Highlights from the 2016 International Symposium on HIV & Emerging Infectious Diseases (ISHEID)  
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Jean-Pierre Routy¹, Christina Psomas², Vicente Soriano³, Patrick Philibert⁴, Hervé Tissot-Dupont⁵ and Alain Lafeuillade⁶*  
¹ McGill Health Centre, Montreal, Canada  
² University Hospital, Montpellier, France  
³ Infectious Diseases Unit, La Paz University Hospital, Madrid, Spain  
⁴ European Hospital, Marseille, France  
⁵ Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France  
⁶ General Hospital, Toulon, France

Abstract

For three days in May 2016, the International Symposium on HIV & Emerging Infectious Diseases gathered participants from all over the world around the theme ‘Fighting deadly viruses’. HIV infection remained the main topic of the meeting but hepatitis, Ebola and Zika viruses as well as other emergent pathogens were also extensively covered. In this article we have tried to summarise what was presented during the plenary lectures, the two keynote lectures, and some of the work accepted for oral presentation. However, all abstracts can be found on the Journal of Virus Eradication website (viruseradication.com/abstract.php)

Keywords: HIV, HIV cure, HIV vaccine, hepatitis C, hepatitis B, hepatitis E, Ebola, Zika, flu, tuberculosis, human papilloma viruses, sexually transmitted infections

Introduction

The 2016 ISHEID combined presentations around four topics: HIV infection, hepatitis viruses, sexually transmitted infections (STIs) and emerging infectious diseases.

News on HIV infection

Healthcare providers come first! Tamar Ginossar (University of New Mexico, Albuquerque, USA) presented on the much-neglected topic of HIV healthcare providers’ burnout [1], defined as a psychological syndrome resulting from prolonged interpersonal stressors in an occupational setting. The goal of the study was to examine the relationship between emotional exhaustion, teamwork, involvement in decision-making and critical appraisal. Encouragingly, teamwork best predicted reduced emotional exhaustion, and critical appraisal best predicted depersonalisation.

Antiretroviral therapy (ART) has transformed the life of millions of people living with HIV, while as a prevention strategy it has dramatically reduced the rate of HIV acquisition in persons with high-risk exposure. Laurent Cotte (Croix-Rousse Hospital, Lyon, France) highlighted the importance of pre-exposure prophylaxis (PrEP) owing to the increasing risk of HIV acquisition in men who have sex with men (MSM) [2]. Among the dozens of PrEP studies, the distinctive ‘on demand’ PrEP Ipergay trial, conducted in France and Canada, showed an 86% efficacy to prevent HIV infection compared to placebo, with a median consumption of 15 pills per month. The efficacy of such a preventive approach has been clearly demonstrated, but the consequences on STIs, drug resistance development and cost remain to be addressed. In the Ipergay trial, a significant number of STIs were diagnosed during study visits, and 39% of the infections were totally asymptomatic. The risk of drug resistance appears extremely low, around 1-in-1000 exposed persons. The cost-effectiveness of PrEP will depend on the price of the drugs, the HIV prevalence in the population targeted, and the risk of sexual disinhibition.

Early initiation of ART is the undisputed optimal strategy to decrease patient morbidity and onward transmission. Vikram Mehraj (McGill University Health Centre, Montreal, Canada) presented on clinical and socio-demographic characteristics associated with early treatment initiation following primary HIV infection in Canada, a country with free and universal access to care [3]. A total of 336 adult HIV-1-infected individuals participated in the Montreal Primary HIV Infection Study and were mainly male (95.7%), MSM (78.7%), and with an average age of 36 years. Importantly, lower socio-economic status and lower education were independently associated with a delayed ART initiation in recently diagnosed individuals, followed up either in community medical or hospital-based centres. These findings highlight new directions for improving the cascade of care even in a country with universal access to care.

