Biomedical AIDS research

Recent and upcoming advances

Contents

Introduction

Scientific evidence is essential for policies and programmes to advance the vision of UNAIDS of zero HIV infections, zero discrimination and zero AIDS-related deaths. New scientific information is becoming available at a rapid pace, and many of the findings are potentially important to guide future action against AIDS. To ensure this, UNAIDS has access to the latest scientific developments; a UNAIDS Scientific Expert Panel was established to advise UNAIDS on major new scientific discoveries and research evidence as well as research gaps and strategic AIDS research needs. The Scientific Expert Panel comprises more than 40 scientists from around the world with expertise in a wide range of disciplines, including epidemiology, behavioural science, virology, diagnostics, pathogenesis, immunology, treatment, prevention and cure.

It is with deep regret that we report that Ward Cates died in March 2016. He was one of the founding members of the UNAIDS Scientific Expert Panel and gave freely of his time and expertise to respond to HIV. He was one of the world's leading experts on HIV prevention and reproductive health, and all of us on the Panel will sorely miss him.

This 2016 report, in its second year of publication, captures the key advances in biomedical science on HIV during 2015 and provides a glimpse of the new research that can be anticipated in 2016. This report primarily focuses on biomedical research. The report does not cover social and behavioural science or broader structural and human rights issues. It does not intend to comprehensively review all research on a particular topic. The brief summaries on each topic are the opinions of the

Scientific Expert Panel members who authored each summary and do not necessarily reflect the views of UNAIDS.

The report is divided into an overview section that articulates the views of the Chair of the Scientific Expert Panel on the top 10 biomedical research advances in 2015 and five important research findings anticipated in 2016. Thereafter, the report provides brief summaries written by Scientific Expert Panel members. The topics are divided into three main categories: advances in treatment of HIV and comorbidities; advances in HIV prevention; and advances in HIV pathogenesis, diagnostics and cure. Linked to each summary is a bibliography that provides a list of key articles for further reading.

The top 10 biomedical research highlights of 2015: what's in store for 2016?

Salim S. Abdool Karim

In 2015, we witnessed several major advances in HIV science, including some emanating from disappointing research results. Such is the nature of science—much is learned from disappointments as well as from success! The UNAIDS Scientific Expert Panel was created in 2013 to enhance scientific contributions in AIDS policy and programming. These top 10 highlights of 2015 provide a quick glance at some of the most significant biomedical research advances and their potential implications for the AIDS response and a reflection on findings from 2015 to predict the scientific progress of 2016.

- **The goal of 15 million on treatment by 2015 achieved—22 million more still need antiretroviral therapy**
  Although treatment coverage has continued to improve, with the ambitious target of 15 million on treatment by 2015 being met ahead of schedule, the cup is not yet even half full. In 2014, there were an estimated 36.9 million people living with HIV. With 15 million people living with HIV currently receiving antiretroviral therapy, another 22 million people still need to start treatment. The scaling up of antiretroviral therapy among children still lags significantly behind adults, with only 32% of eligible children receiving treatment.

- **The World Health Organization's (WHO) 2015 guidelines recommend universal treatment following the START and TEMPRANO trial results**
  The results from two randomized controlled studies, the strategic timing of antiretroviral

therapy (START) and early antiretroviral therapy and/or early isoniazid prophylaxis against tuberculosis in adults living with HIV (TEMPRANO) trials, provided important evidence to support early antiretroviral therapy initiation, regardless of $CD4^+$ cell count. In the START study, immediate initiation of antiretroviral therapy was superior in preventing severe AIDS and non-AIDS events plus deaths. Since no difference was noted in the occurrence of adverse events, early antiretroviral therapy initiation was found to be a safe approach. In the TEMPRANO study, early antiretroviral therapy was significantly associated with lower risk of death and severe HIV-related events. Given these findings, WHO issued revised treatment guidelines in 2015 calling for antiretroviral therapy to be provided to all people living with HIV (adults and children) irrespective of $CD4^+$ cell count. Translating early treatment for all people living with HIV into programmatic implementation by health-care services is, however, a daunting prospect.

- **WHO guidelines recommend oral pre-exposure prophylaxis (PrEP) for high-risk populations**
  The 2015 WHO guidelines recommend oral TDF-containing PrEP as an additional prevention choice for people at substantial risk of HIV (defined as HIV incidence >3%) as part of combination prevention approaches. This long-awaited new guideline adds a new approach to existing tools for combination HIV prevention. The logistics and costs of providing PrEP present substantial challenges at the country level. High-income countries are grappling with PrEP implementation; France has announced the provision of PrEP, but the United Kingdom National Health Service has announced that it will not provide PrEP. Several low- and middle-income countries, including South Africa, have announced their incremental implementation of PrEP, focusing on highest risk populations first. As national programmes begin to implement PrEP, they will need to carefully monitor adherence and effectiveness of PrEP in high-risk populations; efficacy data have been inconsistent, especially for young women.

- **Although more evidence shows that oral PrEP is highly effective, the first resistant-strain infection has been reported**
  Further evidence of the efficacy of oral PrEP emerged in 2015 from the Intervention Préventive de l'Exposition aux Risques avec et pour les hommes Gays (IPERGAY) and pragmatic open-label randomized trial of pre-exposure prophylaxis (PROUD) studies. Both studies were presented at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) and were covered in detail in last year's panel report. As the evidence of the efficacy of PrEP among gay men and other men who have sex with men grows, a rare case of PrEP failure, despite good adherence by a man who has sex with men, has been reported. A highly adherent PrEP user acquired HIV infection with a strain that was already resistant to several medicines. More reports of drug-resistant breakthrough infections are expected as PrEP coverage increases and tenofovir use in first-line therapy becomes more widespread.

- **Dapivirine vaginal ring shows modest efficacy against HIV in two large clinical trials**
  The results from two large trials of the dapivirine vaginal ring were released at the CROI 2016 meeting; in a study to prevent infection with a ring for extended use (ASPIRE) trial, HIV incidence was reduced by 27%; and the Ring Study observed a 31% reduction in HIV transmission. Older women had better protection. There was high hope that the monthly dapivirine ring would remedy the adherence challenges seen in past trials of oral and topical PrEP and thereby achieve consistently high levels of protection against HIV. Based on the medicine detectable in plasma, both studies reported much higher levels of adherence (82% in ASPIRE and 73% in the Ring Study) than seen in most of the other PrEP trials. This bodes well for this new technology, since the high acceptance of monthly vaginal ring insertions is encouraging. The reasons for the lower than expected efficacy need to be better understood to guide the future development of the vaginal ring as a promising new HIV prevention technology.

- **Antiretroviral therapy has enduring HIV prevention benefits—final long-term HPTN 052 results**
  The final results from the preventing sexual transmission of HIV with anti-HIV medicines (HPTN 052) trial provided evidence of the enduring HIV prevention benefits of treatment in HIV-serodiscordant couples. In this trial, there was an overall 93% reduction in transmission with antiretroviral therapy after completion of follow-up of up to eight years. Where transmission occurred, this was either soon after the onset of antiretroviral therapy (probably before viral suppression was achieved) or among people with detectable virus. The findings demonstrate the sustained protection against transmission provided by antiretroviral therapy and the vital importance of ensuring treatment adherence and viral suppression.

