

UNAIDS 2015 | REFERENCE

BIOMEDICAL AIDS RESEARCH: RECENT AND UPCOMING ADVANCES

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INTRODUCTION

Scientific evidence is essential for policies and programmes to advance the UNAIDS vision 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 in guiding future action towards the end of the AIDS epidemic.

To ensure that 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 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.

A main task of the UNAIDS Scientific Expert Panel during 2014 was to produce a report that captures the key 2014 advances in biomedical science on HIV and provides a glimpse of the new research that can be anticipated in 2015. This report primarily focuses on biomedical research. This report does not cover social and behavioural science or broader structural and human rights issues.

This report is not intended to be a comprehensive review of 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 2014 and five important research findings anticipated in 2015. Thereafter, the report provides brief summaries written almost entirely by Scientific Expert Panel members. The topics are divided into three main categories, advances in the 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 2014: WHAT'S IN STORE FOR 2015?

Salim S. Abdool Karim, Chair, UNAIDS Scientific Expert Panel

In 2014, we witnessed several major advances in HIV science, including some that emanated 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 HIV policy and programming. These top 10 highlights of 2014 provide a quick glance at some of the most significant biomedical research advances and their potential implications for the HIV response, with a glimpse into the world of HIV science to identify five new findings that may become available in the coming months.

1. Latest epidemiological estimates: a sober reminder that HIV remains a public health threat despite the global decline in new HIV infections

Globally, the number of people acquiring HIV infection decreased in 2014 as part of an almost decade-long trend in the HIV epidemic. These declines have been particularly prominent among young people who, despite this trend, still remain a major population at higher risk for HIV infection. The good news was tempered by data suggesting that HIV is not declining in several key populations and, indeed, is increasing in some groups such as gay men and other men who have sex with men in several countries. A particular concern is the ongoing high rates of new HIV infections among young women in southern Africa. Further, the number of people living with HIV continued to rise (to about 35 million in 2013) because of people newly acquiring infections and because of improved survival as a result of antiretroviral therapy becoming more widely available.

2. Antiretroviral therapy coverage expands to 13.6 million people, but several million more still to go.

Treatment coverage has continued to improve. By June 2014, an estimated 13.6 million people were receiving antiretroviral therapy. With almost 14 million people receiving treatment, the challenges of retaining people in care and the prospect of antiretroviral resistance are beginning to emerge. Scaling up antiretroviral therapy among children, however, remains a significant challenge, with only 24% of eligible children receiving treatment. In terms of treatment regimens,

clinical trials have shown new advantages of raltegravir in triple antiretroviral combinations. Further, the new class of integrase strand transfer inhibitors, including dolutegravir, have shown great promise, as new studies try to identify their ideal role in the complex treatment terrain.

3. Prevention benefits of treatment

In 2014, UNAIDS adopted a new set of treatment targets aiming to reach durable viral suppression among at least 73% of all people living with HIV worldwide by 2020. New results from serodiscordant couples showed no linked transmission events if the HIV-positive partner had a viral load of less than 200 copies/ml. Results released in 2014 have also shown the clinical therapeutic benefits of earlier initiation of antiretroviral therapy and modelling studies estimated the cost-effectiveness of earlier antiretroviral therapy.

4. The world takes a step closer to eliminating the mother-to-child transmission of HIV

Globally, very good progress is being made in eliminating new HIV infections among children in the most severely affected countries worldwide. New results in 2014 confirmed the effectiveness of triple antiretroviral therapy among pregnant women (option B) in preventing mother-to-child transmission. Some concerns about drug toxicity emerged in this study, but these did not warrant any changes to current guidelines at this time. Linkage to and retention in care for pregnant women needs attention as the *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive* heads towards the end of 2015.

5. At last. A cure for hepatitis C

Major advances were made on hepatitis C treatment in 2014. In particular, clinical trials showed more than 90% cure rate with sofosbuvir when used in combination with simeprevir or ledipasvir. These results are set to change the hepatitis C landscape, provided the drug is made available at an affordable price.

6. Oral antiretroviral prophylaxis is highly effective in preventing HIV among gay men and other men who have sex with men and among serodiscordant couples

Progress is being made in implementing pre-exposure prophylaxis using antiretroviral medicines among gay men and other men who have sex with men following more specific guidance from the United States Centers for Disease Control and Prevention. New evidence from the PROUD study in the United Kingdom supports the current recommendations on pre-exposure prophylaxis for gay men and other men who have sex with men. The IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les hommes Gays or

intervention to prevent high-risk exposure by and among gay men) trial extends current pre-exposure prophylaxis recommendations based on the 86% efficacy demonstrated by intermittent on-demand pre-exposure prophylaxis among gay men and other men who have sex with men in France and Canada. A secondary analysis of the iPrEX trial of daily pre-exposure prophylaxis among gay men and other men who have sex with men provided further support for intermittent pre-exposure prophylaxis. The use of daily oral pre-exposure prophylaxis by the HIV-negative partner in serodiscordant couples for the first six months after the HIV-positive partner initiated antiretroviral therapy reduced HIV acquisition substantially. Results in 2014, also from this pre-exposure prophylaxis study in serodiscordant couples, showed that daily tenofovir-containing pre-exposure prophylaxis is effective, albeit partly, in preventing infection with herpes simplex virus type 2. Given the close links between herpes simplex virus type 2 and HIV acquisition, tenofovir-containing oral pre-exposure prophylaxis may have an additional mechanism to affect HIV transmission in the longer-term.

7. A new focus on marginalized key populations

Key populations, comprising sex workers, gay men and other men who have sex with men, transgender people and people who inject drugs, continue to experience unacceptably high HIV incidence, despite the encouraging global trends of declining HIV incidence. Several studies have highlighted the challenges of prevention among and treatment access by key populations, who tend to use too few health services and who are discriminated against in many societies. Failure to provide HIV services to these groups undermines global progress in the HIV response.

8. Antibody findings bring new hope for a vaccine

Hope for a vaccine, which had waned following the results of the STEP trial, in which the adenovirus 5 vaccine increased HIV risk, rose substantially in 2014 based on new animal data showing that broadly neutralizing antibodies, while effective in preventing a simian/human immunodeficiency virus (SHIV) challenge in monkeys, may also have therapeutic benefits and even raised the prospect of a cure. New target sites for neutralization, including a site at the gp120–gp41 interface, and isolation of even more potent neutralizing monoclonal antibodies to the V2 apex and the high mannose patch on gp120 were identified in 2014.

9. Mississippi baby not cured

One of the greatest disappointments of 2014 was the report that the Mississippi baby, whom many had hoped had been cured of HIV with early initiation of antiretroviral therapy, turned out to be harbouring HIV in quiescent reservoirs. Similarly disappointing re-emergence of HIV was reported among two people from Boston receiving stem cell transplants. A new study in 2014 showed that the reservoir is seeded very early during HIV infection, even before HIV can be detected in the blood. These important findings highlight the enormity of the challenges in seeking a cure for HIV.

10. A future for gene therapy?

A study among 12 people showed that a genetic approach to treatment, where the CCR5 gene is "edited", was both feasible and safe. This study investigated the impact of CCR5-modified autologous CD4 T-cell infusions on CD4 cell counts, a promising approach that requires substantial further research.

Several important research findings are expected in 2015, including the following:

1. **The first in-human neutralizing antibody trial results.** Results are expected from the study of VRC01, a broadly neutralizing monoclonal antibody to reduce mother-to-child transmission.
2. **Sustainability of the prevention and prognostic benefits of early antiretroviral therapy initiation among HIV-serodiscordant couples.** Follow-up of participants in the HPTN 052 trial ends in 2015 and is expected to provide data on the sustainability of the effect of antiretroviral therapy in preventing HIV infection.
3. **Cash incentives for HIV prevention in adolescents.** The results of the CAPRISA 007 trial and the HPTN 068 are expected in 2015/6.
4. **Novel vaccine candidates.** Safety studies of a recombinant CMV-HIV vector vaccine, which has shown promise in animal model experiments, is anticipated to start soon.
5. **HIV cure strategies by activating the latent reservoir.** The results from several HIV cure-related clinical trials evaluating latency activation with romedepsin and high-dose disulfiram, immunomodulation with anti-PD1 and enhanced approaches using gene therapy to eliminate CCR5 are also likely to become available in late 2015.