Patrick Philibert (European Hospital, Marseille, France) presented results from a survey in a routine HIV clinical setting regarding comorbidities through a systematic screening approach [4]. Among the 163 patients screened, 146 were male, with a mean age of 48 years, mainly MSM (85%). This study also identifies the contribution of low economic status and tobacco usage as major contributors for morbidities including STIs (40%), viral hepatitis co-infection (21%), cardiovascular, and most importantly respiratory complications such as COPD and asthma. This study highlights the need for tobacco cessation strategies in this population.

Kristel Van Laethem (University of Leuven, Leuven, Belgium) presented on next-generation sequencing for HIV testing [5]. She pointed out the importance of monitoring multiple genome regions for drug resistance testing, as well as the benefit of complete genome sequencing for viral research. Ultra-deep sequencing offers a more accurate characterisation of viral populations at the individual level owing to a lower detection limit and improved minority species detection. Ultra-wide sequencing can also allow for parallel testing of multiple viral genetic regions. MiSeq, when compared to Sanger analytical evaluation, provides a higher nucleotide concordance, which translates into a higher sensitivity and specificity. Diagnostic methods have also to be selected according to the characteristics of patient populations, and prevalence of drug resistance. However, implementation of

*Corresponding author: Alain Lafeuillade, General Hospital Sainte Musse, 54 rue Henri Sainte Claire Deville, 83056 Toulon, France

Email: alain.lafeuillade@ch-toulon.fr

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next-generation sequencing in clinical practice remains limited by costs and turnaround time.

Following cell infection by a virus, the antiviral cell response, the interferon-induced RNA-activated protein kinase (PKR), regulates the cellular and viral translation. Interferon (IFN)-stimulated genes are produced following viral infections aiming at limiting viral replication. Anne Gatignol (McGill University, Montreal, Canada) studied the role of three different RNA binding proteins, ADAR1, PACT and PKR in vitro with respect to HIV immune responses [6]. Findings indicated the existence of a multiprotein complex with a strong combined inhibition of PKR activation by ADAR1, PACT, Tat and TAR. This HIV-induced network contributes to viral presence by decreasing the innate host defences against HIV.

Gilles Darcis (Brussels University ULB, Gosselies, Belgium) analysed patient samples from two recent HIV reactivation studies [7]. The objective was to investigate ex vivo, using cultures of analysed patient samples from two recent HIV reactivation studies. That and TAR. This HIV-induced network contributes to viral presence by decreasing the innate host defences against HIV.

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Léa El Khoury (Sorbonne University, Paris VI, France) presented results from her study on the inhibitory mechanism of HIV-1 integrase by diketoacid molecules [8]. Using fluorescence anisotropy titrations and computational chemistry calculations, dolutegravir showed a better interaction and higher affinity with processed viral DNA than elvitegravir, two commercial integrase inhibitors. Design of dolutegravir derivatives by substitution of F by an NH$_2$ or CH$_3$NH group, shift of F and substitution of another F by an NH$_2$ or CH$_3$NH group strengthen the interaction with viral DNA and show a more specific interaction potential, contributing to an increased antiviral effect of the integrase inhibitor.

Lucy Dorrell (University of Oxford, UK) presented on new immunological tools for HIV research [9]. Interestingly, the CD4/CD8 ratio is re-emerging as a useful indicator of immune reconstitution. The ratio is normalised only in individuals who started ART in acute infection compared to those initiating ART 6 months after seroconversion (13.5%). However, the HIV-specific response was not able to control viral rebound when ART was discontinued with the exception of a very few post-treatment controllers. Studies have shown that the antiviral inhibitory capacity of CD8+ T cells predicts both the CD4+ T cell decline and viral load set point. Such CD8+ T cell antiviral activity is associated with the preferential targeting of regions that are susceptible to loss of function upon mutation within the HIV proteome. Importantly, such response can be enhanced by therapeutic vaccination and is, in part, preserved by early ART initiation.