- **New therapeutic drug options—TAF approved in a combination pill (Genvoya)**
  In November 2015, the United States Food and Drug Administration approved first oral TAF-based regimen, Genvoya, which combines EVG, COBI, FTC and TAF, for the treatment of HIV infection. TAF is a novel targeted prodrug of tenofovir that has demonstrated high antiviral efficacy at a dose less than one tenth that of TDF, with improved renal and bone safety compared with TDF-based regimens. Data show that, because TAF enters cells, including HIV-infected cells, more efficiently than TDF, it can be given at a lower dose, and there is 91% less tenofovir in the bloodstream.

- **Future drug options: dolutegravir (DTG) plus 3TC fully suppressed viral load among antiretroviral therapy–naive people**
  Simplified treatment regimens using the potent integrase strand transfer inhibitor, DTG, taken with a single well-tolerated NRTI such as 3TC (dolutegravir-lamivudine as dual therapy in naive HIV-infected people [PADDLE] study), have been shown to fully suppress viral load among people starting antiretroviral therapy for the first time.

The possibility of a dual antiretroviral first-line combination is emerging.

- **Cash incentives for high school students reduce herpes simplex virus-2 (HSV-2) but not HIV infection in Africa**
  The results from two randomized controlled trials among rural schoolchildren in South Africa were announced at the 2015 CROI meeting. The CAPRISA 007 trial showed that the cash incentives for good school performance, participation in a school HIV education programme and HIV testing affected sexually transmitted HSV-2 infection but not HIV infection, because of a lower than expected HIV incidence rate in this population. The HPTN 068 trial of cash incentives for school attendance did not find any effect on HIV incidence, possibly because of the pre-existing excellent school attendance in the study schools. The potential role of cash incentives in HIV prevention needs further investigation, with greater clarity on the criteria for the incentives.
- **Broadly neutralizing antibodies (bNAbs) can suppress viral load, but escape mutants emerge rapidly**
  Two CD4 binding site antibodies have demonstrated the ability to suppress viral load among viraemic people, with greater impact among those with lower initial viral loads. However, this benefit is rapidly eroded as escape mutant viruses emerge. These results point to the future potential of broadly neutralizing monoclonal antibodies in treatment, but combinations of antibodies or combinations of antibodies with antiretroviral medicines may be needed to reduce the risk of escape mutants. The world awaits the completion of larger human trials to identify the role of bNAbs in treating HIV infection.

Reflecting on 2015 to predict the scientific progress of 2016

Although 2015 has generated momentous results for the use of antiretroviral medicines in both treatment and prevention, new challenges are rapidly emerging. Principal among these is how to implement the new WHO guidelines for maximal therapeutic and prevention benefit. For treatment, UNAIDS has set a 90-90-90 treatment target to be achieved by 2020. The UNAIDS strategy has also set a target of 3 million people to be taking PrEP by 2020. Scaling up PrEP will undoubtedly be key for effective HIV prevention in several high-risk populations. In 2016, a stream of implementation science studies is expected to generate results, particularly on community-based strategies to enhance both treatment and prevention. Many sections of this report include the opinions of the panel members on the areas they consider most likely to have an impact in the next few years. These new data are going to be key in guiding policy development and programme implementation to achieve the UNAIDS Fast-Track goals for 2020.

Advances in treatment of HIV and comorbidities

New antiretroviral agents and strategies

Andy Gray and Pedro Cahn

A key set of evidence has informed changes to global policy on when to initiate antiretroviral therapy. Two prospective randomized trials confirmed what had been learned from cohort and ecological studies. No CD4 threshold was found to be protective against HIV-associated diseases, and immediately initiating antiretroviral therapy resulted in 44% and 57% reductions in HIV morbidity in the START and TEMPRANO studies, respectively.

Applying a test-and-treat approach requires access to simplified and better tolerated regimens. Among treatment-naive people, the 96-week data from the GARDEL study (LPV/r plus 3TC) showed continuing non-inferiority compared with a standard triple regimen, regardless of initial viral load. Early 24-week data from the proof-of-concept PADDLE study (DTG plus 3TC) were encouraging. A fully powered clinical trial of this regimen will be initiated in 2016. Among virologically suppressed people, non-inferiority of switching to a ritonavir-boosted ATV/r plus 3TC dual regimen was shown in both the simplification to atazanavir/ritonavir + lamivudine as maintenance therapy (SALT) and ATLAS-M studies.

There is continuing interest in nucleoside/nucleotide-sparing regimens. Data at 96 weeks for the long-acting antiretroviral therapy enabling (LATTE) trial of daily oral cabotegravir and RPV, initiated as a maintenance strategy for virologically suppressed people after 24 weeks of induction with conventional antiretroviral therapy, showed sustained virological response. The LATTE-2 trial of

long-acting intramuscular cabotegravir plus long-acting intramuscular RPV, the first all-injectable dual regimen, given every 4 or 8 weeks, is as effective as the oral regimen in maintaining viral suppression.

Emerging evidence has also shown that the new direct-acting antiviral agents are effective in treating people coinfected with HIV and hepatitis C. Sustained virological responses of 96% and 97% were achieved in the ION-4 (sofosbuvir plus ledipasvir) and ALLY2 (sofosbuvir plus daclatasvir) studies, respectively. Similar results were obtained for regimens that still included a ribavirin component, such as in the TURQUOISE (ombitasvir, ritonavir-boosted paritaprevir, dasabuvir plus ribavirin) and PHOTON-2 (sofosbuvir plus ribavirin) studies. ION-4 and TURQUOISE were conducted only in hepatitis C genotype 1 infections, whereas ALLY-2 and PHOTON-2 also included genotypes 2, 3 and 4. Data remain scarce for other genotypes. Although the goal of a pan-genotypic, all-oral regimen appears to be attainable, there are still serious concerns about the high cost of these new treatments in many parts of the world. The expansion of the mandate of the Medicines Patent Pool to include medicines for hepatitis C and the swift conclusion of an agreement with Bristol-Myers Squibb in relation to daclatasvir was therefore widely welcomed.

HIV treatment for children

Dianne Gibb and Anna Turkova

Globally, 2.6 million children are living with HIV; with recent change in guidance to treating everyone living with HIV, the proportion of children receiving treatment was estimated at 32% in 2015 but still lags behind treatment among adults (41%). Following new evidence from the adult START and TEMPRANO trials, universal antiretroviral therapy has been endorsed for all adults and children by WHO, the United States Department of Health and Human Services, the European AIDS Clinical Society and the Paediatric European Network for Treatment of AIDS. Although randomized controlled trial evidence beyond infancy is lacking, these recommendations take into account recent evidence on improved growth, pubertal development and immune recovery and reduced risk of treatment failure and viral reservoir size with early antiretroviral therapy.

Evidence from the Children with HIV-1 in Africa, Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS-3) trial supports WHO guidance recommending ABC + 3TC as the preferred first-line NRTI backbone. Recent approval by the United States Food and Drug Administration of once-daily dosing and licensing of junior dispersible ABC + 3TC (120 + 60 mg) fixed-dose combination by generic manufacturers allows the first once-daily regimens for children aged older than 3 years when co-administered with EFV. A triple fixed-dose combination (ABC + 3TC + EFV) is being developed. TAF, a safer analogue of TDF with high potency at a low milligram dose, was approved for children aged older than 12 years as part of EVG + COBI + FTC + TAF fixed-dose combination known as Genvoya. Dose-finding studies among younger children are ongoing.