ADVANCES IN THE TREATMENT OF HIV AND COMORBIDITIES

NEW ANTIRETROVIRAL AGENTS AND STRATEGIES

Andy Gray and Pedro Cahn

As global HIV testing and treatment strategies move forward towards the UNAIDS 90–90–90 targets for 2020, which aim for 90% of all people living with HIV knowing their HIV status, 90% of the people with diagnosed HIV infection receiving sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy having viral suppression, easy-to-take, effective, safe and affordable regimens are needed that fit growing budget constraints. Drug-sparing and long-acting regimens might emerge as new options. Continued access to affordable generic versions will be critical. In this regard, the licensing of both dolutegravir and tenofovir alafenamide (TAF) to the Medicines Patent Pool are notable. Much is expected from the Paediatric HIV Treatment Initiative, a joint initiative of UNITAID, the Drugs for Neglected Diseases initiative and the Medicines Patent Pool.

Efavirenz (EFV) has been the preferred third drug in first-line therapy in high-income countries for 15 years and is recommended in fixed-dose combination together with tenofovir disoproxil fumarate (TDF) and either emtricitabine (FTC) or lamivudine (3TC) by the World Health Organization (WHO). EFV has high potency and viral suppression rates, prolonged efficacy and simple daily dosing but also displays a low genetic barrier for resistance, and associated central nervous system adverse effects may persist. Direct comparisons show that EFV is inferior to the integrase strand transfer inhibitor raltegravir after five years and dolutegravir at 48 weeks. The preferred first-line combination may, however, be associated with long-term renal toxicity and reduced bone density. The combination of TAF + FTC + elvitegravir + cobicistat was associated with significantly less renal tubular proteinuria and smaller changes in bone mineral density compared with TDF + FTC + elvitegravir + cobicistat (the Quad tablet). A Phase 2b study showed that a new non-nucleotide reverse-transcriptase inhibitor (NNRTI), doravirine, has similar potency to and fewer adverse effects than EFV.

Adherence can be improved by increasing convenience and developing long-acting agents. Four single-tablet regimens are currently available: TDF + FTC (or 3TC) + EFV; abacavir + 3TC + dolutegravir; TDF + FTC + elvitegravir + cobicistat; and TDF + FTC + rilpivirine. In addition, the combination of TAF + FTC + darunavir + cobicistat is being developed. Two long-acting injectable preparations, long-acting

rilpivirine and long-acting cabotegravir, are also being developed and are being tested in the ongoing LATTE-2 study.

Although combination antiretroviral therapy with three agents remains the standard of care, various strategies for reducing drug burden are being explored. Protease inhibitor (PI) monotherapy failed to show non-inferiority to triple therapy among treatment-naïve people and is not recommended. Other strategies include reducing drug dose, class-sparing strategies and dual therapy including 3TC. The GARDEL study demonstrated that dual therapy with lopinavir + ritonavir (LPV/r) and 3TC was non-inferior to triple therapy after 48 weeks, regardless of baseline viral load. Virologic failure did not result in PI resistance, potentially preserving a wide range of second-line options. The OLE study reported that switching to LPV/r + 3TC (or FTC) was non-inferior to continued LPV + RTV plus two nucleoside reverse-transcriptase inhibitors (NRTIs) among virologically suppressed people. The NEAT 001 study provides evidence for NRTI-sparing regimens as an alternative option among antiretroviral therapy-naïve people, showing that a dual-therapy regimen including boosted darunavir and raltegravir is non-inferior to a triple drug combination, except for people with baseline CD4 counts of less than 200 cells/mm³. However, the evidence for using NRTI-sparing regimens is strongest in antiretroviral therapy-experienced people, as has been shown in the SECOND-LINE, OPTIONS and EARNEST studies.

HIV TREATMENT FOR CHILDREN

Dianne Gibb and Anna Turkova

Globally in 2013, 240 000 children newly acquired HIV; of these, >90% live in 22 countries with a high burden of HIV infection, 21 are in sub-Saharan Africa, the other is India. The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommended antiretroviral therapy for all pregnant and breastfeeding women (option B), expanded to lifelong antiretroviral therapy in countries with generalized epidemics for programmatic reasons (option B+), now adopted by about half the countries with a high burden of HIV infection. With expanding programmes to eliminate new infections among children, the number of children acquiring new HIV infections has fallen by 58% since 2002, the most rapid fall of about 50% in the past five years. In 2013, less than 45% of HIV-exposed infants had HIV diagnosis by polymerase chain reaction by age two months and few started antiretroviral therapy.

Early infant antiretroviral therapy has been shown to reduce mortality four-fold, highlighting the urgency of improving early infant diagnosis technology and programmes. For programmatic reasons, the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend antiretroviral therapy for all children younger than five years, and some countries have gone beyond this to recommend antiretroviral therapy for all children younger than 15 years. By 2014, 740 000 children worldwide had started antiretroviral therapy, but coverage was only 24% (versus 38% for adults). Nevirapine-based antiretroviral therapy for children still dominates globally, and the only low-cost triple fixed-dose combinations contain nevirapine. Recent data show that exposure to single-dose nevirapine for preventing mother-to-child transmission was not associated with virological failure among children.

Recent data from the CHAPAS-3 trial support using solid-based fixed-dose combinations for young children. This trial also showed no differences in toxicity or viral load and CD4 responses between zidovudine, abacavir or stavudine given with lamivudine and efavirenz + nevirapine. Lopinavir + ritonavir has been recommended for children younger than three years in the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, based on 24-week results from the IMPAACT P1060 trial, but remains very challenging for programmes and has not been taken up

by many national guidelines in resource-limited settings. Lopinavir + ritonavir pellets have been developed, which helps with storage issues, but problems with taste and administration remain.

Lopinavir + ritonavir is available as a combination tablet and liquid for children, but disappointingly, it was shown to be inferior if given once daily. A major disadvantage for once-daily PIs (atazanavir and darunavir) is the need to boost with ritonavir, since very unpleasant-tasting syrup or relatively large 100-mg tablets are difficult for young children to take. Second-line NNRTI-based antiretroviral therapy for young children starting lopinavir + ritonavir (such as in South Africa) is problematic given the poor adherence because of low barriers to resistance; the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend not switching until children are older than three years. Raltegravir is licensed for infants and may be a good first- or second-line alternative to lopinavir + ritonavir; it has disadvantages of twice-daily dosing, lack of fixed-dose combinations and high cost. Once-daily dolutegravir is promising and is going to be evaluated in the planned global ODYSSEY (PENTA 20) trial starting in 2015. A nucleoside-sparing new trial (SMILE, PENTA 17) starting in 2015 will evaluate daily boosted darunavir with elvitegravir among children with viral load suppression.

With antiretroviral therapy, children are reaching young adulthood. A global collaboration through the International AIDS Society is undertaking a cohort study on adolescent outcomes and duration of first-line antiretroviral therapy (CIPHER). Observational studies in the United States of America, France and the United Kingdom are evaluating the impact of lifelong HIV infection and long-term antiretroviral therapy on health and social outcomes compared with HIV-negative controls (AMP UP, COVERTE and AALPHI cohorts). New results from the BREATHER (PENTA 16) trial show that depending on the combination of drugs used, it is safe to interrupt antiretroviral therapy among children on EFV during weekends.

Ongoing pharmacovigilance of the antiretroviral drugs used for children will inform about long-term safety; data on long-term outcomes from exposure to tenofovir in utero and in HIV-positive children are needed, as are data to expedite licensing of TAF, a prodrug of tenofovir with a better safety profile. Long-acting injectable drugs (rilpivirine and cabotegravir) may be particularly useful for adolescents facing adherence problems. Finally, although the Mississippi baby was not cured, very early treatment of infants could contribute to viral control. IMPAACT is starting a new trial of very early antiretroviral therapy for HIV-positive infants.