On a touching note, Roy Gulick (Cornell University, New York, USA) presented the Joep Lange Keynote Memory Lecture about the future of HIV care [10]. Sixteen million people currently receive antiretroviral therapy worldwide, using 29 approved drugs from six mechanistic classes. Current treatment guidelines (US DHHS 2016, IAS–USA 2014, EACS 2015, UK 2015, WHO 2015) recommend a first-line regimen consisting of a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a third drug, which should be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI/r), or an integrase inhibitor (II). Current ART regimens have proven their antiviral activity, their safety and tolerability, and their convenience. One-pill, once-daily regimens are widely available and current virological suppression rates can exceed 90% in clinical trials and cohort studies. Newer strategies involve investigation of novel approaches (nuc-lite, nuc-sparing, PI/r+II), two-drug regimens, new formulations (co-formulations of drugs that reduce pill counts), long-acting injectable compounds (rilpivirine, cabotegravir), implantable devices and other new technologies. The investigational pipeline contains new agents in existing classes with less toxicity than current drugs (tenofovir prodruk TAF; doravirine) and new mechanistic antiretroviral classes (CD4 attachment inhibitors such as BMS-663068 and the HIV maturation inhibitor BMS-955176). The current scientific goal remains the cure of HIV infection; while only one patient is considered to have been cured to date, research efforts are developing strategies to specifically identify and decrease the HIV latently infected cellular reservoir. Meanwhile, tremendous improvements in life expectancy of people living with HIV have been observed, and in some cohorts, life expectancy is greater than in the general population, potentially as a result of very regular medical check-ups. While awaiting the further exploration of HIV cure research strategies, we can currently control HIV infection long-term with potent, safe and convenient antiretroviral therapy based on the strategy of treatment as prevention (TasP).

Digging further into the search for an HIV cure was the presentation by Daniel Kuritzkes (Harvard Medical School, Boston, USA) [11]. We currently experience a substantial reduction in AIDS-related mortality under ART and a tremendous increase in adult life expectancy in developing countries. Nevertheless, a treatment that led to durable drug-free remission or eradication (cure) of HIV-1 could reduce the burden, cost, toxicities and stigma associated with long-term ART, and might lower immune activation and the associated risk of non-AIDS clinical events. The search for a cure therefore remains a high priority for clinicians, investigators and patients. To date, only a single individual (Mr Timothy Ray Brown, known as the ‘Berlin patient’) has had apparent cure of HIV infection. The virus has not rebounded after ART interruption and has remained undetectable during more than 7 years of follow-up. Attempts to repeat the same therapeutic approach in other patients have been unsuccessful to date. Current efforts at eradicating HIV infection or inducing long-term, ART-free remission include activation of HIV transcription in latently infected CD4+ T cells (LRAs, mainly histone deacetylase inhibitors or HDACi); enhancing HIV-specific immunity in order to target and destroy cells harbouring latent infectious proviruses (immune activation with TLR-7 agonists or use of anti-PD-L1 agents for instance); and cell-based therapies using genetically modified CD4+ T cells (gene therapy) or haematopoietic stem cell transplantation. Several exploratory pilot studies are under way with each of these approaches. Major challenges include the lack of surrogate markers of cure (difficulty of quantifying the HIV reservoir, for instance, during the monitored ART pause or ‘test of cure’), the uncertain safety of the experimental treatments under study, and the need to balance the risk of these interventions against the generally well tolerated and proven efficacy of long-term ART.

Dan Barouch from Harvard Medical School, Boston, USA, analysed prospects for an HIV-1 prophylactic vaccine [12]. Although in more than 30 years, HIV vaccine efficacy studies have tested only four concepts, two HIV-1 vaccine candidates are currently moving towards clinical efficacy trials: (1) ALVAC prime with clade C virus and gp120 boost from Sanofi/GSK, and (2) Ad26 prime with a global mosaic virus and gp140 boost from Janssen/Harvard. His team has recently reported the partially protective efficacy of Ad26/MVA and Ad26/Env SIV vaccines against repeated intrarectal SIVmac251 and SHIV-FP162P3 challenges in rhesus monkeys. In this case, the role of the Env gp140 protein is to boost functional antibody responses (Fc functionality of Env-specific antibody
responses) that correlate with improved protection. Indeed, 90% of reduction of per-exposure acquisition risk for Ad/Env (P=0.001) and 50–66% of complete protection (P=0.01) against acquisition of neutralisation-resistant SIVmac251 and SHIV-SF162P3 challenges were observed in rhesus monkeys. These success rates are superior to those observed in previously clinically tested HIV-1 vaccine candidates. The Ad26 prime, Env protein boost vaccine has proven its safety and immunogenicity in healthy adults in Phase 1/2a clinical trials in the United States, East and South Africa, and Thailand (IPCAVD 001). A Janssen-led consortium is currently planning to evaluate its clinical efficacy.