The United States Food and Drug Administration approved LPV/r pellets for children in May 2015 and will help with logistics of transportation and storage, although palatability remains suboptimal. A new taste masked sprinkle has been developed; bioequivalence studies seem promising, and pharmacokinetic studies among children should start in 2016. Another drawback with LPV/r is the need for twice-daily dosing among children, as shown in the recently published KONCERT (PENTA-18) trial. The NEVEREST-3 trial demonstrated the safety of replacing EFV with LPV/r among children older than 3 years, with no increased viral rebound or failure over 48 weeks of post–antiretroviral therapy substitution. Preliminary results from a study in South Africa showed that super-boosting LPV/r with ritonavir (1:1 ratio) can overcome the inducing rifampicin effect for children with TB and HIV coinfection.

Integrase inhibitors, a promising third agent for first-line antiretroviral therapy, are included in the new WHO 2016 guidelines for adults and adolescents (DTG) and children younger than 3 years (twice-daily RAL). The United States Food and Drug Administration and the European Medicines Agency have approved DTG for children older than 12 years as a single drug and an ABC + 3TC + DTG fixed-dose combination. Dose evaluation of DTG among younger children is ongoing in the International Maternal, Pediatric, Adolescent AIDS Clinical Trial (IMPAACT) P1093 study with 25-mg and 10-mg tablets and a new dispersible 5-mg tablet for the youngest cohort. ODYSSEY (PENTA-20), a global strategy trial starting in 2016, will compare the efficacy and safety of DTG versus standard care as part of first- and second-line antiretroviral therapy among about 700 children.

BREATHER (PENTA-16) demonstrated the non-inferiority of short-cycle therapy (5 days on and 2 days off) of EFV-based antiretroviral therapy in maintaining viral suppression and inflammatory markers over 48 weeks in a geographically diverse group of 200 children, adolescents and young adults. This offers potential to reduce overall antiretroviral therapy intake and costs for young people who want weekends off. The long-term follow-up to 3–4 years will finish in 2016. In the European Pregnancy and Paediatric HIV Cohort Collaboration, 20% of 3696 children switched to second-line within 5 years of antiretroviral therapy initiation, with the median time to switch of 30 (interquartile range 15–58) months, more rapid for adolescents.

In summary, an exciting change to treating all children occurred in 2015, with significant advances towards once-daily dosing for first- and second-line antiretroviral therapy. Research gaps include assessment of the long-term efficacy and safety of DTG, TAF and EFV 400 mg equivalent among children and innovative treatment strategies addressing the lifestyle needs of adolescents, including the use of long-acting injectables.

HIV-associated malignancies—progress on cancer related to human papillomavirus

Mark Bower

Interest has been increasing in recent years on the morbidity and mortality of non-AIDS defining cancer, especially the pathogenesis, screening

and prevention of cancer related to human papillomavirus (HPV) among people living with HIV. HPV infection is associated with all types of cervical cancer, 80–90% of the types of anal cancer and a high percentage of other genitourinary malignancies including penile, vulval and vaginal cancer as well as a significant proportion of the cases of oropharyngeal cancer.

In conjunction with this recognition that HPV is implicated in the pathogenesis of anogenital cancer in all populations is the attempt to roll out cost-effective cervical cancer screening programmes, especially in lower-income countries. Globocan 2012 estimated that there are more than 500 000 diagnoses and more than 250 000 deaths from cervical cancer per year, and the majority occur in resource-poor countries. Optimal strategies for screening and treating cervical intraepithelial neoplasia have been explored in both African countries and India, with visual inspection with acetic acid and immediate cryotherapy providing possibly the most cost-effective and deliverable option for screening women living with HIV.

In contrast to the value of cervical screening in reducing the burden of cervical cancer, the use of screening for preventing anal cancer remains controversial. Optimal screening methods, the influence of antiretroviral medicines on pre-invasive disease and cost–effectiveness all remain unresolved. The 2015 guidelines of the United States Centers for Disease Control and Prevention conclude that "Data are insufficient to recommend anal cancer screening with anal cytology in people living with HIV, gay men and other men who have sex with men and the general population, based on available evidence."

Vaccination holds the key to the future prevention of HPV-associated cancer, but vaccine availability and routine vaccination policies vary between countries. Trials have demonstrated the efficacy of bivalent and quadrivalent vaccines in cervical disease and also in preventing anal cancer and anal intraepithelial neoplasia among gay men and other men who have sex with men. As a consequence, recent guidelines recommend vaccinating gay men and other men who have sex with men younger than 26 years old and people living with HIV and advocate the use of the quadrivalent or the newer nonavalent HPV vaccines in these settings.

Although the evidence is limited, six studies suggest that using the bivalent and quadrivalent HPV vaccine is safe and immunogenic for people living with HIV. The longer-term efficacy of the strategy in preventing cancer remains uncertain but is being investigated in several trials. Questions remain around the cost–effectiveness of HPV vaccination for people living with HIV. However, reduced cervical screening may alter these calculations. A final important issue concerns the role of HPV vaccination as secondary prophylaxis among people living with HIV. Some evidence suggests that vaccinating HIV-negative women with cervical intraepithelial neoplasia reduced the recurrence rate, and Markov models suggest that a similar strategy for managing anal intraepithelial neoplasia among HIV-positive gay men and other men who have sex with men may be cost-effective.

Hepatitis coinfection and treatment

Karine Lacombe and Peter Reiss

With more than 185 million people affected worldwide, chronic hepatitis C (HCV) has emerged as a major public health problem. Together with chronic hepatitis B, it ranks among the top 10 causes of deaths in the Global Burden of Disease study, being responsible for at least 1 million liver-related deaths each year.

The advent of combinations of direct antiviral agents targeting multiple steps of the HCV viral replication cycle has changed the management of chronically infected people. Sustained virological responses of 96% and 97% were achieved in the ION-4 (sofosbuvir plus ledipasvir) and ALLY2 (sofosbuvir plus daclatasvir) studies, respectively. Similar results were obtained for regimens that still included a ribavirin component, such as in the TURQUOISE (ombitasvir, ritonavir-boosted paritaprevir, dasabuvir plus ribavirin) and PHOTON-2 (sofosbuvir plus ribavirin) studies. These novel combination regimens now enable more than 90% of the treated people to achieve a sustained virological response 12 weeks after the end of treatment. These antiviral agents have led to a marked improvement in long-term clinical outcomes of all the infected people, including the ones most severely affected, such as people with HIV coinfection, people with cirrhosis and people with post-liver transplant.

Importantly, this development has the potential to curb the global HCV epidemic, provided that advocacy for insuring universal access to HCV treatment for those most in need is successful. Indeed, many issues alongside the continuum of care remain to be addressed. First, large-scale screening strategies must be designed and implemented, based on point-of-care tests that enable the hidden part of the HCV epidemic to be identified, especially in hard-to-reach key populations among which the highest number of individuals with HCV are concentrated. Second, implementing test-and-treat procedures based on the use of simple tools to identify end-stage liver disease and to follow up people being treated is a key factor for scaling up implementation. In this context, rapid dissemination of combination regimens with pan-genotypic activity against HCV genotypes is also key in moving towards the successful global elimination of HCV.

Recent data have shown that being HIV positive does not negatively impact the response to these novel HCV treatments and for the first time allows such people to be considered without difference from those without HIV.

The response to viral hepatitis has entered a new era, and recently there have been very encouraging signs that governments, advocacy groups and global health organizations are all mobilizing to advocate for universal access to treatment and care for HCV. Since HCV is more common among people who inject drugs, the success or failure of programmes will be closely tied to their ability to integrate with existing well-founded harm-reduction programmes. Successful integration could bring benefits well beyond the treatment of HCV to many hard-to-reach populations.