HIV-ASSOCIATED MALIGNANCIES

Mark Bower

While the incidence of AIDS-defining cancers, especially Kaposi's sarcoma and non-Hodgkin's lymphoma are declining among people living with HIV, the incidence of non-AIDS defining malignancies is rising in the United States of America. A recently published meta-analysis assessing the impact of combination antiretroviral therapy on cancer incidence among more than 600 000 people living with HIV confirmed the declining risk of Kaposi's sarcoma (relative risk = 0.3) and non-Hodgkin's lymphoma (relative risk = 0.5) and the rising risk of non-AIDS-defining malignancies (relative risk = 2). The decline in Kaposi's sarcoma and non-Hodgkin's lymphoma has also been demonstrated in the Kampala cancer registry, the longest established cancer registry in Africa. Similarly, the percentage of deaths attributable to non-AIDS-defining malignancies has risen during the past decade.

Against this background, the outcomes of cancer therapy among people living with HIV have improved steadily, so that several recent publications have documented that the outcomes of cancer treatment and overall survival are the same for people living with HIV as for the general population as long as the same cancer treatment is given. However, an evaluation of cancer treatment among 3045 people living with HIV and 1 087 648 people with cancer and without HIV from cancer registry data of three states in the United States of America, all diagnosed since the widespread availability of combination antiretroviral therapy, showed that people living with HIV were less likely to receive standard anticancer therapy for non-Hodgkin's lymphoma, Hodgkin's lymphoma, prostate cancer, colorectal cancer and lung cancer. This disparity in clinical care for people living with HIV follows the well documented routine exclusion of people living with HIV from clinical trials of cancer therapy with little or no justification. Oncologists need to consider pharmacokinetic interactions and opportunistic infection prophylaxis when prescribing systemic anticancer therapy to people living with HIV.

WHO has recently published guidelines on the treatment of skin and oral HIV-associated conditions in children and adults, which includes the management of advanced Kaposi's sarcoma with systemic chemotherapy based on a Cochrane review. Now that the considerable benefits of cancer treatment for people living with HIV have been established, the roll-out of HIV cancer care needs to be supported at the local, national and international levels.

HEPATITIS COINFECTION AND TREATMENT

Karine Lacombe and Peter Reiss

After initially having been associated with transmission through contaminated blood products and nosocomially within hospitals, transmission of hepatitis C virus rapidly moved to affect people who inject drugs. Despite the demonstrated effectiveness of numerous harm reduction strategies, including needle and syringe programmes, opioid substitution and safe injecting facilities, injecting drug use remains the primary route of hepatitis C virus transmission around the world. However, among people living with HIV, the hepatitis C virus epidemic experienced a major shift in the mid-1990s, with sexual transmission, particularly among gay men and other men who have sex with men, surfacing as a major mode of acquiring hepatitis C virus.

Until recently, therapeutic options in hepatitis C virus infection had been quite limited and largely based on using a combination of pegylated-interferon alpha and ribavirin, yielding disappointing cure rates among people living with HIV. As a result of recent breakthroughs in hepatitis C virus research, new therapeutic targets within the virus replication cycle have been discovered. After the release in 2011 of the first direct acting antiviral agents inhibiting the hepatitis C virus NS3/4 protease, novel drugs with additional modes of action have been discovered. This has greatly accelerated the development of various interferon-free combination regimens that are far more effective and have much improved tolerability profiles. These have led to remarkable changes in hepatitis C virus treatment: once-daily, highly active and easily tolerated regimens, administered for a short period of time, curing hepatitis C virus infection in more than 90% of people, independent of whether they have failed prior treatment, the level of fibrosis and the presence of comorbidities such as HIV infection. This has the potential to curb the global hepatitis C virus epidemic, provided that advocacy for providing universal access to hepatitis C virus treatment to people most in need is successful.

The next global challenge in the response to hepatitis C virus may be how epidemics will be dealt with in low- and middle-income countries. In these countries, screening and access to care and treatment are hampered by inadequate disease surveillance, lack of high-quality tools to assess chronic liver disease and an underestimated need for human and financial resources. In most countries, chronic hepatitis may still be considered a silent and neglected killer. However, the global effort to address viral hepatitis is facing a new era in which governments, advocacy groups and global health organizations are all mobilizing to advocate for universal access to treatment and care for hepatitis C virus infection.

HIV AND TB COINFECTION

Kogieleum Naidoo and Nesri Padayatchi

Despite substantial progress in tuberculosis (TB) control, it remains the leading cause of morbidity and mortality among people living with HIV globally. The current rate of decline in TB incidence is insufficient to meet the elimination targets set out by the STOP TB Partnership (defined as less than one case per million people per year). In addition, the increase in multidrug-resistant and extensively drug-resistant forms of TB has transformed the dual epidemics into a public health crisis that threatens to reverse any gains made thus far.

Data from studies addressing the clinical complexities of managing HIV and TB coinfection continued to emerge in 2014. Recent data have confirmed previous findings with respect to immune reconstitution inflammatory syndrome as well as antiretroviral therapy and TB drug interactions and pharmacogenomics. New findings include a demonstration that different doses of rifabutin did not significantly affect lopinavir + ritonavir plasma concentrations and that PA-824, a novel antituberculosis nitroimidazole, could be co-administered with lopinavir/r without dose adjustment. In an assessment of the effect of the timing of antiretroviral therapy initiation on TB treatment outcomes for people living with HIV with CD4 counts >220 cells/mm³, recent data demonstrated that 8.5% of those receiving early antiretroviral therapy (two weeks from TB therapy) and 9.2% of those with delayed antiretroviral therapy (after completing TB treatment) developed the primary endpoint of TB treatment failure: TB recurrence and death within 12 months (relative risk 0.91; 95% CI 0.64–1.10; $P = 0.9$). Since the benefits of early antiretroviral therapy from both an individual and programmatic level are convincing, this new evidence is unlikely to lead to changes in WHO guidelines.

Recent data on the treatment of HIV-associated TB show that TB treatment cannot yet be shortened with the current drugs. This includes the Remox study, which demonstrated that treatment-shortening regimens using moxifloxacin were non-inferior to an ethambutol-containing regimen. Efficacy and safety results are expected for many new TB drugs, and new TB drug classes currently being developed. These include bedaquiline; delamanid; PA-824; sutezolid and other oxazolidinones; SQ-109, an ethambutol analogue; and long-acting rifamycins, such as rifapentine. A recent report from an early-phase clinical trial among both HIV-positive and HIV-negative people demonstrated

that sutezolid has good early bactericidal activity at 14 days at doses of 1200 mg once daily and 600 mg twice daily and is generally safe and well tolerated. We are likely to hear about these drugs and other advances in managing HIV and TB coinfection in 2015 and beyond.

WHO has only recently recommended single-drug or combination regimens of isoniazid and/or rifapentine + rifampicin for individuals at high risk of developing the disease. The ACTG 5279 study is evaluating the safety and effectiveness of a four-week regimen of rifapentine and isoniazid versus a standard nine-month regimen of isoniazid for people living with HIV who are at risk of developing active TB and aims to provide a significantly shorter TB prophylactic regimen. Since the lifetime risk of progression to active TB disease is 5–15% for people with latent infection, treating latent TB infection is critical to sustained control of TB.

Another ongoing study that can potentially affect HIV and TB treatment is the REMEMBER (A5274) study investigating whether initiating TB treatment among people living with HIV at high risk of infection, but without current TB infection, reduces morbidity and mortality. This strategy study is important, since it addresses the high morbidity and mortality among people living with HIV despite access to antiretroviral agents.

Recent results from the TEMPRANO study suggest that early antiretroviral therapy initiation among people with a CD4 count >500 cells/mm³ reduced HIV morbidity, particularly TB, compared with people who initiated antiretroviral therapy at CD4 counts <200 cells/mm³. It remains unclear as to whether initiating antiretroviral therapy at CD4 counts >500 cells/mm³ is advantageous compared with initiating antiretroviral therapy at CD4 counts ≤ 500 cells/mm³. The results of the START study, due in 2017, are awaited to address this question.