A second series of experiments aimed to define the intercept between antibody and virus by performing serial necropsy studies in rhesus monkeys in the model of protection with the neutralising antibody PGT121 protection against SHIV/SF162P3 and followed by virological, immunological and transcriptomics analysis. Data suggested that ‘sterilising’ protection with PGT121 does not appear to involve complete blockade of virus at the mucosal surface, because low levels of virus are found in distal lymphoid and gastrointestinal tissues by 24 hours and persist for at least 7 days. Early disseminated virus induces a distinct transcriptomic signature of innate immunity and viral replication in viral RNA (+) tissues from PGT121-treated animals. This virus is replication competent and infectious as shown by adoptive transfer studies. These data suggest that antibody-mediated protection can involve systemic clearance of distal virus over 7 days.

Marie-Claire Gauduin (Texas Biomedical Research Institute, San Antonio, Texas, USA) presented experiments trying to recreate the Berlin patient’s treatment using the non-human primate model for AIDS [13]. The principle for the use of engineered zinc finger nucleases (ZFNs) is based on their capacity to permanently disrupt the CCR5 open-reading frame and obtain cells with mutations, which mimic a CCR5delta32 mutation and are thus resistant to infection by CCR5-tropic HIV-1. She demonstrated the feasibility of using ZFN technology to establish mature CD4+ T cells and haematopoietic stem cells resistant to SIV infection in macaques.

News on viral hepatitis

News on viral hepatitis attracted much attention at ISHEID 2016, largely because of the expectation created by the newest direct-acting antivirals (DAA) for treating HCV, the prospects for forthcoming drugs to treat hepatitis B, and the two rising hepatitis E epidemics that cause chronic hepatitis in transplant recipients and acute hepatitis following water-borne contamination.

Hepatitis C

On 25 May, coincident with the first day of the conference, the French authorities announced that payment for DAA will be made for all chronic hepatitis C patients in France, regardless of hepatic fibrosis stage, removing previous restrictions that only allowed drugs to be prescribed in patients with advanced liver fibrosis or cirrhosis [14]. The good news was given by Stanislas Pol (Cochin Hospital, Paris, France) [15], who pointed out that this pioneer decision is in line with all scientific evidence that unanimously demonstrates a reduction in liver-related complications and deaths as well as extrahepatic benefits on cardiovascular risk, diabetes, lipids, and neurocognitive performance in patients cured of hepatitis C [16,17]. Hopefully, the French step forward will help to rapidly expand HCV treatment access to everyone infected and living in other countries [18]. Access to generics has been quite successful as long as medication quality is ensured. Gilead has already made agreements with pharma companies in India, Egypt and other countries to produce sofosbuvir or Harvoni. People can access and buy these drugs more cheaply (US$1500 for 3 months of Harvoni) through several websites (i.e. www.hepcfix.com).

Although anecdotal reports have suggested that HCV cure with DAA may contribute to regression of hepatocellular carcinoma (HCC) [19], a recent report has alerted to the contrary [20]. In a multicentre study conducted in Spain, early tumour recurrence was recognised within 6 months of SVR in one-third of 58 patients who had been treated for HCC with complete response [20]. The authors hypothesised that this paradoxical phenomenon could be explained by the rapid disappearance of immune control of tumour cells following HCV elimination. Marc Bourlière (Saint Joseph Hospital, Marseille, France) highlighted that HCV genotype 3 patients are more prone to rapid progression to cirrhosis and therefore to develop liver cancer, and accordingly they should be checked carefully for HCC [21].