Tuberculosis and HIV infection

Richard Chaisson

Tuberculosis (TB) remains one of the most serious threats to people living with HIV, and HIV continues to fuel high rates of TB illness and death. WHO recently reported that TB caused more deaths than HIV in 2014, with 1.5 million dying from TB versus 1.2 million dying from HIV. Importantly, an estimated 400 000 people living with HIV died from TB. This means that one third of the people dying from HIV-related causes died from TB, and almost one quarter of TB-related deaths are related to HIV. The Millennium Development Goals ended in 2015. Although there has been progress in reducing the burden of TB, the benchmarks for TB mortality and TB incidence have not been met, primarily because of TB and HIV co-epidemics in sub-Saharan Africa. A recent study in South Africa reported that, among adults who died at home without a known diagnosis and not having seen a health professional (25% of all deaths in South Africa fall into this category), 32% were attributable to TB. Although this study did not determine HIV status, a very high proportion of these deaths were probably HIV-related. Thus, the impact of TB on people living with HIV, and vice versa, continues to extract a huge burden.

The two major therapeutic tools to control HIV-related TB are antiretroviral therapy and isoniazid preventive therapy. Antiretroviral therapy lowers TB risk by restoring cellular immune function and reducing HIV viral load. Isoniazid preventive therapy treats latent TB infections, preventing them from progressing to active disease. Two landmark studies were published in 2015 documenting the effects of antiretroviral therapy and isoniazid preventive therapy on improving the clinical outcomes of people living with HIV. The START study was a trial of immediate versus deferred antiretroviral therapy for people with CD4 cell counts >500/mm^3. The study demonstrated that early antiretroviral therapy reduced the risk of TB by 71%. The TEMPRANO study examined the impact of providing antiretroviral therapy, isoniazid preventive therapy or both to people with CD4 counts higher than the cut-off points for treatment initiation recommended by WHO at the time of entry into the trial. Either antiretroviral therapy or isoniazid preventive therapy significantly reduced the risk of developing serious AIDS-related conditions, especially TB, and the combination of antiretroviral therapy and isoniazid preventive therapy reduced TB risk more than either treatment alone. A third study, the REMEMBER trial, reported that treating people with very advanced HIV infection (CD4 <50/mm^3) with antiretroviral therapy and isoniazid preventive therapy was as effective as giving antiretroviral therapy with empirical multidrug TB chemotherapy and actually resulted in lower rates of TB during six months of follow-up. Together, these three studies support the use of antiretroviral therapy among all people living with HIV. The TEMPRANO and REMEMBER studies document the additional benefit of providing isoniazid preventive therapy along with antiretroviral therapy.

In 2016, more research on improved methods of TB case detection is anticipated to be completed, providing important insights into both new technologies and improved strategies for controlling HIV-associated TB. Several additional

trials of empirical TB treatment for people with advanced HIV infection will be reported, and ongoing studies of new medicines for treating drug-resistant TB among people living with and without HIV will help define the potential benefit of new antimicrobial agents in combating these difficult-to-treat forms of the disease. Regardless of progress made, however, TB will continue to contribute to substantial morbidity and mortality among people living with HIV. Acceleration of research to address coinfection remains an urgent priority.

Drug resistance and second- and third-line antiretroviral therapy options

Praphan Panupak and Beatriz Grinsztejn

The use of antiretroviral therapy has substantially reduced morbidity and mortality. As of June 2015, 15.8 million people were actively receiving antiretroviral therapy. Even though drug access has expanded, limited access to viral load monitoring and lack of co-formulated and safe second-line treatments play a major role in limiting the scaling up of antiretroviral therapy.

The current second-line therapy recommended by WHO is LPV/r plus an NtRTI backbone. The second-line and Ernest study results showed that a combination of RAL plus LPV/r was not superior to the standard WHO recommendation. New data in 2015 from the SELECT and the 2LADY studies further supported this.

The 2LADY study (ANRS 12169) was a randomized, open-label, non-inferiority trial conducted in Burkina Faso, Cameroon and Senegal comparing the efficacy and safety of the current WHO standard regimen (LPV/r plus two NtRTIs) versus two alternatives. These alternatives included two NtRTIs plus DRV, a next-generation PI providing improved tolerability and ABC, ddI and LPV/r, a combination still used in low- and middle-income countries because of drug availability and limited exposure during first-line therapy.

The SELECT study (ACTG A5273) was a Phase III, open-label, randomized, non-inferiority study conducted at 15 sites in 9 low- and middle-income countries in Africa, Asia, South America and Haiti; 512 adults living with HIV failing an NNRTI-based regimen received LPV/r plus a NtRTI backbone or LPV/r with the integrase-inhibitor RAL. Most (95%) individuals at study baseline had NtRTI and NNRTI resistance, with half having ≥3 resistance mutations. Extensive NtRTI resistance was associated with the duration of drug exposure and advanced disease.

Ability to tolerate PIs and poor adherence to the current second-line regimens are major barriers to the success of second-line therapies, and novel second-line strategies remain necessary.

Access to third-line antiretroviral therapy remains quite limited in most low- and middle-income countries, and two trials are underway in these settings. THILAO (NCT02025868) is an ANRS-sponsored study ongoing in Burkina Faso, Côte d'Ivoire, Mali and Senegal. THILAO uses behavioural adherence interventions for people for whom second-line antiretroviral therapy has failed as well as DRV/r plus RAL-based third-line antiretroviral therapy for people with

persistent virologic failure. A5288/MULTI-OCTAVE (NCT01641367) is underway globally at 20 sites to evaluate resistance test-based antiretroviral therapy strategies using DRV, ETR and RAL in an algorithmic approach in combination with a randomized cell phone-based adherence intervention. Results from these studies are expected to be available in 2016 and will help guide the need for third-line antiretroviral therapy in these settings.

A key concern for many low- and middle-income countries is the high cost of second- and third-line medicines and the ongoing budget commitments needed to fund antiretroviral therapy programmes over the next years.

Several novel antiretroviral medicines, including those that may be appropriate for people previously exposed to multiple antiretroviral medicines, are currently in Phase II and III drug trials. These include the attachment inhibitor fostemsavir-BMS 663068, the HIV maturation inhibitor BMS-955176 and PRO 140, which is a humanized monoclonal antibody to the chemokine receptor CCR5 that is used weekly as a subcutaneous injection.

Global progress on programmes for rolling out antiretroviral therapy

Wafaa El-Sadr

The UNAIDS 90–90–90 treatment target continues to drive and inform the scaling up of antiretroviral therapy. Several scientific advances and policy decisions have provided critical information to advance this effort.

For the first step in the cascade of HIV treatment, a large study (Project STATUS) evaluated three models for HIV testing in outpatient departments in South Africa, Uganda and the United Republic of Tanzania: (1) referral to onsite voluntary counselling and testing after clinical consultation, (2) offer of HIV testing and counselling during clinical consultation after group talk in the waiting room or (3) sending people to another waiting area for group talk and offer of HIV testing and counselling before clinical consultation. The proportion of 19 953 age-eligible people tested was highest in the third model, followed by the first and second models; the proportion of test-eligible people tested was highest for first, followed by second and then third models. However, entry into care was low overall, highlighting the importance of further work to enhance linkage to care and engagement in care.

Another important advance in HIV testing is HIV self-testing. In a study conducted in Malawi in which community workers offered oral HIV self-testing kits to community residents, 76.5% of 14 004 residents took up self-testing and 75.8% shared their results. Overall, 99.4% indicated satisfaction with the test, with no cases of partner violence or suicides reported and only 2.9% indicating feeling "forced to test", usually by their main partner. There was also high concordance between the self-test result and repeat HIV testing and counselling, with sensitivity of 93.6% and specificity of 99.9% for the self-test.