DRUG RESISTANCE AND SECOND- AND THIRD-LINE ANTIRETROVIRAL THERAPY OPTIONS

Praphan Panupak and Beatriz Grinsztejn

During the past decade, antiretroviral therapy access has increased substantially in low- and middle-income countries. However, many people living with HIV who are receiving treatment and for whom first-line antiretroviral therapy is failing are still awaiting transition to second-line antiretroviral therapy. Global access to second- and third-line antiretroviral therapy remains limited. An analysis from three clinical trials by the AIDS Clinical Trials Group evaluating virological failure on first-line boosted PI (PI/r)-based antiretroviral therapy showed that, for people for whom treatment is failing with no or limited drug resistance, remaining on the same regimen coupled with strategies to improve adherence are effective to achieve virologic suppression.

Poor adherence rather than HIV drug resistance drives most failures of second-line treatment, with almost 22% of the people living with HIV receiving treatment not reaching viral suppression within six months. Optimizing adherence, performing resistance surveillance and improving treatment monitoring are critical for long-term prevention of drug resistance. Improving procurement and supply management procedures is an important step. Food insecurity has also been associated with poor adherence.

The SECOND LINE trial evaluated alternative second-line treatment strategies in 15 middle- and high-income countries, comparing a ritonavir-boosted lopinavir (lopinavir/r) plus a nucleoside or nucleotide reverse-transcriptase inhibitor (NtRTI) backbone with a novel dual-treatment approach combining lopinavir/r with the integrase inhibitor raltegravir (RAL). The RAL plus LPV/r was non-inferior to the current WHO-recommended second-line regimen. In the RAL arm, major integrase mutations emerged in 20.3% (16 of 79). The LPV/r + RAL regimen was associated with less bone loss than the LPV/r + NRTI regimen.

Without performing routine viral load monitoring or resistance testing, the EARNEST trial evaluated RAL + LPV/r; LPV/r + two NtRTIs; and LPV/r monotherapy regimens. The use of RAL was not superior to the NtRTIs, which retained substantial virologic activity without increased toxicity; the LPV/r monotherapy regimen was inferior, further supporting the

current WHO-recommended second-line regimen. Ongoing additional second-line treatment studies will provide information on alternative treatment strategies (2LADY and SELECT/5273). Although LPV/r-based regimens are effective, novel second-line strategies are necessary because of the tolerability and toxicity issues with this regimen. Dolutegravir for salvage therapy was shown to be successful in the SAILING and VIKING-3 studies, although cost challenges are associated with twice-daily dosing requirements because of drug resistance.

The results from recent studies have shown that both (a) initiation of third-line therapy partnered with adherence reinforcement and (b) use of resistance testing to assess people on current second-line strategies and guide third-line antiretroviral therapy regimen decisions are cost-effective in low- and middle-income countries. Two third-line trials are underway in low- and middle-income countries. A trial named THILAO uses behavioural adherence interventions plus a 48-week follow-up phase. People who reach viral suppression continue second-line antiretroviral therapy combined with adherence reinforcement; people with persistent virologic failure are switched to darunavir/r + raltegravir-based third-line antiretroviral therapy. Resistance testing is performed retrospectively. The second trial, A5288/MULTI-OCTAVE, is underway globally at 20 sites. It will evaluate resistance test-based antiretroviral therapy strategies and the utility of randomized mobile phone-based adherence intervention.

Transmitted drug resistance is increasing in key populations in low- and middle-income countries where pre-antiretroviral therapy resistance testing is not routinely performed. Resistance testing has been shown to be cost effective in several settings; efforts should be made to increase access to resistance testing in low- and middle-income countries to ensure the sustainability of antiretroviral therapy programmes.

GLOBAL PROGRESS ON PROGRAMMES FOR ROLLING OUT ANTIRETROVIRAL THERAPY

Wafaa El-Sadr and Suniti Solomon

Evidence of the efficacy of antiretroviral therapy for preventing HIV transmission in HPTN 052 along with knowledge of effectiveness of antiretroviral therapy for preventing HIV-related morbidity and mortality have informed the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. The updated guidelines expand the criteria for initiation of antiretroviral therapy and call for continued efforts for rapidly scaling up antiretroviral therapy programmes. Such an approach is reflected in the UNAIDS 90–90–90 targets for 2020, which aim for 90% of all people living with HIV knowing their HIV status, 90% of the people with diagnosed HIV infection receiving sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy having viral suppression. Getting to 90–90–90 will not be easy and will require empirical data from the field on what rates of coverage can realistically be achieved and how to maximize these.

Recent data provide reason for optimism. By June 2014, 13.6 million people were receiving antiretroviral therapy and the number of AIDS-related deaths continued to decrease, with 1.5 million people dying from AIDS-related causes in 2013, a 35% decrease from the peak in 2005. Although this is encouraging, AIDS-related mortality remains a major public health burden. An estimated 2.1 million people acquired new HIV infections in 2013, a 38% decrease from 2001, although the decrease seems to be less marked in recent years. There is also encouraging evidence on how expanding antiretroviral therapy affects the HIV incidence at the community level. In one study in rural South Africa, using antiretroviral therapy was associated with a decrease in HIV incidence among household members of the opposite sex.

Despite these successes, treatment coverage for adults is estimated to be only 38% and only 24% for children eligible for treatment in accordance with WHO guidelines. Inadequate modalities for HIV testing, ineffective linkage to care, delayed treatment initiation and suboptimal adherence compromise treatment and prevention outcomes.

Various approaches have been evaluated to strengthen steps along the HIV care continuum. Efforts to expand HIV testing using new approaches have been examined. These include reaching individuals

within households for HIV testing. One study conducted in Uganda used a multi-disease health campaign to rapidly increase HIV testing rates and identify people with undiagnosed HIV infection, resulting in HIV tests being performed among 98.3% of participants (4795 of 4879), with 38% reporting no prior HIV testing. In a cluster randomized trial in rural Lesotho among 3197 individuals, HIV testing through mobile units was compared with home-based testing, with evidence supporting both approaches and information garnered on how each approach enables reaching different populations. In addition, HIV self-testing offers a new opportunity to expand testing. Findings from a randomized clinical trial in Malawi demonstrated high acceptability of HIV self-testing, particularly among younger cohorts, which tend to be hard to reach, and its association with more rapid initiation of antiretroviral therapy.

Studies have also described challenges in linking people living with HIV to HIV care because of the challenges they face on an individual basis as well as factors related to structural facilities. Retention in care is also recognized as an important challenge in HIV care and treatment programmes. At the same time, recent studies have shed light on factors that may lead to overestimating loss to follow-up, including transfer of patients and transient interruption of care. Importantly, insights into the reasons for treatment interruption have been described that will be critical in shaping programmatic interventions. In addition, recent reviews have described interventions for enhancing linkage and retention. For example, point-of-care CD4+ testing was shown to be associated with enhanced linkage, initiation of antiretroviral therapy and survival and was shown to be cost-effective.

The limited scale-up of effective HIV care and treatment among vulnerable and key populations has also received recent scientific attention. Recent studies have demonstrated that adolescents and young people have higher losses to follow-up in HIV programmes while remaining at substantial risk for HIV infection.

Finally, simplifying the treatment model will be critical in enhancing a public health approach to reaching global targets through large-scale implementation of antiretroviral therapy programmes.

ADVANCES IN HIV PREVENTION

HIV VACCINES

Bruce D. Walker and Pontiano Kaleebu

The quest for an HIV vaccine is gaining momentum, and much progress has been made in the past year, but huge challenges remain. Among these are new animal model data indicating that the viral reservoir is seeded before plasma virus becomes detectable in acute infection, so the window of opportunity for vaccine efficacy may be smaller than previously anticipated. Further, direct measurements of the dynamic properties of envelope trimers on infected cells have revealed that they are spontaneously transitioning between multiple conformations and creating a moving target for neutralizing antibodies. Despite detection of broadly neutralizing antibodies in natural infection, we still do not know how to induce these.

