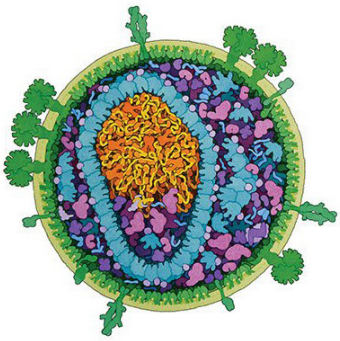
# ADVANCES *in* INFECTIOUS DISEASES

**Journal** of independent publications and comments about advances in infectious diseases

JOURNAL



## ESPECIAL POST-CROI

## CROI

Conference on Retroviruses and Opportunistic Infections

aid Andalusian Association of Infectious Diseases

www.saei.org

Publishes by the Andalusian Association of Infectious Diseases

# CONTENTS

## 6. RESISTANCE STUDY



## 7. PRE-EXPOSURE PROPHYLAXIS (PREP)



## 8. ERADICATION OF THE EPIDEMIC AND A CURE FOR HIV INFECTION



## THANKS

# FOREWORD

The Conference on Retroviruses and Opportunistic Infections (CROI) is, without a doubt, the scientific congress related to HIV infection with the greatest interest and impact worldwide. It brings together the most prestigious researchers who present numerous scientific papers at the highest level in various areas of HIV infection. In March of 2019, the 26th edition of the CROI took place in Seattle (USA). As in previous years, around 4000 congressmen have attended this scientific meeting. A total of 2048 communications have been sent, of which 1027 have been accepted and 110 have been chosen to be presented as oral communications. In this special issue of Advances in Infectious Diseases (AID) we have selected the plenary sessions, workshops and communications presented at CROI 2019 with, in our opinion, a greater clinical impact. We have structured this special issue in 8 thematic areas: sexually transmitted infections, hepatitis A virus, new therapies, antiretroviral treatment during pregnancy, transmission clusters, resistance study, HIV cure and pre-exposure prophylaxis. A team of physicians attending this conference, has been responsible for writing a summary and/or comment on each of the scientific works. The aim of this special issue of AEI is to make available to all professionals who treat patients infected with HIV the news presented in the CROI 2019 with greater relevance for the management of these patients in a simple and accessible for all members of our society. From the Andalusian Group for the Study of HIV (Spanish acronym GAEVIH) we want to thank all the members who have participated in this initiative with their comments and we hope that it will be useful for all clinicians who want to update on the subject.

**Dras. Nuria Espinosa e Inés Pérez**
President and Secretary of the Andalusian Group for the Study of HIV (GAEVIH) of SAEI.

# 1. SEXUALLY TRANSMITTED INFECTIONS

## DENIAL, DOOM OR DESTINY? RESURGENT ITS IN HIV CARE AND PREVENTION.

Jeanne Marrazzo. University of Alabama. Birmingham, AL, USA. Sesión plenaria 1. martes 5 marzo 2019.

We are witnessing an increase in the cases of sexually transmitted infections (STI) in patients infected with HIV in the HAART age, while we face new challenges such as the increased resistance to the treatment of gonorrhea, the rise in the cases of syphilis back to numbers characteristic of the preHIV time, and the re-emergence of classic STIs, such as lymphogranuloma vereneum. Analysing the syphilis epidemic in the U.S.A., in 2017 it was reported that there was an increase in the cases, namely in men (80% of the cases), of whom 80% were MSM and 46% were infected with HIV. And not only in MSM; there was also an increase in the female population, and in the cases of congenital syphilis. Regarding the infection by Neisseria gonorrhoeae, the increase is similar, with the additional difficulty of extragenital localizations, and the increasing prevalence of resistances. In over 80% of the countries from which there are available data, there is a high resistance to azithromycin and in the last year there has been an outbreak of joint resistance to ceftriaxone and azithromycin in the United Kingdom, requiring treatment with ertapenem in these patients. With respect to the treatment, there are currently new antimicrobials under study for gonorrhea (zoliflodacin, gepotidacin, solithromycin, delafloxacin), with different results, some of which are promising. Studies about the vaccine show numerous difficulties. The results of the clinical trial conducted in New Zealand with the vaccine against meningitis B (Bexero -GSK) showed that this vaccine provided 33% protection against gonorrhea, without reducing the risk in the cases of gonorrhea-Chlamydia co-infection. This allowed finding a possible target for its future development. With regard to pre-exposure prophylaxis for STIs, in the substudy of ANRS IPERGAY, researchers analysed the results of doxycycline administration (200 mg between 24 and 72 hours after exposure) versus no treatment, showing an improvement as the appearance time for syphilis and Chlamydia infection increased, although not for gonorrhea. It could be an option due to the relative safety of this treatment, its ease of use and its acceptance among MSM, although the possible emergence of resistances and adverse events should be taken into account. Lastly, in the session it was stated that STIs must be controlled in order to reduce the number of cases of HIV infection, due to their joint transmission and to the greater transmitability of this infection when a STI is present. Despite this, most of the “getting to zero” strategies to reduce HIV transmission are applied regardless of STIs and their consequences.

**COMMENT:** Dra. Isabel A. Pérez Hernández

Internal Medicine Service. District Hospital of Melilla.