In terms of initiating antiretroviral therapy, another critical step in the 90–90–90 cascade, findings from two studies, START and TEMPRANO, provided

support for the early initiation of antiretroviral therapy. These studies informed the 2015 WHO guidelines, which recommend initiation of antiretroviral therapy for all people living with HIV irrespective of $CD4^+$ count. Most national HIV programmes are expected to adopt this approach by the end of 2016.

Achievement of the last 90% in the UNAIDS target is contingent on the availability of viral load testing, which remains limited in many countries. This has implications for identifying virologic failure on first-line regimens and thus promptly initiating second-line regimens to achieve virologic suppression, the critical outcome. In one study that included data from 16 countries in sub-Saharan Africa, 3% of participants switched from first- to second-line antiretroviral therapy, and the probability of switching was highest when routine viral load monitoring was used versus with targeted viral load monitoring, $CD4^+$ monitoring and clinical monitoring. Thus, the availability of routine viral load monitoring may allow more rapid switching to second-line antiretroviral therapy and viral suppression on the new regimen.

Important innovations continue to be reported to enhance the retention of people living with HIV in HIV care and to support antiretroviral therapy adherence. In one study conducted in Swaziland, decentralization of HIV services in a hub-and-spoke model was associated with decrease in loss to follow-up, but not death, and use of treatment supporters was also associated with reduced loss to follow-up. In addition, in a programme of community-based adherence clubs for stable people in South Africa, only 6% were lost to follow-up at 12 months and less than 2% had experienced virological failure.

During 2015, the global target of reaching 15 million people living with HIV was achieved. Nevertheless, continued research and innovations are needed to achieve the 90–90–90 target in 2020.

Advances in HIV prevention

HIV vaccines

Bruce D. Walker and Pontiano Kaleebu

Research to develop an effective vaccine to prevent HIV gained momentum on multiple fronts in 2015:

Understanding pathways that lead to the development of broadly neutralizing antibodies (bNAbs)
One of the foremost challenges in HIV vaccine development is the need for antibodies to undergo extensive somatic hypermutation for development of neutralization breadth. This requires sequential viral diversification during years of chronic infection. Through longitudinal evaluation of an African person who developed such a potent bNAb response to the V1V2 region of the HIV envelope, the initiating viral species that stimulated the germline precursor was defined, as were subsequent variations of the virus that drove this response to full neutralization breadth.

New approaches to immunogen design to engage germline precursors that lead to bNAb development
A major challenge in B-cell lineage immunogen design for inducing bNAbs is that the HIV envelope binds poorly to the rare antibody germline precursors that need to be engaged to initiate this process. This challenge may at least theoretically be overcome by designing immunogens specific for the germline precursor. This has recently been achieved in a mouse model genetically engineered to express the germline for a CD4 binding site antibody, one of the most promising target sites for bNAbs. Another immunogen approach using a native-like trimeric form of the HIV envelope termed SOSIP (SOS,

a disulfide between residues 501 and 605; IP, an Ile-to-Pro mutation at residue 559) is also promising, since this vaccine has for the first time induced antibody responses in rabbits that are able to neutralize the autologous tier 2: difficult-to-neutralize viruses. The recently developed knock-in mouse models expressing human immunoglobulin genes will undoubtedly accelerate these studies in the future.

Identification of new sites of neutralization on the HIV envelope

Progress has also been made in defining targets of bNAbs, with the structural characterization of a fifth binding site for bNAbs. This binding site spans the gp120-gp41 interface, and is thus specific for the envelope trimer. At least some of these antibodies are able to recognize both open and closed forms of envelope, which occur naturally, and antibodies with these characteristics may be particularly potent at inhibiting HIV by targeting the intact trimer on the virus.

Promising efficacy trials in monkey models, providing a strong rationale for trials in humans

In a 2015 proof-of-concept study, monkeys were immunized with a combination of an Ad26 vector expressing Gag, Pol and Env and boosting with an adjuvanted envelope gp140 protein with characteristics of the natural trimer. Complete protection was observed in 50% of vaccinated animals, and protection was shown to correlate with functional envelope-specific antibody responses, but not with neutralizing antibodies, which were poorly induced with this regimen. Phase I studies of this regimen are currently underway in humans. Even more impressive in terms of potency and neutralization breadth was an engineered construct called eCD4Ig consisting of CD4 protein conjugated to immunoglobulin, to which a sulfated peptide that specifically binds to CCR5 was added. This construct was able to neutralize 100% of isolates tested and, when expressed in monkeys through an AAV vector, was shown to protect all animals from high-dose intrarectal challenge. Although the challenges remain daunting, these studies provide evidence for consideration for progression to human studies.

HIV vaccine trials underway in humans

The year 2015 has also seen progress towards clinical efficacy trials of candidate vaccines. These include the P5, which represents a follow-up of the successful RV144 Thai trial involving ALVAC™ and an envelope protein boost, refigured for use in a clade C endemic region. The first Phase I/II trial HVTN 100 has started, and the Phase III trial (HVTN 702) will start in 2016. In parallel, Phase I studies of a mosaic HIV prophylactic vaccine that combines low seroprevalent Ad26 and MVA vectors with mosaic inserts for global coverage, together with a trimeric clade C Env protein boost for improved humoral immunity, have been initiated.

Effect of BNAbs on viral load among people living with HIV

A trial of a BNAb directed at the CD4 binding site of the HIV envelope, 3BNC117, was undertaken among people living with HIV who were not receiving treatment with persistent plasma viraemia and demonstrated a 0.8 to 2.3 log decline in plasma viraemia, which gradually increased as antibody levels declined.

Prevention benefits of treatment

Myron Cohen and Richard Hayes

Previous research has demonstrated that heterosexual HIV transmission is closely correlated with viral load and that the risk of transmission from people living with HIV who are receiving antiretroviral therapy with viral suppression is very low. This research underpins the concept of universal testing and treatment whereby, if a sufficiently high proportion of people living with HIV know their status, start antiretroviral therapy and are virally suppressed, then transmission and HIV incidence may be reduced to a very low level.

The HPTN 052 trial provided key evidence of the efficacy of treatment as prevention. Following an interim review in 2011, showing a 96% reduction in HIV transmission, all participants in the control arm were offered immediate antiretroviral therapy. The trial cohort was followed up for four more years, and final results were presented in 2015. Based on observational analysis, those receiving antiretroviral therapy had an overall 93% reduction in transmission, and where transmission occurred this was either soon after initiation of antiretroviral therapy (probably before viral suppression was achieved) or among people with detectable virus. The findings demonstrate the sustained protection against HIV transmission provided by antiretroviral therapy and the vital importance of ensuring treatment adherence and viral suppression.

The results of the Strategic Timing of Antiretroviral Therapy (START) trial were also reported during 2015, showing clear evidence of the clinical benefits of immediate antiretroviral therapy for the individual person, in accordance with earlier evidence from the TEMPRANO trial. Based on these findings, as well as the evidence of the prevention benefits of treatment, WHO issued revised treatment guidelines in 2015 calling for antiretroviral therapy to be provided to all people living with HIV irrespective of CD4 count.