Despite these and other challenges, steady progress is being made. A small fraction of people living with HIV generate effective neutralizing antibodies, and important new sites for neutralization have been identified in the past year, including a site at the gp120-gp41 interface, and even more potent neutralizing monoclonal antibodies to the V2 apex and the high mannose patch on gp120 have been isolated. Thus, the number of potential targets for neutralization is increasing. Important longitudinal studies in individuals from the time of acute infection are beginning to shed light on the developmental pathways that lead to broadly neutralizing antibody responses, and, at least in certain instances, this is through initial selection of B cells with a long CDR3 region, which then requires less somatic hypermutation. Evidence that monoclonal neutralizing antibodies are effective as adoptive therapy in vivo in mice and monkey models of HIV infection provide encouragement and have revealed that escape from neutralizing antibody by alteration of glycosylation sites can render the mutated virus sensitive to antibodies in vivo that would otherwise not be able to gain ready access for binding. In addition to these advances in neutralizing antibodies, a wealth of additional information indicates that the non-neutralizing antibodies, through a variety of effector mechanisms, may also be effective. Such antibodies induced by RV144 lowered infection risk, likely influenced by genetic polymorphisms in the Fc receptor, although low-dose passive transfer of non-neutralizing antibodies has thus far failed to show a protective effect.

Progress toward clinical vaccine trials is also being made, with a number of candidates to elicit T-cell and B-cell responses entering into phase I clinical trials on the path toward efficacy studies. The most advanced in clinical development include mosaic Ad26 vectors that are likely to be used in conjunction with a trimeric envelope protein or mosaic modified vaccinia virus Ankara (MVA) boost, as well as clade C ALVAC and NYVAC vectors that will be used in conjunction with an adjuvanted bivalent clade C gp120 protein immunogen. New immunogens are also being developed, including conformationally stable protein scaffolds mimicking envelope neutralization epitopes, which may provide a means to engage appropriate germ-line antibody responses and enhance appropriate somatic hypermutation through the use of serial immunogens. Other non-vaccine immunological approaches are also underway. A human trial of an adeno-associated virus (AAV) expressing a broadly neutralizing antibody directed at the V2 apex has been initiated. Passive transfer studies of potent neutralizing monoclonal antibodies were also initiated in humans in 2014, and subsequent planned studies should provide a unique opportunity to define the parameters required for an effective preventive and therapeutic neutralizing antibody. A recombinant cytomegalovirus-HIV vector is also in development and has shown more than 50% efficacy in animal model experiments.

Prevention technologies for HIV continue to advance, and based on the demonstrated efficacy of RV144 and the advances outlined above, optimism is growing that effective vaccination will ultimately be achieved.

THE PREVENTION BENEFITS OF TREATMENT

Myron Cohen and Richard Hayes

Previous research has demonstrated that heterosexual HIV transmission is closely correlated with viral load, that the risk of transmission from people receiving antiretroviral therapy with viral suppression is very low and—in a randomized controlled trial—that earlier initiation of antiretroviral therapy reduced HIV transmission by 96%. Modelling studies showed that, at the population level, the offer of the test-and-treat strategy could reduce HIV incidence substantially, although projections varied widely. Observational data from the KwaZulu-Natal province of South Africa showed that higher antiretroviral therapy coverage at the population level was associated with lower HIV incidence. Empirical evidence of the prevention benefits of treatment at the community level is currently limited, but several large-scale community-randomized studies have recently been initiated to assess the potential effect of expanded testing and treatment on HIV incidence and on the control of the epidemic at the community level.

Key advances during 2014 include observational data from the PARTNER study that showed zero linked transmission events in serodiscordant couples in which the HIV-positive partner had a viral load of less than 200 copies/ml. Importantly, this included both heterosexual couples and couples with gay men and other men who have sex with men, complementing previous research focused on heterosexual transmission.

A systematic review and meta-analysis of studies of HIV transmission among heterosexual couples in which the HIV-positive partner had been receiving antiretroviral therapy for at least six months showed an estimated transmission rate of less than 13 per 100 000 unprotected sex acts. Further study results released in 2014 have shown the clinical benefits of earlier usage of antiretroviral therapy; the potential cost-effectiveness of earlier antiretroviral therapy based on modelling studies; and uncertainty about the importance of detecting and treating people with acute and early HIV infection, again based primarily on model simulations. One concern about the widespread use of treatment as prevention is the potential for behavioural disinhibition. Although many studies have shown that this concern is unfounded, one study among HIV-negative gay men and other men who have sex with men in Australia showed that the perception that the partner's viral load may be undetectable was associated with increased practice of unprotected anal intercourse but was not associated with increased HIV seroconversion in

this cohort. Presentations at the 20th International AIDS Conference in Melbourne, Australia on 20–25 July 2014 have drawn attention to the potential impact of placing the responsibility for HIV prevention solely on the HIV-positive partner.

Increasing access to HIV testing and knowledge of HIV status are key to scaling up access to treatment. Data from Project Accept, a multicountry community-randomized trial, have shown that testing rates can be significantly increased through a package including mobile voluntary counselling and testing services, with a potential effect on HIV incidence.

In the next year, the HPTN 052 trial will end and provide data on the durability of treatment as prevention among heterosexual couples followed for 5–10 years. The START trial is also scheduled for completion in the next 1–2 years, and this study will provide further evidence regarding the clinical benefit of starting antiretroviral therapy early at CD4 counts exceeding 500 cells/mm³.

MICROBICIDES AND PRE-EXPOSURE PROPHYLAXIS

Ward Cates and Quarraisha Abdool Karim

There have been significant advances in the use of antiretroviral medicines, as oral or topical pre-exposure prophylaxis, for HIV prevention in the past few years. The recent approval by the United States Food and Drug Administration of the first antiretroviral drug Truvada® (emtricitabine and tenofovir disoproxil fumarate) as pre-exposure prophylaxis for reducing the risk of sexually acquired HIV has led to antiretroviral pre-exposure prophylaxis being included as part of a comprehensive HIV prevention package. This has increased HIV prevention options for gay men and other men who have sex with men and for serodiscordant couples. Since it was approved, there has been much debate on how best to scale up pre-exposure prophylaxis. The initial experiences with pre-exposure prophylaxis uptake and delivery in three different settings in San Francisco, California show that interest in pre-exposure prophylaxis is high and that pre-exposure prophylaxis can be an important component of comprehensive HIV prevention programmes.

The IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les hommes Gays, or intervention to prevent high-risk exposure by and among gay men) trial assessed an on-demand pre-exposure prophylaxis dosing strategy in a cohort of HIV uninfected gay men and other men who have sex with men. Participants took two pills 2–24 hours before each act of sexual intercourse, another pill 24 hours after sex and a fourth pill 48 hours after sex. This on-demand pre-exposure prophylaxis reduced the incidence of HIV by 86% (95% confidence interval: 39.4–98.5%, $P = 0.002$) compared with placebo. Secondary analysis from the iPrEX and iPrEX OLE studies, published in 2014, showed that oral pre-exposure prophylaxis can be effective when taken at least four times per week. These results have provided the first evidence that intermittent oral pre-exposure prophylaxis is highly effective in preventing HIV infection among gay men and other men who have sex with men.

New evidence of 86% reduction in HIV incidence from the PROUD (Pragmatic Open-Label Randomised Trial of Pre-exposure Prophylaxis) study in the United Kingdom support the current recommendations on daily Truvada® as pre-exposure prophylaxis for gay men and other men who have sex with men. The Partners Demonstration project among HIV-serodiscordant heterosexual couples in Kenya and Uganda showed

that a programme that delivers both pre-exposure prophylaxis for HIV-negative partners and/or antiretroviral therapy for HIV-positive partners could virtually eliminate HIV transmission (reducing the risk of HIV infection by 96%). These results highlight the potential impact of combining pre-exposure prophylaxis and antiretroviral therapy to slow the HIV epidemic.