Despite rates of HCV cure above 90% using most currently used all-oral DAA regimens, several predictors of treatment failure have been identified (Table 1), including advanced cirrhosis, HCV genotype 3 or 1a, and high serum HCV-RNA [22]. Philippe Halfon (European Hospital, Marseille, France) pointed out that the presence of resistance-associated variants, either selected upon failure or present as natural polymorphisms at baseline, may impair DAA response [23]. Prevention and management of DAA treatment failure has become a particular challenge, especially for cirrhotics who are at particular risk for developing decompensated liver events and cancer [24]. Vicente Soriano (La Paz University Hospital, Madrid, Spain) showed that the good news is that very promising new regimens will soon be available (Table 2), most of which are pan-genotypic and/or active against drug-resistant viruses [25].

Treatment failure after completion of a course of DAA therapy is generally a relapse to the original HCV strain. It must be distinguished from HCV re-infection. Mark Nelson (Chelsea and Westminster Hospital, London, UK) pointed out that up to 25% of HIV-positive homosexual men at his clinic in London experienced a second episode of HCV infection within the 3 years following successful treatment of acute hepatitis C [26]. High-risk sexual

Table 1. Predictors of directly active agents (DAA) failure

| Baseline | On-treatment |
|----------|--------------|
| • Cirrhosis | • Drug adherence |
| • Genotype 3 | • Drug interactions |
| • RAVs | • Side effects |
| • Prior interferon failure | • Elevated serum HCV-RNA |
| • Elevated serum HCV-RNA | • IFN-L4 unfavourable |
| • IFN-L4 unfavourable | • AA ethnicity |
| • AA ethnicity | • HIV (7) |

Table 2. Forthcoming DAA regimens

- Sofosbuvir + velpatasvir (Gilead)
- Sofosbuvir + velpatasvir + voxilaprevir (Gilead triple)
- ABT-493 + ABT-530 (AbbVie)
- Grazoprevir + elbasvir (Merck)
- Grazoprevir + MK-8408 + MK-3682 (Merck triple)
- ABT-493 and voxilaprevir are new NS3 protease inhibitors, ABT-530 and MK-8408 are new NS5A inhibitors, MK-3682 is a new nucleotide analogue NS5B polymerase inhibitor.
practices, along with drug use, were involved in most cases of HCV re-infection.

Hepatitis B

New estimates of HBsAg carriers are of 150 million people worldwide, with more than two-thirds living in Asia and Africa. There, HBV is still largely transmitted perinatally or in early infancy despite the availability of an effective HBV vaccine for the past 25 years. Markus Cornberg (Hannover University, Germany) addressed the current strategies used for controlling hepatitis B with antiviral therapy and highlighted that prospects for HBV cure, as in the hepatitis C field, are on the horizon but still far away [27]. The persistence of cccDNA in HBV-infected hepatocytes has proven to be an extraordinary reservoir for HBV reactivation once antiviral therapy is discontinued, even in patients with long-term suppression of viral replication, either with tenofovir or entecavir, the most preferred anti-HBV oral agents. He postulated that future hepatitis B therapies would most likely rely on a combination of antivirals and immunotherapeutic agents. In this regard he suggested that a functional cure, represented by serum HBsAg loss despite intrahepatic cccDNA persistence, may be a more feasible goal as an intermediate step towards complete HBV cure. Serum HBsAg clearance is associated with a marked reduction of the risk of liver cancer and hepatic disease [28]. Ongoing studies are using new antivirals, such as tenofovir alafenamide (TAF) or myrcludex, or new treatment strategies, such as add-on pegylated interferon-alpha and/or discontinuing long-term nucleoside analogue therapy.

