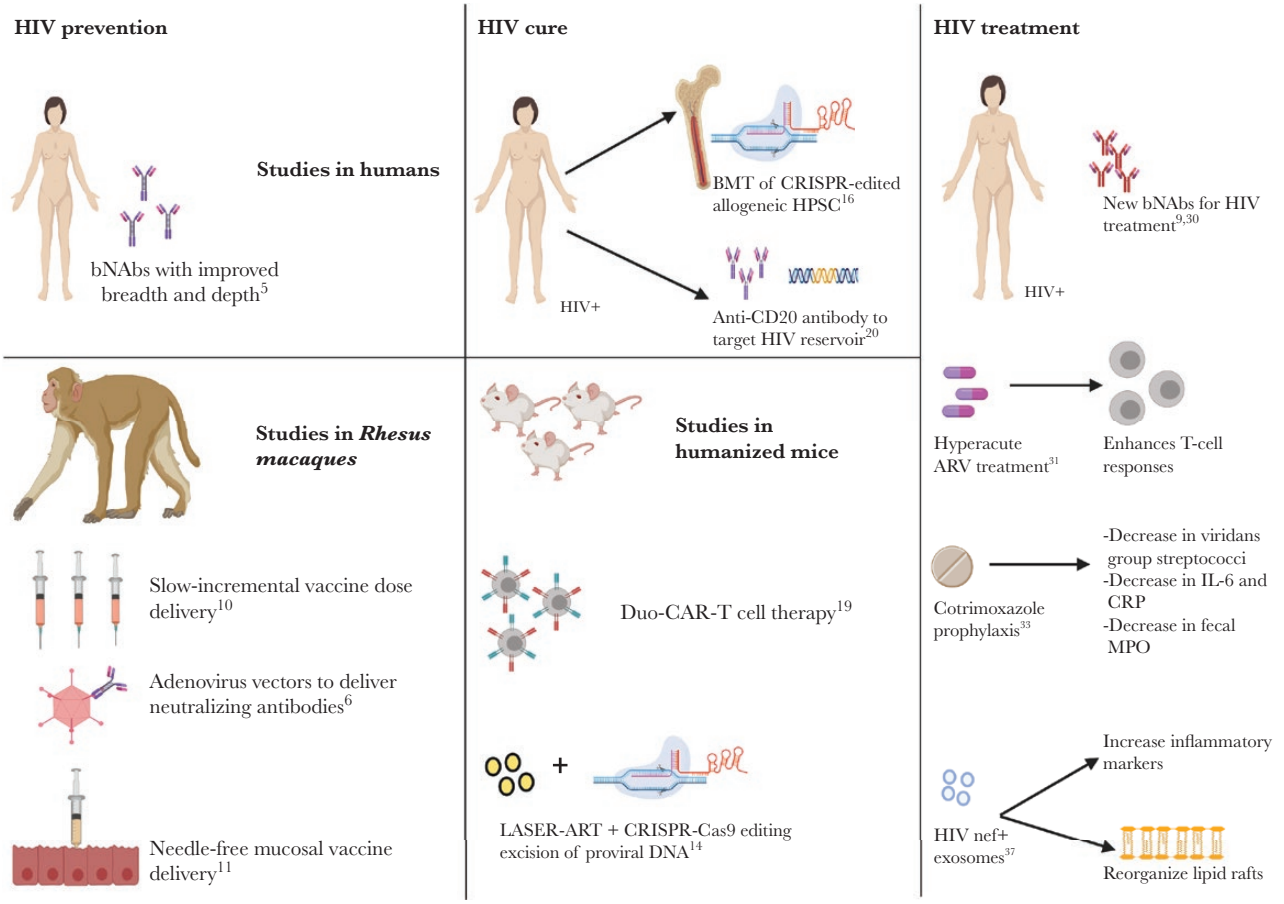

Figure 1. A visual summary of "what's hot" in HIV basic and translational research in 2019—novel advances in prevention, cure, and treatment (created using www.biorender.com software). Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; BMT, bone marrow transplant; bNAbs, broadly neutralizing antibody; CAR, chimeric antigen receptor; CRP, C-reactive protein; HPSC, human primary stem cell; LASER, long-acting slow effective release; MPO, myeloperoxidase.

[31]. Fiebig staging [32] was used to define study participants with hyperacute infection (detectable HIV-RNA but no detectable antibody) and acute infection (detectable HIV-RNA and detectable antibody). Participants received ART within 24–48 hours of diagnosis by detection of HIV-RNA in blood [31], after which functional and transcriptional phenotypes of HIV-specific T-cell responses were evaluated. These were compared with responses in individuals for whom ART was started later (Fiebig stages II and IV) or deferred until CD4 counts dropped <350 cells/mm^3.

Hyperacute ART resulted in reduced immune activation, reduced the size of the HIV reservoir, and improved T-cell (CD4$^+$ and CD8$^+$) functionality in terms of cytolytic activity and cytokine production. These findings have implications for functional cure strategies and show the benefits of identifying and treating hyperacute HIV infection. Nonetheless, in a real-world setting, identifying these individuals can be very challenging.

Targeting Chronic Inflammation and Immune Activation

Even in the setting of suppressive ART, residual inflammation is independently associated with increased morbidity and mortality [33]. Interventions that target inflammation may provide additional benefits to the treatment of persons with HIV-1 [34]. Bourke et al. hypothesized that cotrimoxazole prophylaxis improves HIV-1 morbidity and mortality by reducing inflammation [35]. They tested this in a substudy of the ARROW trial to determine the mechanisms of improved outcomes in children with HIV-1 receiving cotrimoxazole prophylaxis [36]. They noted reductions of systemic C-reactive protein and interleukin (IL)-6 in children randomized to continue cotrimoxazole prophylaxis compared with children in whom prophylaxis was discontinued. They also observed that reductions in *viridans* group streptococci seen in the stool of partcipants receiving prophylaxis correlated with lower fecal myeloperoxidase (MPO), a biomarker of mucosal leukocyte activity. These findings suggest that cotrimoxazole reduced systemic and mucosal inflammation, which could explain the clinical benefits in children who continued prophylaxis.

Mukhamedova et al. examined exosomes, extracellular vesicles secreted by HIV-infected cells, containing the HIV-1 protein Nef as a potential driver of inflammation in chronic HIV infection [37]. They found that Nef exosomes affect

cholesterol metabolism and trigger inflammation in uninfected bystander cells. Cells treated with Nef exosomes also exhibited increased production of the pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha. These findings demonstrate that a single viral protein released from infected cells into circulation may trigger a range of pathogenic effects and present a potential target for interventions aimed at reducing inflammation in persons with HIV.

CONCLUSIONS

The outlook for HIV research going into a new decade is promising. Novel treatments and preventative and curative strategies in the pipeline now make the goal of ending the HIV epidemic in our lifetimes attainable. While awaiting outcomes of human clinical trials of novel interventions, ensuring that people with HIV can access existing treatments and preventing new infections in healthy individuals must remain our top priorities.

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