Using topical pre-exposure prophylaxis (microbicides) is an important strategy being developed for vaginal application among women and rectal application among gay men and other men who have sex with men to prevent sexual acquisition of HIV. Currently, the clinical pipeline for microbicides includes several antiretroviral drugs (such as tenofovir, dapivirine and maraviroc) being delivered in gels and monthly vaginal rings. New advances in 2014 have focused on understanding microbicide efficacy behaviourally and biologically. A series of articles published in 2014 captured the key issues regarding adherence in microbicide trials: specifically, measurement of adherence, strategies for enhancing adherence and factors influencing adherence. These articles underscore the importance of ongoing adherence support through an interactive, nonjudgemental process between microbicide users and providers, enhancing self-reports of adherence with biological measures, a nuanced understanding of perceived HIV risk and the importance of contextual and relationship issues, including gender-power dynamics that influence decisions to use or not use microbicides. Data on adherence from the VOICE trial, which studied daily oral and topical tenofovir, are starting to emerge. Secondary analysis from this trial suggests a protective effect against herpes simplex virus type 2 in the tenofovir gel arm. Disappointingly, new results from the FACTS 001 study, undertaken as a confirmatory study of the effectiveness of coital tenofovir gel, did not confirm the efficacy shown in the CAPRISA 004 trial because of suboptimal adherence. The results of the VOICE and FACTS 001 trials have been a setback in realizing an HIV prevention strategy that can be controlled by women, and attention has shifted to strategies that are less user-dependent, such as monthly vaginal rings.

In 2015, we anticipate results from the phase II study (MTN 017) of the reduced glycerine formulation of 1% tenofovir gel for rectal use among gay men and other men who have sex with men. Two phase II trials of the three-monthly injectable cabotegravir (long-acting) and a phase II trial of the two-monthly injectable rilpivirine for HIV prevention are scheduled to begin during 2015.

ELIMINATING MOTHER-TO-CHILD TRANSMISSION

Elaine Abrams and Hoosen Coovadia

During the past decades, a series of randomized clinical trials and observation studies on preventing mother-to-child HIV transmission have demonstrated the efficacy of antiretroviral medicines to prevent HIV transmission and have advanced understanding of the pathophysiology of perinatal infection. Antiretroviral medicines given during pregnancy and delivery and throughout the duration of breastfeeding coupled with optimal breastfeeding practices (exclusive feeding for six months with the addition of complementary feeding thereafter) have been demonstrated to reduce transmission risk to less than 5% and improve survival of women living with HIV and maternal health outcomes. Globally, with the scale-up of antiretroviral medicines and programmes for preventing mother-to-child HIV transmission, most resource-limited high-prevalence countries report substantial progress in preventing children from acquiring HIV infection. However, in 2013, there were an estimated 240 000 new HIV infections in children globally, with more than 95% attributed to mother-to-child transmission. Accelerated progress is warranted to reach the 2015 targets for the *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive*.

In 2014, several studies released findings that made important contributions to the field. The PROMISE study (Promoting Maternal and Infant Survival Everywhere), a multicountry randomized clinical trial, demonstrated the superiority of triple-medicine antiretroviral prophylaxis compared with monotherapy during pregnancy for preventing mother-to-child transmission during pregnancy among women not eligible for lifetime antiretroviral therapy. The study also found overall low rates of adverse events but significantly higher rates of side effects among mothers and higher rates of prematurity, low birth weight and infant mortality in the triple-medicine arm compared with monotherapy. The study confirms the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommending triple antiretroviral medicines for all pregnant and breastfeeding women. The Paediatric HIV/AIDS Cohort Study's Surveillance Monitoring of Antiretroviral Therapy Toxicities Study, a prospective cohort study of HIV-exposed infants in the United States, published data in 2014 demonstrating low rates of congenital anomalies among babies exposed to antiretroviral medicines at the time of

conception. The overall risk of congenital anomalies among 2580 infants was low, and the authors found no association between first-trimester exposure and congenital anomalies for any single antiretroviral medicine, antiretroviral medicine combination regimens or any single antiretroviral medicine class. There was a relative increase in risk in successive years of observation and with atazanavir exposure. The French Perinatal Cohort also reported on congenital anomalies among infants exposed to first-trimester antiretroviral medicines. Although the overall rates were reassuringly low, they reported a higher rate of heart defects among infants exposed in utero to zidovudine and a possible association between efavirenz and neurological defect. Findings from both studies underscore the need for continued vigilance, particularly as more women conceive on triple-medicine regimens. Finally, two additional studies offered important insights into the challenges of implementing successful programmes for preventing mother-to-child HIV transmission. In Botswana, a country with a mature, highly successful programme and a reported mother-to-child HIV transmission rate of <4%, an analysis of all new HIV infections among children in Francistown from June 2005 to December 2012 revealed substantial weaknesses in the postnatal infant cascade of care. Of 10 923 HIV-exposed infants, only 71% were tested for early infant infection; only 75% of mothers of 202 children testing positive received infant test results, and only 60% of babies initiated treatment. In Malawi, a detailed analysis from the national option B+ programme for preventing mother-to-child HIV transmission found that women starting antiretroviral therapy during pregnancy were five times more likely to fail to return after their initial visit compared with people starting antiretroviral therapy for their own health.

The association between hormonal contraception and HIV risk remains contentious. In 2014, WHO reviewed the available evidence and recommended no changes to the medical eligibility criteria for contraception but proposed that women at high risk of HIV be informed that progestogen-only injectables may or may not increase their HIV risk and advised on condom use.

In the years ahead, we can expect more results from the PROMISE study, especially on long-term maternal and child health outcomes, as well as the INSPIRE studies, an implementation research collaboration studying approaches to increase access to effective programmes for preventing mother-to-child HIV transmission. Finally, preliminary studies on the use of monoclonal antibodies to reduce mother-to-child HIV transmission have been undertaken and could potentially provide a model for immunization against HIV transmission through breast-milk.

MEDICAL MALE CIRCUMCISION

Helen Weiss and Elly Katabira

Modelling studies undertaken in 2009–2011 estimated that circumcising 80% of adult males in 14 priority countries in eastern and southern Africa within five years, and sustaining coverage levels thereafter, could prevent 3.4 million people from acquiring HIV infection within 15 years. In response, WHO and UNAIDS launched the joint strategic action framework for accelerating the scale-up of voluntary medical male circumcision for HIV prevention in southern and eastern Africa, calling for 80% coverage of adult male circumcision by 2016—around 20 million men. Voluntary medical male circumcision continued to be scaled up in 2013 and 2014, and an estimated 6 million men had been circumcised by December 2013.

Several innovative studies completed in 2014 evaluated novel strategies to increase the uptake of voluntary medical male circumcision, including randomized trials of financial compensation in the form of food vouchers in Kenya and a 60-minute single-session sports-based programme led by circumcised men in Zimbabwe and monetary compensation in South Africa. The economic incentive trial, undertaken in Nyanza region, Kenya, showed that uptake of circumcision within two months of enrolment was highest in the group receiving US\$ 15 or US\$ 8.75 (9.0% and 6.6% respectively) compared with lesser amounts (<2% uptake). The sports-based cluster randomized trial (MCUTS), undertaken in Bulawayo, Zimbabwe, showed that the intervention increased the uptake of voluntary medical male circumcision from 0.8% in the control arm to 5.4% in the intervention arm. However, the overall low rate of uptake, even in the intervention arms of both trials, is notable.

An area of rapid growth is the potential of new devices for voluntary medical male circumcision such as the ShangRing and PrePex™. Several studies have shown devices such as PrePex™ to be safe and acceptable in adult men, with similar rates of adverse events compared with surgery, although the risk of severe adverse events and particularly the potential risk of tetanus means that devices should be used only within reach of surgical facilities.