Adoption of the new guidelines requiring immediate treatment should not be confused with universal testing and treatment, which requires substantial expansion of HIV testing and linkage to care in the community. Without these measures, the full impact of treatment as prevention will not be realized. Several large-scale community-randomized studies to measure the effects of different approaches to universal testing and treatment in eastern and southern Africa are continuing, and the results are expected in 2017.

The success of universal testing and treatment may hinge on the relative contribution of unrecognized and untreated acute and early HIV infection, although a recent study in Malawi showed that only a small proportion of newly diagnosed people living with HIV had acute and early HIV infection. The effectiveness of universal testing and treatment may also be reduced by the migration of untreated people into a "treated" community. Data from rural Uganda have shown that a large proportion of the people who have recently acquired HIV may have been infected from outside the community. Phylogenetic studies may be helpful in quantifying the proportion of new infections attributable to these and other factors.

In an attempt to promote higher rates of testing, antiretroviral therapy and viral suppression and to capture the full prevention benefits of treatment, UNAIDS has promulgated its 90–90–90 target, whereby: 90% of the people living with HIV know their HIV status; 90% of those who know their HIV-positive status receive antiretroviral therapy; and 90% of those receiving antiretroviral therapy have suppressed viral loads. This ambitious target is to be achieved by 2020, and the coming year is likely to see an expansion of research on how to reach these targets and of the coverage attained by a range of approaches.

Microbicides and pre-exposure prophylaxis

Ward Cates and Quarraisha Abdool Karim

Overall, 2015 has been an important year for consolidation of the prevention benefits of oral pre-exposure prophylaxis (PrEP), and early 2016 has provided the first evidence of modest protection against HIV by the dapivirine intravaginal ring. As discussed in last year's report, 2015 also saw the disappointing results of the FACTS trial, in which provision of 1% tenofovir gel, which was supposed to be used pericoitally, did not reduce HIV incidence among young women in South Africa.

The 2015 WHO guidelines recommend daily, oral tenofovir-based regimens for PrEP among HIV-negative people at high risk of acquiring HIV. Earlier in 2015, the IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les hommes Gays) intermittent FTC + TDF study added to the growing body of clinical trial efficacy data on PrEP. The open-label Pre-exposure Option for Reducing HIV in the United Kingdom: Immediate or Deferred (PROUD) study and data from implementation programmes in San Francisco in the United States of America confirm the ability to translate daily PrEP provision into clinical practice. The WHO guidelines provide impetus for country-level policy formulation and programmatic scale-up of PrEP for high-risk populations. National programmes will need to carefully monitor the effectiveness of PrEP in high-risk populations for which consistent data on effectiveness and efficacy are not yet readily available, especially young women. At present, only FTC + TDF is licensed for PrEP. To reduce costs, TDF alone or 3TC + TDF are cheaper options but do not have the same level of evidence as FTC + TDF and are not licensed for PrEP by any regulatory body.

The use of newer formulations of tenofovir such as TAF and F/TAF, which has about 10 times higher potency than FTC + TDF and fewer side effects, are being tested for their prevention benefit and may have potential for intermittent PrEP use.

Oral PrEP also offers a self-initiated prevention option for women 15–24 years old, who continue to bear the brunt of the HIV epidemic in sub-Saharan Africa. Research is needed to overcome some of the key challenges in PrEP implementation, including low awareness of HIV risk, unknown patterns of PrEP utilization by individuals at higher risk, novel strategies to enhance adherence, health-care providers being poorly prepared for providing PrEP, limited data on potential adverse effects

from long-term use of PrEP by uninfected people and the stigma associated with PrEP use. Many of these challenges are similar to those faced when antiretroviral therapy is being rolled out.

The focus of topical PrEP (antiretroviral-based topical formulations, also known as microbicides) has shifted to addressing the adherence challenges of daily or intermittent product use among women through the use of a novel drug-delivery mechanism such as the vaginal ring. Results presented at CROI 2016 showed that the dapivirine vaginal ring achieved high levels of adherence (82% in ASPIRE and 73% in the Ring Study—by plasma drug levels). HIV incidence was reduced by 27% (95% CI: 1–46%) in the Microbicide Trials Network's ASPIRE trial and by 31% (95% CI: 1–51%) in the International Partnership for Microbicides' Ring study. In the ASPIRE trial, HIV incidence declined by 56% among women older than 21 years (95% CI, 31–71%, $P < 0.001$) but increased by 27% (95% CI, −133% to 31%, $P = 0.45$) among women 21 years old or younger. Among women 21 years or younger, ring adherence was consistently above 70% throughout the trial, but this level of adherence was significantly lower than the adherence observed among women older than 21 years. Open-label extension studies will be initiated in 2016.

Good progress is being made on two injectable antiretroviral medicines (two-monthly RPV and three-monthly cabotegravir) as potential long-acting agents for PrEP. The results of a treatment trial (LATTE-2) presented at CROI 2016 showed high efficacy in maintaining viral suppression at 32 weeks, with pharmacokinetic results suggesting that cabotegravir may have to be administered twice monthly to maintain therapeutic levels. The HPTN 077 study will provide greater clarity on the safety and appropriate dosing frequency of cabotegravir. Plans are underway for Phase III efficacy trials of cabotegravir among gay men and other men who have sex with men and among women. The results of MTN 017, a Phase II trial of the reduced glycerine formulation of tenofovir gel among gay men and other men who have sex with men that was presented at CROI 2016, were favourable and supported the progression of this product to large-scale efficacy trials.

Elimination of mother-to-child transmission

Elaine Abrams and Hoosen Coovadia

In 2015, several studies released findings that made important incremental contributions, advancing understanding of optimal approaches to preventing children from becoming newly infected with HIV and keeping their mothers alive.

Several studies provided new information on the efficacy and safety of antiretroviral medicines during pregnancy, breastfeeding and the first year of life. The ANRS 12174 study, a randomized controlled trial of extended PrEP with twice daily LPV/r versus 3TC among the infants of women with CD4 counts >350 cells/mm^3, provides evidence of the efficacy of both antiretroviral medicines for preventing HIV transmission from mother to child through 12 months of breastfeeding. The cumulative transmission was 1.4% and 1.5%, respectively, with

no difference between arms. Two observational studies provided somewhat reassuring evidence of the safety of triple-drug antiretroviral regimens during pregnancy. A study in Botswana reported on birth outcomes among nearly 10 000 women living with HIV. Although the rates of adverse outcomes (stillbirth, preterm delivery and small for gestational age) were high overall, no evidence indicated any increased risk associated with using the currently recommended TDF + FTC + EFV regimen. Similarly, in Zambia, an observational study of more than 4000 pregnant women found no evidence indicated any increased risk of low birth weight associated with antiretroviral therapy initiation or antiretroviral therapy duration during pregnancy.

With the roll-out of the lifelong antiretroviral therapy (formerly known as option B+) approach, investigators are beginning to assess the challenges and successes of initiating lifelong treatment during pregnancy and breastfeeding. A study of pre and post B+ implementation in Lilongwe, Malawi found overall improved outcomes for mothers (uptake and duration of antiretroviral therapy and decreased mortality) and infants (fewer infected) but also significant ongoing challenges with retention. Providing evidence of another potential benefit of universal treatment and the lifelong antiretroviral therapy approach, an analysis of HIV transmission from mother to child in France in 2000–2011 documented no transmission among women who conceived while receiving antiretroviral therapy and maintaining viral suppression throughout pregnancy.