Hepatitis E

During the last decade it has become clear that hepatitis E virus (HEV) infection is the most frequent agent involved in acute viral hepatitis worldwide [29]. This is largely due to the widespread use and success of the hepatitis A and B vaccines, as well as the arrival of more confident tests for HEV infection. Moreover, the recognition of chronic HEV infection among immunosuppressed individuals such as transplant recipients has received much attention in recent years [30], given its characteristic rapid course to cirrhosis and fortunately good response to ribavirin. Harry Dalton (University of Exeter Medical School, Truro, Cornwall, UK) underlined that HEV genotypes 1 and 2 are the major genotypes responsible for acute hepatitis outbreaks in south-east Asia, where the virus is mainly transmitted by contaminated water. In contrast, HEV genotypes 3 and less frequently 4 are the major agents of chronic hepatitis E, pigs being the major reservoir and uncooked meat the main source of human infection [31]. Besides liver injury, exposure to HEV has been associated with several neurological syndromes, including Guillain–Barre and polyneuropathies [32]. Solving problems with diagnostic tools and moving ahead with vaccination may provide unique opportunities to counteract the burden of HEV epidemics.

The French surveillance system for STIs

French authorities decided on a 4-year plan in 2010, leading to new management of health services, the purpose being to fight HIV and STIs. Thierry Troussier (French Ministry of Health) [33] described new approaches towards STI screening and diagnosis with the new CeGiDD model of care, creating a unique structure by the merger of STI Diagnosis, Screening and Information Centres (CIDDIST) and Anonymous and Free HIV Screening Centres (CDAG). In a report published in 2016, the French High Committee for Public Health (HCSP) considered that sexual health support is currently fragmented among many institutions and in various planning structures or public health policies, with no real connection between them. Health indicators are alarming, including persistence and spread of the HIV epidemic among MSM and resurgence of STIs in this population and among younger people. Based on the HCSP recommendations on sexual and reproductive health, a national strategy was developed for sexual and reproductive health function, information, education, training, reproductive health, prevention and screening for STIs. This new strategy is a national challenge that requires a multidisciplinary approach between the legal system and human rights, education, society, culture, the economy and health systems.

An important topic was presented – the recrudescence of syphilis in France since 2000. After a brief natural history of this illness, Nadjat Benhaddou (Cochin Hospital, Paris, France) [34], showed how the national surveillance network of syphilis is based upon ‘RésIST’ (Volunteer Clinicians’ network), ‘Rénago’ and ‘Rénachla’ (Laboratory network), as well as Reference National Centres. The STI surveillance data in 2014 showed that patients diagnosed in Ile-de-France represent almost 30% of all national cases. These individuals were mostly men (80%), 84% MSM, had a mean age of 36 for men and 29 for women, 61% were symptomatic, 33% were HIV-infected with 3% newly diagnosed during the diagnosis of syphilis. The systematic use of condoms during oral sex was described as rare (<2% in 2014).

Agnès Gautheret-Dejean (Paris Descartes University, Paris, France) [35], presented data concerning the performance of rapid tests for the screening of HIV infection during primary infection and at the chronic stage. In order to target the end of the AIDS epidemic by 2030, world health authorities have proposed three objectives for 2020: 90% of the people living with HIV should know their HIV status, 90% of the people who know their HIV status should receive treatment, and 90% of the people who receive treatment should have suppressed viral load. The diagnosis of HIV infection has thus become a priority for public health.

Advantages of the use of HIV rapid diagnostic tests are:

- Speed: result available within 30 minutes;
- Simplicity: no need for sophisticated material or electricity, storage at room temperature;
- Closer to the population to be tested: outside the laboratory;
- Easy to use;
- Differentiation between HIV-1 and HIV-2 for some tests.

Disadvantages of the use of HIV rapid diagnostic tests are:

- Subjectivity of visual reading;
- Technical limits: analytical performances, matrices (nature and quality);
- Errors of interpretation;
- High price: US$0–6.00 for finger stick; US$4–11 for oral fluid; US$31–45 for self-testing; and US$1 for ELISA;
- No traceability;
- Only HIV tested;
- Production and distribution controls.