Services for voluntary medical male circumcision are delivered across multiple service levels, with considerable potential for variability in service quality. An adapted version of the WHO Quality Assessment Toolkit has

recently been evaluated (SYMMACS—Systematic Monitoring of the Medical Male Circumcision Scale-up) and validated in Kenya (Nyanza region), South Africa, the United Republic of Tanzania and Zimbabwe. A comparative assessment of facilities in these four countries using the SYMMACS tool showed mixed results in terms of facility preparedness. Another study focusing on the quality of surgical care based on observing voluntary medical male circumcision procedures found many challenges in rapidly developing large numbers of new voluntary medical male circumcision sites with the necessary equipment, supplies and protocols.

Further funding and work are needed to address challenges in meeting the 2016 target for voluntary medical male circumcision. The current rate at which voluntary medical male circumcision is increasing is not adequate, and further work on designing, evaluating and scaling up innovative strategies, including adding other services of interest for men, is needed. In addition, further work on new technologies including the use of devices in adolescents and by different types of provider will be very useful, as will a focus on increasing uptake among infants, as the end of the catch-up phase among adult and adolescent men approaches in some settings. Finally, focus is needed on how best to strengthen health systems so that they can adequately support the scaling up of voluntary medical male circumcision, including involving the private sector to complement the public health service delivery system as a partnership.

PREVENTION AND TREATMENT FOR PEOPLE WHO INJECT DRUGS

Adeeba Kamarulzaman and Wu Zunyou

Although the overall HIV incidence and mortality have declined globally, people who inject drugs have not benefitted from improvements in HIV prevention and treatment activities. The HIV prevalence among people who inject drugs is 28 times greater than among the general population, and people who inject drugs comprise 30% of the people acquiring new HIV infection outside sub-Saharan Africa. Inadequate HIV prevention and treatment services for people who inject drugs continue to fuel volatile HIV epidemics in eastern Europe, the Middle East and North Africa and South-East Asia, with emerging epidemics also being reported in several countries in sub-Saharan Africa. However, promising policy changes have taken place in some countries with very high prevalence of HIV infection among people who inject drugs, leading to increased coverage of key programmes such as needle-syringe programmes and opioid substitution therapy in China, Malaysia, Viet Nam and Ukraine, although many policy and legislative challenges remain in these countries.

In addition to needle-syringe programmes and opioid substitution therapy, one study has shown that pre-exposure prophylaxis with tenofovir reduced the risk of acquiring HIV among people who inject drugs by about 49%, although the data should be interpreted with caution since HIV transmission that occurs through sex and that occurring parenterally cannot be distinguished. Multiple considerations including long-term safety, optimal testing strategies, how to best deliver pre-exposure prophylaxis and how to optimize cost-effectiveness are being explored.

Adherence and retention in care pose substantial challenges in providing treatment for people who inject drugs who are living with HIV. Directly administered antiretroviral therapy, opioid substitution therapy and integrating HIV and drug dependence services have been shown to improve antiretroviral therapy outcomes among people who inject drugs. However, a recent randomized controlled trial comparing directly administered antiretroviral therapy and self-administered therapy among people living with HIV did not show any benefit from directly administered antiretroviral therapy compared with self-administered therapy. Nevertheless, although directly administered antiretroviral therapy is associated with the need for increased human resources and

is logistically challenging, a recent cost–effectiveness study integrating directly administered antiretroviral therapy into opioid substitution therapy supports its use, especially in low- and middle-income countries. Meanwhile, a study examining the integration of opioid substitution therapy, HIV and TB treatment services in Ukraine found improved outcomes for each condition as well as improved adherence and retention in TB treatment.

Although progress has been made in HIV prevention and treatment for people who inject drugs, substantial challenges remain: (a) ensuring the delivery of high-quality care for treating drug dependence as well as HIV and related diseases, (b) policy and legal environments that continue to criminalize drug use and (c) pervasive stigma and discrimination towards people who inject drugs within the community. Changing patterns of drug use, especially non-injecting drug use such as cocaine (including crack) and methamphetamine, in addition to new and emerging substances (such as synthetic cannabinoids, cathinones and other amphetamine analogues) are increasing the risk of sexual transmission of HIV and provide additional challenges for HIV prevention and control. Research into programmes that address this new challenge is urgently needed, including drug dependence treatment as well as behaviour risk reduction, combination HIV prevention and structural interventions. Further, models of care that improve the engagement and retention of people who inject drugs across the HIV care continuum need to be investigated further. Eliminating HIV among people who inject drugs is critical to the global aim of ending the AIDS epidemic as a public health threat by 2030.

ADVANCES IN HIV PATHOGENESIS, DIAGNOSTICS AND CURE

MUCOSAL VIRAL ENTRY AND ESTABLISHMENT OF SYSTEMIC INFECTION

Ashley Haase and Daniel Douek

Several studies, especially those in South African cohorts, have shown a correlation between inflammatory profiles in the female genital tract and risk of HIV acquisition. Importantly, an immune quiescent profile seems to be associated with protection from acquisition upon repeated HIV exposure. These studies extend the mounting body of evidence that markers of gut dysfunction, inflammation and coagulopathy, particularly soluble markers in plasma such as IL-6, sCD14 and d-dimers predict morbidity and mortality from AIDS-related and non-AIDS-related conditions independently of plasma virus load or CD4 T-cell count.

In contrast, the identification of several host restriction factors that impede the replicative cycle of HIV, such as APOBEC3G, MX2, tetherin, cGAS and SAMHD1, and many of which are interferon-stimulated genes associated with an innate immune response, suggest that inflammation may also confer benefit during acquisition. Indeed, two studies showed that transmitted and founder HIV clones are relatively resistant to interferon- α (IFN α), implying antiviral pressure during acquisition. This dichotomy was recently addressed directly in acutely simian immunodeficiency virus (SIV)-infected rhesus macaques, and found that administering IFN α reduced virus acquisition after intra-rectal challenge, whereas blockade of IFN α signalling led to greater virus replication and more rapid disease progression to AIDS. Thus, inflammation may have both beneficial and detrimental effects, which may differ in impact during transmission, acute and chronic infection and may also differ depending on the anatomical location of virus transmission. Although interventions to reduce microbial translocation and subsequent immune activation during chronic HIV infection among humans have proved only marginally effective, such interventions during SIV transmission and acute infection among macaques have conferred considerable benefit in terms of virus load, immune activation and CD4 T-cell depletion.

Translating these insights into the roles of the innate immune and inflammatory response to prevent infection, one of the correlates of protection conferred by a live attenuated SIV vaccine was related to inhibition of the facilitating aspects of the innate response to vaginal challenge in the SIV–rhesus macaque model of HIV-1 transmission to women. In unvaccinated animals, vaginal exposure to SIV elicits

recruitment of CD4 T cells that fuel local expansion of infected founder populations, thus paradoxically facilitating transmission. Vaccination with SIV with a deleted nef gene induces a system of antibody production and concentration in the female reproductive tract. The concentrated antibodies form immune complexes that engage the inhibitory Fc receptor IIb in the lining epithelium and a subsequent inhibitory programme that epitomizes the evolution of the immune system to distinguish between what it has and has not previously encountered.

Looking forward, discovering combinations of interventions that strike the right balance between activating the immune system and circumventing transmission-promoting components of that activation could lead to more effective prevention strategies.

VIRAL RESERVOIRS, DEVELOPMENT OF VIRAL LATENCY AND APPROACHES TO CURING HIV INFECTION

Deborah Persaud and Sharon Lewin

There is general consensus now that the word remission—meaning maintaining viral control while no longer receiving antiretroviral therapy—is currently a more realistic target for the HIV cure effort. In 2014, cure terms shifted away from a “functional or sterilizing cure” to “remission” or “antiretroviral-free viral suppression”. The shift in language was largely a result of recent reports of eventual rebound viraemia among people no longer on antiretroviral therapy, despite no detectable HIV DNA or RNA before stopping treatment, following bone marrow transplantation in the two people in Boston and following very early antiretroviral therapy in the Mississippi baby.

Early antiretroviral therapy, within hours or days of either HIV or SIV infection, can dramatically reduce the level of HIV DNA, a surrogate measure of long-lived latently infected cells, among children and adults living with HIV, but how frequently this translates into prolonged antiretroviral-free viral suppression remains unknown. Among SIV-infected macaques, very early antiretroviral therapy within days of infection dramatically reduced the level of HIV DNA and delayed viral rebound off antiretroviral therapy—but the virus still returned in all animals.