Although most countries in sub-Saharan Africa have endorsed and are scaling up the lifelong antiretroviral therapy approach, many countries with a high burden of HIV infection have struggled to implement effective approaches to preventing HIV transmission from mother to child. The Healthy Beginning Initiative, a cluster randomized trial, studied whether a church-based intervention could increase the uptake of HIV testing and linkage to care in Nigeria. Pregnant women attending churches with onsite health education and laboratory testing implemented during baby showers held at church were significantly more likely to have an HIV test compared with pregnant women attending non-intervention churches.

In 2016, we can expect to see the results of studies from the INSPIRE and ALLIANCE networks, two sets of implementation science studies intended to identify optimal approaches to the delivery of services to prevent mother-to-child HIV transmission and improve maternal and child health outcomes.

Medical male circumcision

Helen Weiss and Elly Katabira

The scaling up of voluntary medical male circumcision continued to expand in 2015, and an estimated total of 10 million men were circumcised worldwide by December 2015. A 2015 modelling study estimated that support from the United States President's Emergency Plan for AIDS Relief for antiretroviral therapy, medical male circumcision and prevention of mother-to-child transmission combined prevented about 2.7 million people from acquiring HIV infection between 2004 and 2013. However, no further voluntary medical male

circumcision targets have been set, and support for research on voluntary medical male circumcision and other biomedical prevention strategies is declining. In light of this, recent modelling studies have estimated how to improve the efficiency of the voluntary medical male circumcision scale-up: for example, by giving priority to young sexually active males at greatest risk of HIV infection, alongside other targeted strategies for HIV prevention.

A continuing area of interest is the potential for sterile, single-use, disposable devices for voluntary medical male circumcision. The ideal device should make voluntary medical male circumcision easier, safer, faster, sutureless, inexpensive, less painful, require less infrastructure and more acceptable to the men and should not require follow-up visits. The PrePex™ device was the first to receive WHO prequalification in May 2013, and in June 2015, WHO prequalified the ShangRing™ for circumcision of males aged 13 years and older based on the results of studies of the device involving almost 2000 placements in Kenya, Uganda and Zambia. These studies showed that men circumcised with the ShangRing™ had higher levels of satisfaction compared with men undergoing conventional surgery. Studies on new devices for early infant male circumcision have also been recently published, including trials in Botswana and Zimbabwe that found that the single-use AccuCirc® device was safe and acceptable.

A safety issue arose in 2015, regarding 12 tetanus cases that occurred in five countries in sub-Saharan Africa in 2012–2015. A review of these cases concluded that voluntary medical male circumcision is safe, but sensitive surveillance systems are needed to monitor all adverse events.

Innovative research to increase the uptake of voluntary medical male circumcision has continued: for example, the Maternal and Child Health Integrated Program in the United Republic of Tanzania successfully began using geographical information systems to strategically plan the location of outreach campaigns.

In 2016, we expect further data on tetanus and other safety issues as well as pragmatic implementation science studies that are expected to share new experiences and data on how to implement and scale up circumcision.

Advances in HIV pathogenesis, diagnostics and cure

Progress in HIV therapeutics towards sustained HIV remission while off antiretroviral therapy

Deborah Persaud and Sharon Lewin

Biomarkers predicting HIV remission remain critically important but elusive. In a recent study of antiretroviral therapy during acute HIV infection, the duration of HIV remission (defined as viral load <50 copies/ml) after antiretroviral therapy ended was associated with the reservoir size at the time of treatment interruption as measured by HIV DNA and with the expression of immune checkpoint markers, markers of T-cell exhaustion, before the initiation of antiretroviral therapy.

Tissue reservoirs on antiretroviral therapy, specifically lymphoid tissue in either lymph nodes or in the gastrointestinal tract, remain very important for eliminating HIV persistence. A subset of infected T cells, T follicular helper cells that are localized in B-cell follicles in lymph nodes, are a source of persistent infectious virus in elite controller SIV-infected rhesus macaques and in SIV-infected macaques following antiretroviral therapy. The B-cell follicle is a unique anatomical compartment that limits the entry of cytotoxic T cells, and strategies to disrupt these follicles may therefore potentially lead to enhanced clearance of infected cells. These findings highlight the need for incorporating tissue-based studies in HIV cure research, which poses some significant challenges, especially in populations such as children.

The strategy of "shock and kill" through activating latency was tested in several informative clinical

trials and reported in 2015. A small non-randomized clinical trial of the potent histone deacetylase inhibitor romidepsin among people living with HIV receiving antiretroviral therapy led to an increase in viral transcription, as shown for the less potent histone deacetylase inhibitors vorinostat and panobinostat, but in this study an increase in plasma viraemia was also observed. An observational dose escalation study of disulfiram among people living with HIV receiving antiretroviral therapy led to an increase in HIV transcription, and at the highest dose tested of 2 g daily, a modest but significant increase in plasma viraemia was observed. In contrast to histone deacetylase inhibitors, disulfiram is very safe, has no adverse immunological effects and could be given for a prolonged period. Other newer latency-reversing agents that show promise both in vitro and in animal models include TLR7 agonists (now in human trials) and the protein kinase C agonist ingenol (human trials soon to start). In vitro, combining latency-reversing agents can lead to synergistic activation and may be an alternative approach for future clinical trials.

BNAbs are promising as immunotherapeutics for HIV remission and cure. These antibodies neutralize virus particles, rendering them non-infectious, but may also mediate antibody-dependent cellular cytotoxicity. The first studies of bNAbs among people living with HIV showed suppression of plasma viraemia. Further studies of bNAbs in the setting of antiretroviral therapy are now underway. Bispecific antibodies may also play a role in eliminating infected cells; this was recently successfully demonstrated in vitro. These antibodies work by having two targets—one end that binds HIV proteins and the other end that binds and therefore activates CD3, leading to killing the target cells.

In 2016, we are likely to hear results from clinical trials evaluating bNAbs and other therapeutic vaccines on HIV persistence on antiretroviral therapy, combination studies of vaccines with latency-reversing agents, combination latency-reversing agent studies, effects of CCR5 co-receptor manipulation with gene therapy, effects of very early antiretroviral therapy on remission following treatment interruption among adults and children and the effects of anti-PD1 and anti-CTLA-4 on HIV persistence. Minimizing the generation of viral escape mutations will also be critical for immunotherapeutic strategies, and this might best be achieved through early antiretroviral therapy. There are efforts to diversify study participants into cure trials to include women and people in resource-constrained settings, but this area still needs significant effort and investment.

HIV diagnostics and viral genetics

Papa Salif Sow and Eduard Karamov

HIV diagnostics

The accurate identification of recent HIV infection continues to be an important research area and has implications for HIV prevention and treatment interventions. Molecular genomics methods that explore the dynamics between the timing of infection and viral evolution are now emerging as a promising approach. The combination of serological and molecular methods may provide

a solution to identify recent HIV infection in cross-sectional data.

This year, the Medical Care Criteria Committee of New York State recognized the ongoing need to raise clinical awareness among providers to increase the identification and assessment of acute HIV infection and released guidelines emphasizing the critical importance of diagnosing acute HIV infection.

Viral genetics
The current HIV epidemic is characterized by the emergence of new recombinant and mosaic viruses in most regions.

Originally, HIV transmission in Europe and the United States of America comprised predominantly clade B viruses. However, in Europe this situation is rapidly changing as a result of demographic shifts and migration fluxes. A cluster of CRF02_AG is expanding among gay men and other men who have sex with men in various regions of Europe and has spread to Japan. This cluster is part of a larger one, comprising viruses from European countries and Ecuador. The propagation of diverse genetic forms of HIV among gay men and other men who have sex with men is changing the genetic composition of the epidemic in this population.