We can dream of the ideal rapid diagnostic test:

- Combining: p24 Ag, HIV-1 Ab, HIV-2 Ab, HBs Ag, HBc Ab, HCV Ag, HCV Ab;
- With high sensitivity and specificity;
- Using a low volume of capillary blood;
- Easy use and interpretation.
Anal infection: doxycycline 200 mg/day for 7 days for strains treating urethritis/cervicitis with azithromycin. Continuous monitoring of proctitis highlights cases of monitoring should continue as the epidemic progresses.

Chlamydiae trachomatis is a good candidate for screening. It is asymptomatic, the most common STI and responsible for serious complications such as infertility but easy to diagnose and also to cure. Its incidence has been increasing in France in the last decade (Table 3). C. trachomatis detection in three sites (anus, throat, urine) is possible and testing should be highly recommended. There were 106 positive cases in at least one of the three sites among 698 MSM in the speaker’s experience.

A focus on lymphogranuloma venereum (LGV) proctitis is necessary:
- Monitoring should continue as the epidemic progresses
- Continuous monitoring of proctitis highlights cases of recurrent LGV (132 cases in the period 2010–2015)
- The increase in LGV diagnosis and the growing number of reinfections show that the LGV epidemic is poorly controlled

Therapeutic recommendations are:
- Treating urethritis/cervicitis with azithromycin 1 g or doxycycline 200 mg/day for 7 days
- Anal infection: doxycycline 200 mg/day for 7 days for strains D–K and ≥21 days for LGV

Treatment failure is estimated at 10% but acquired resistance is not described. The reasons could be persistence or recontamination. In conclusion, C. trachomatis infection is increasing in the general population and in high-risk populations (MSM). We must intensify screening using self-collected samples (vaginal swab, urine, anal swab).

**Emerging infectious diseases**

Ten years after the SARS epidemic, zoonotic and emerging viruses have become a growing field of research. Christian Drosten (University of Bonn, Germany) showed how some remarkable descriptions of novel virus in animals have demonstrated how ignorant we are of the diversity of viruses around us [37,38]. Among the biggest challenges in this field is the integration of the concepts of virus–host co-divergence, and viral host switching. In addition, assessments of viral reservoirs with the intention of predicting future pandemic threats will have to take into account important host and virus traits. Among the viruses borne in such reservoirs, there may be some that are more promiscuous in their choice of hosts than others, potentially due to the preservation of their receptor structures or the way they interfere with conserved or not-so-conserved immune properties. A synopsis of available approaches demonstrates how much work needs to be done before we will be able to assess functional, rather than genetic diversity of reservoir-borne viruses.

| Table 3. Epidemiology of Chlamydiae trachomatis and Neisseria gonorrhoeae in the world in 2012 |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| C. trachomatis                  | N. gonorrhoeae                  |
| **Number of cases** | **Incidence/100,000 population** | **Number of cases** | **Incidence/100,000 population** |
| USA                             | 1,423,000 | 457 | 335,000 | 107 |
| France [37]                     | 59,000   | 257 | 13,000  | 39  |
| Europe (ECDC)                   | 346,911  | 175 | 30,179  | 12.6 |

The last topic of this session was about *Chlamydia* screening and prognosis. Bertille de Barbeyrac (University of Bordeaux, France) [36], described how all the strains of *Chlamydia* are sent to her laboratory and how clinicians have to manage this infection through the results of the French national survey.

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Human papillomavirus (HPV) is a widespread infection, with a global prevalence of 11.7% cervical samples, and 12.4% in male genital samples in Europe [39]. Persistent infection can lead to a significant burden of disease. HPV-related diseases can be prevented by vaccination or screening. The HPV FASTER programme (vaccine up to 45 years old and HPV test from 30 onwards) is an affordable strategy combining the available technologies to control cervical cancers [40].