The discovery that the size of the reservoir may be about 60 times larger than initially thought highlighted new insights into the challenge of eliminating latently infected cells. When a person is receiving antiretroviral therapy, latently infected cells maintain themselves through self-renewal, and these infected cells may preferentially survive based on where the virus integrates into the human gene. Controversy still exists about the relative contribution of non-T-cell reservoirs to virus persistence.

Histone deacetylase inhibitors (HDACi) are being investigated as a scalable strategy to “purge” the reservoir, and multiple clinical trials using these agents were reported in 2014. Multiple doses of the HDACi vorinostat given to study participants living with HIV receiving antiretroviral therapy induced an increase in HIV transcription among most participants but no change in plasma HIV RNA. Although work in vitro suggested that HDACi stimulation of latently infected cells did not generate intact virions, two further clinical trials did not support this

concept for the more potent HDACi, panobinostat and romedepsin, among people living with HIV receiving antiretroviral therapy. Both clinical trials demonstrated a significant increase in plasma HIV RNA, demonstrating that production of virions was possible. Unfortunately, no trials to date of HDACi have led to a reduction in the number of latently infected cells, so additional immune interventions with a vaccine, broadly neutralizing antibody (BNAbs) or immunomodulators such as anti-PD1 will probably be needed. The other main concerns with HDACi are that only a small fraction of latently infected cells seem to respond, the safety implications of long-term changes in gene expression post-drug and the potential suppressive effects on the HIV-specific T-cell response. More potent and less toxic latency-reversing agents still need to be developed.

In 2015, we are likely to hear the results of several clinical trials evaluating latency activation (romedepsin and high-dose disulfiram), immunomodulation with anti-PD1 and therapeutic vaccines (including the first-in-human studies of BNAbs) and enhanced approaches using gene therapy to eliminate CCR5, in addition to modifying circulating T-cells. New biomarkers to define latently infected cells and novel assays that predict rebound following a monitored antiretroviral pause are urgently needed in addition to enhanced understanding of the basic biology of how latency is established, maintained and reversed in T cells and the role of non-T-cell reservoirs.

HIV DIAGNOSTICS AND VIRAL GENETICS

Papa Salif Sow and Eduard Karamov

Point-of-care testing and new devices for diagnosing HIV, including acute HIV infection, are being developed, including the following.

- **Point-of-care nucleic acid–based test for early infant HIV diagnosis.** These tests amplify and detect one or more of several target sequences located in specific HIV genes, such as HIV-I gag, HIV-II gag, HIV env or HIV pol.
- **Microchip europium nanoparticle immunoassay for sensitive point-of-care HIV detection.** This assay is based on lab-on-a-chip or microchip concept. Lab-on-a-chip is a subset of a microelectromechanical system emphasizing chemical and biological processes.
- **HIV self-test (home test/home-based test).** HIV self-testing may be an additional way to meet the need for confidential, convenience and privacy in HIV testing and may discourage current unregulated self-testing. The limited available data suggest that HIV self-testing may have lower sensitivity than other HIV testing, and information about self-testing should therefore emphasize that the self-test result should be considered screening rather than a definitive test. Home-based tests include the oral fluid HIV test, which is performed by taking an oral swab, and the finger-stick whole-blood HIV-1 and -2 home-based tests. OraQuick®, which provides results within 20 minutes, is an example of a home-based HIV test approved by the United States Food and Drug Administration.
- **Immunoassay test for HIV based on using smartphones.** The assay employs what is called reflective phantom interface technology. Reflective phantom interface enables the detection of biomolecules in water-based fluids, such as blood. In particular, reflective phantom interface devices (such as smartphones equipped with special cartridges) can measure several parameters simultaneously, such as detecting HIV, hepatitis C virus and hepatitis B virus in the same serum sample.

The emergence and spread of advanced technologies for detecting HIV calls for the development of regulatory requirements and attention to the bioethical problems potentially arising out of the use of new platforms.

In addition to the existing HIV diagnostics, a new technology has been developed that reveals the motions of proteins on the surface of HIV, which are key to the ability of HIV to infect human immune cells. This technology enables real-time images of processes happening on the surface of intact HIV particles.

Ideally, the complete diagnostic picture, which would allow both forecasting HIV infection dynamics and optimizing treatment protocols, is only possible when the interacting parties (the virus and the host) are genetically characterized. A number of new circulating recombinant forms (CRF) have recently been identified, including: CRF58_01B (Malaysia), CRF62_BC (China), CRF63_02A1 (Russian Federation), CRF64_BC (China), CRF65_cpx (China) and CRF72_BF (Brazil).

GENE THERAPY

Marina Cevazzana-Calvo

Interest in gene therapy for HIV infection has grown after the eradication of the virus following haematopoietic stem cell transplantation from a CCR5-delta32 homozygous donor in the “Berlin patient”.

Two main gene therapy strategies are being investigated:

- transfer of autologous T cells expressing recombinant receptors that target HIV antigens; and
- engineered autologous haematopoietic stem cells expressing anti-HIV inhibitors.

These two strategies (alone or combined with other approaches) are being developed with the goal of achieving a functional cure for HIV. One key advantage of transducing haematopoietic stem cells (rather than engineering solely T-cells) relates to the stem cells' capacity to differentiate into all the various haematopoietic lineages (including macrophages, microglia and dendritic cells, which are important virus reservoirs).

Recently, research has focused on a strategy aimed at blocking HIV replication via modification of the host cell genome. This strategy is based on knock-down of the HIV receptors. Various approaches have emerged for the specific recognition of DNA target sequences for selective gene editing of the CCR5 or CXCR4 nucleotide sequence. The most frequently used approach is based on zinc finger nucleases (ZFNs); these are chimeric proteins in which a non-specific FOK1 nuclease domain is fused to DNA-binding zinc finger domains specific for the HIV-1 co-receptors CCR5 and CXCR4 and for the integrated HIV-1 DNA genome. CCR5- and CXCR4-specific ZFNs have been studied *in vitro* and *in vivo*, and have been shown to confer resistance to HIV-1 infection. Based on these preclinical results, a number of recent clinical trials have yielded preliminary results. Early data suggest that it is safe to infuse autologous CD4+ T cells in which the CCR5 gene has been rendered permanently dysfunctional by a ZFN. Twelve patients were enrolled in an open-label non-randomized, non-controlled study using this strategy. Soon after the infusion of gene-modified cells, most of the patients displayed an increase in CD4+ cell counts and a slight, concomitant decrease in blood HIV DNA levels. Longer follow-up of these patients is required in order to establish

whether this moderate benefit is stable over time. Greater levels of correction will be necessary before cessation of antiretroviral medicines can be considered.

Other strategies have been also set up in the last few years, the most common of which is the intracellular expression of antisense RNA from a transgene construct. Antisense RNAs are short synthetic single-stranded RNA molecules that target HIV-1 mRNAs in a sequence specific manner; this forms non-functional RNA duplexes that are subsequently destroyed by the cell.

Of the many genetic inhibitors of HIV, genes that block the viral life cycle prior to integration appear to have advantages over late-inhibitory agents, since they are expected to lead to the accumulation of uninfected, gene-protected cells- thus preventing the generation of provirus and the continued replenishment of viral reservoirs. Given the high mutation rate of HIV, another promising anti-escape strategy involves targeting cellular cofactors that are essential for viral replication. Lastly, to increase the potency of antiretroviral drugs and achieve long-term control of HIV-1 replication, several inhibitory agents (blocking different steps in the viral life cycle) will need to be simultaneously delivered to target cells.

After preliminary gene therapy trials including more than 250 people living with HIV, only the feasibility and safety of gene-transduced autologous haematopoietic stem cell transplantation have been proven; no obvious therapeutic effects have been reported. There are probably several reasons for this, including the low numbers of reinfused, transduced cells and the absence of a conditioning regimen.

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