A significant outbreak of CRF19 was detected in Cuba. CRF19 is a recombinant of subtype D (C-part of Gag, PR, RT and nef), subtype A (N-part of Gag, Integrase, Env) and subtype G (Vif, Vpr, Vpu and C-part of Env). CRF19 has an evolutionary advantage in being a very fit virus and causes rapid progression to AIDS among many individuals who have newly seroconverted in Cuba.

Analysis of the epidemic in the Middle East and North Africa revealed a complex mosaic of diverse HIV subtypes and circulating recombinant forms across the region.

The current situation in eastern Europe and the Russian Federation is characterized by a decrease in the circulation of the previously predominant HIV-A1, broad introduction of CRF63 and the appearance of multiple new unique recombinant forms: A1/B (several species) and A1/CRF02_AG (several species).

Global monitoring of HIV infection remains an important goal of biomedical research.

Gene therapy

Marina Cavazzana-Calvo

The establishment of a latent HIV reservoir constitutes a major obstacle to viral clearance in the chronic phase of infection. Consequently, the latent reservoir also represents a huge barrier to developing effective vaccines. Thus, eliminating latent viral genomes in the reservoir is a major challenge in developing potentially curative treatment strategies.

The CRISPR/Cas9 system is known to have a major role in the adaptive immune response to foreign plasmids and viruses in about 40% of bacteria. CRISPR/Cas9 has been successfully used for targeted genome editing in a range of cell types (including human cells). In particular, the system has been used to target and disrupt the reverse-transcribed products of lentiviral RNA genomes

within host cells. It has been shown that the CRISPR/Cas9-specific targeting of HIV long terminal repeats in human primary $CD4^+$ T cells reduced virus production more than threefold (relative to controls).

The targeting of non-coding regions (such as those containing long terminal repeats) is of great interest for targeting inactive HIV in both the pre-integration stage and provirus stages. Two technical improvements could further increase the effectiveness of this antiviral system: (1) the use of a CRISPR/Cas9 that simultaneously targets several conserved sequences and thus minimizes the emergence of resistant viral variants; and (2) stable insertion into T cells, which might confer long-term protection against HIV infection. Lastly, one can expect to see this system used in developing novel therapies for other currently incurable viral diseases.

The rapid emergence of viral variants when only one viral gene is targeted is an issue for all HIV gene therapy strategies. This was highlighted by the case of the Essen patient—an HIV-positive lymphoma patient allotransplanted with an HLA-matched donor who was homozygous for the CCR5 delta32/delta34 mutation. A CXCR4-tropic HIV-1 variant rebounded rapidly after transplantation.

An in-depth comparison of the Berlin patient and the Essen patient might lead to the discovery of new genetic determinants of susceptibility to HIV infection and/or shifts in HIV tropism.

Clinical trial results for therapies designed to engineer cellular resistance to HIV infection (using a dual therapeutic lentiviral vector) are expected in the coming year. These results might tell us whether or not two targets are enough to confer stable resistance to HIV. The "Cal-1" dual anti-HIV lentiviral vector (LVsh5/C46) is intended to downregulate CCR5 expression (via RNA interference) and to inhibit HIV fusion (via the cell surface expression of cell-membrane-anchored C46 anti-viral peptide). The vector targets two points of inhibition for R5-tropic HIV and is active against HIV strains that do not use CCR5 (such as X4-tropic HIV-1); it has been shown to protect transduced cells against HIV infection in vivo.

An ongoing Phase I/II clinical trial (sponsored by Calimmune Inc.) is examining the safety and feasibility of infusing Cal-1-modified $CD34^+$ cells and $CD4^+$ T cells in treating people living with HIV previously exposed to antiretroviral therapy. The protocol includes the use of busulfan conditioning agent to enhance the engraftment of Cal-1-modified $CD34^+$ cells.

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a Unfortunately, Ward Cates died in March 2016. He was a major contributor to the UNAIDS Scientific Expert Panel and will be sorely missed as one of the world's foremost experts in HIV prevention and reproductive health.

Abbreviations

2LADY	evaluation of three strategies for second-line antiretroviral therapy in Africa
3TC	lamivudine
ABC	abacavir
Ad26	adenovirus subtype 26
ALLIANCE	NIH-PEPFAR-PMTCT Implementation Science Alliance
ALLY	daclatasvir plus sofosbuvir for hepatitis C virus among people coinfected with HIV
ANRS	Agence Nationale de Recherche sur le Sida
ASPIRE	a study to prevent infection with a ring for extended use
ATV/r	ritonavir-boosted atazanavir
bNAbs	broadly neutralizing antibodies
BREATHER	breaks in adolescent and child therapy using efavirenz and two nucleoside reverse-transcriptase inhibitors
CCR5	chemokine (c-c motif) receptor 5 (gene/pseudogene) is a protein coding gene; diseases associated with CCR5 include susceptibility or resistance to HIV infection and west Nile virus
CHAPAS-3	children with HIV-1 in Africa, pharmacokinetics and adherence and acceptability of simple antiretroviral regimens
CRISPR/Cas9	clustered regularly interspaced short palindromic repeat
COBI	cobicistat
CRF	circulating recombinant form
CROI	Conference on Retroviruses and Opportunistic Infections
ddI	didanosine
DNA	deoxyribonucleic acid
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
F/TAF	emtricitabine + tenofovir alafinamide
FTC	emtricitabine
HCV	hepatitis C virus
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HSV-2	herpes simplex virus type 2
HVTN	HIV Vaccine Trials Network
Ig	immunoglobulin
INSPIRE	integrating and scaling up the prevention of mother-to-child transmission of HIV through implementation research
IPERGAY	Intervention Préventive de l'Exposition aux Risques avec et pour les hommes Gays
KONCERT	a Kaletra® once-daily randomized trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy among children living with HIV-1
LATTE	long-acting antiretroviral therapy enabling
LPV/r	ritonavir-boosted lopinavir
MULTI-OCTAVE	management using latest technologies to optimize combination therapy after viral failure
MVA	modified vaccinia Ankara—an attenuated vaccine of a poxvirus
NNRTIs	non-nucleoside reverse-transcriptase inhibitors
NRTIs	nucleoside reverse-transcriptase inhibitors
NtRTI	nucleotide reverse-transcriptase inhibitor
ODYSSEY	once-daily dolutegravir in young people versus standard therapy
P5	Pox-Protein Public-Private Partnership
PEPFAR	United States President's Emergency Plan for AIDS Relief
PENTA	Paediatric European Network for the Treatment of AIDS
PHOTON	sofosbuvir plus ribavirin for treatment of hepatitis C virus among people coinfected with HIV
PI	protease inhibitor
PKC	protein kinase C
PrEP	pre-exposure prophylaxis
Project STATUS	strengthening HIV test access and treatment uptake study
PROUD	pragmatic open-label randomized trial of pre-exposure prophylaxis
RAL	raltegravir
RPV	rilpivirine
SIV	simian immunodeficiency virus
SELECT	study of options for second-line effective combination therapy
SOSIP	structure and antigenicity of soluble, cleaved (an HIV-1 Env trimer)
START	strategic timing of antiretroviral therapy
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEMPRANO	early antiretroviral therapy and/or early isoniazid prophylaxis against tuberculosis among adults living with HIV
THILAO	third-line antiretroviral therapy optimization in sub-Saharan Africa
TLR7	toll-like-receptor-7
TURQUOISE	ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin for hepatitis C virus among people coinfected with HIV
WHO	World Health Organization

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