Zika virus (ZIKV), a flavivirus closely related to dengue, re-emerged in 2007 to cause epidemics in the South Pacific and in the Americas, reaching pandemic levels. A keynote lecture on this topic was given by Nikolaos Vasilakis (Institute of Human Infections and Immunity, Galveston, USA) [41]. Human transmission cycles involve *Aedes* spp. mosquitoes and human amplification hosts. It is often misdiagnosed because of its mild flu-like illness. The unprecedented numbers of people infected during recent outbreaks in the South Pacific and the Americas may have resulted in enough ZIKV infections to bring attention to the relatively rare congenital microcephaly, Guillain–Barre and other ocular or auditory syndromes. Another hypothesis is that phenotypic changes led to these disease outcomes. Potential strategies are needed to diagnose and control the ongoing outbreak, through vector-centric approaches, and the development of vaccines and therapeutics [42].

Ebola virus disease (EVD) has been known since 1976. Despite its previous outbreaks, Médecins Sans Frontières (MSF) was not prepared for the devastating 2014–2016 epidemic, as Armard Sprecher (MSF Brussels, Belgium) showed in his presentation [43], and was forced to make strategic choices to concentrate on the management of 15 Ebola treatment and transit centres in the three countries, while supporting and training other agents [44]. The international response came late, and the importance of engaging affected communities was underestimated. MSF decided to engage in clinical trials to rapidly identify agents improving survival or diminishing transmission, facing risks and unforeseen challenges related to choice of intervention, trial design, community acceptance and result interpretation. It remains uncertain whether the world is better prepared for future outbreaks of unknown or neglected pathogens [45].

Influenza viruses are emerging and re-emerging threats with both economic and medical impact. Beside the yearly epidemics due to seasonal influenza whose burden can be very high, alerts relate to avian viruses that may result in pandemic viruses in cases of adaptation [46,47]. Challenges include better monitoring and anticipation of the epidemics, and better disease management with the antivirals and vaccines available today. Tools for the rapid identification of the antigenic variants escaping vaccine-induced protection were recently implemented. We hope to become able to anticipate these mutations, and prepare vaccines that would protect against future variants, leading to personalised influenza vaccination. The monitoring, surveillance and management of avian influenza viruses both in human cases and during large-scale infections in birds is also crucial. The adaptive mutations required for these avian viruses to infect and subsequently spread in the human population are identified, but the rapid development and implementation of large vaccination campaigns remain difficult. The number of available antivirals to treat influenza cases remains limited and there is a need for additional drugs. We need to be prepared to face unexpected events during seasonal epidemics or during a pandemic.
Multidrug resistant tuberculosis (MDR-TB) was addressed by Maryline Bonnet (IRD, Kampala, Uganda) [48]. It is caused by M. tuberculosis strains that are resistant to the most potent anti-tuberculosis drugs in standard treatment: isoniazid and rifampicin. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB. MDR-TB is especially prevalent in Eastern Europe and Central Asia, with one-third of new TB cases, also increasing in Africa. Besides acquired drug resistance, the spread of MDR-TB, particularly in Eastern Europe and Central Asia, is associated with the Beijing genotype [49]. Despite an increase of MDR-TB detection, allowing simultaneous detection of M. tuberculosis and rifampicin drug resistance, in 2014 only one in four of the 480,000 estimated patients worldwide, were diagnosed. In 2014, an estimated 190,000 people died of MDR-TB. The lack of a safe and effective treatment is a major obstacle. Patients are exposed to 18–24 months of toxic, poorly tolerated treatment regimens, resulting in frequent default and drug resistance to second-line drugs. On average, 9.0% of MDR-TB cases have extensively drug-resistant TB (XDR-TB), defined by additional resistance to an injectable agent and a fluoroquinolone. Finally, in 2013 and 2014, two new anti-TB drugs, bedaquiline and delamanid were approved by stringent regulatory authorities for the treatment of MDR-TB. Integration of these drugs in novel, shorter oral, MDR-TB treatments are under investigation [50,51].

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