Since several years ago, we have faced an exponential increase of STIs (also in Spain), with predominance in MSM, but not only in this population. The beginning of PrEP, brought by the increase of unprotected sex, the use of Chem-sex and the risks involved, and the loss of risk perception in these behaviours, raise many questions. In Spain, we still do not know how to tackle PrEP, where and how it should be provided, whether physicians should do it, or how it should be funded, when we are already considering prophylaxis against other STIs through the use of doxycycline. On the other hand, the importance of screening these infections in our asymptomatic patients is very clear, taking into account the high prevalence and that the presence of STIs favor the transmission of HIV infection. To this end, it is necessary to have a range of rapid and accurate diagnostic tests for the detection of STIs, especially in those places where the number of cases of HIV infection is very high, which would allow reducing syndromic management and empirical treatments, and facilitate resistance studies. The multi-resistance outbreak of N. gonorrhoeae in the United Kingdom has raised the alarm again, especially due to its epidemiologic relationship with other countries and world regions, which is a new risk. Therefore, emphasizing the prevention of these infections, both in patients who have a regular follow-up in the doctor’s office and reaching people with risk behaviors, while also trying to treat contacts as much as possible and foster research on new treatments and vaccines, should be short-term objectives for the control of this epidemic.

**Abstract 1011**

**EFFECTIVE TREATMENT OF LYMPHOGRANULOMA PROCTITIS WITH EXTENDED AZITHROMYCIN REGIMEN.**

José L. Blanco, Irene Fuertes, Jordi Bosch. Hospital Clinic of Barcelona, Barcelona, Spain.

*"I like azithromycin"*

LGV, doxycycline or azithromycin. José Luis Blanco presented a non-randomised study on LGV proctitis that compared the standard treatment of three weeks with doxycycline vs three weekly doses of azithromycin 1g. With a design that is rather curious for a non-randomised study, the results showed a very high efficacy in the two regimens. Comments: attractive treatment with a more comfortable dosage and great tolerability. It supports the use of azithromycin, at least in mild manifestations of LGV. We do not know the results of those who changed the treatment during the study. The emergence of Mycoplasma genitalum could contraindicate the empirical use of azithromycin. Although a randomised study is necessary, *"I like azithromycin".*

**COMMENT:** Dr. Jesús Santos González

UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

attractive treatment with a more comfortable dosage and great tolerability. It supports the use of azithromycin, at least in mild manifestations of LGV. We do not know the results of those who changed the treatment during the study. The emergence of Mycoplasma genitalum could contraindicate the empirical use of azithromycin. Although a randomised study is necessary, *"I like azithromycin".*

## 2. HAV IN PATIENTS WITH HIV

**Abstract 620**

**LOW IMMUNE RESPONSE RATE OF HIV-POSITIVE PATIENTS TO SINGLE INJECTION OF HAV VACCINE.**

Noel L, Valantin MC, Wirden M. Assistance Publique – Hôpitaux de Paris, Paris, France, et al.

Observational, unicentre study that evaluates the immune response to a single dose of a vaccine against HAV in HIV-positive patients who had been previously vaccinated in the year 2017, in which double doses were not administered due to lack of supply. The authors analised the serum of the patients before vaccination and, at least, 30 days after vaccination, and compared the immuno-respondents with the non-immuno-respondents. There was a total of 73 patients (93.2% MSM), with a median age of 49.4 years and most of them with good immunovirologic control (93.2% VL<50 cop/mL, CD4 median = 658/mm3, and CD4/CD8 median = 0.9). After a median of 106 days between the vaccination and the second serologic test, 59.7% showed immune response. The CD4/CD8 median of the non-respondents was below that of the respondents. The authors concluded that the immune response to a single vaccine dose against HAV is low in HIV-positive patients, which makes it a risk factor for it to have a low CD4/CD8 rate. They suggest that, in this context, serological control after vaccination should be recommended in order to ensure protection.

**Abstract 621**

**LOSS OF HEPATITIS A VIRUS SEROPROTECTION IN PERSONS LIVING WITH HIV.**

Chanderraj R, Cichocki M, Gandhi T, University of Michigan, Ann Arbor, MI, USA, et al.

Descriptive study of a cohort of HIV-positive patients who had lost their seroprotection against HAV. The study was developed in the context of an outbreak of hepatitis by HAV in Michigan, which began in August 2016 and persists in the present, with 895 cases; 26 of these are co-infected by HIV, of whom 4 were vaccinated against HAV and 2 had positive serologic tests when they were diagnosed with the HIV infection. When the authors observed this, they carried out serologic tests for HAV in all those patients of the HIV Clinic of the University of Michigan who had not had it in the last 5 years and they described the characteristics of those who seroreverted (their serology switches from positive to negative): upon receiving the vaccination, 50% of them had a detectable VL of HIV, with an average of 27,500 copies/mL, and the other 50% were cases of aids. The mean time between positive and negative serology was 11.37 years. The conclusion of the authors is that previously vaccinated patients infected with HIV are susceptible to being infected by HAV, thus repeating the serologic

test could identify those patients at risk, who could benefit from revaccination.

**COMMENT to abstracts 620 y 621:** Dra. Rosario Palacios Muñoz
UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

The individuals infected with HIV present a lower immune response to most vaccinations compared to the general population, especially when CD4 lymphocyte count is low. In fact, it is recommended to delay the vaccinations until CD4 lymphocytes are, at least, above 200/mm3. HAV, whose transmission is fecal-oral, is considered as a sexually transmitted infection and, in fact, as reported in these two studies presented in the CROI, also in Spain there have been outbreaks of acute hepatitis by HAV in MSM, with and without HIV infection. Although I think these two studies have some limitations, they tackle aspects of importance to daily clinical practice. The current recommendation is that HIV-positive patients should receive a double-dose vaccine against HAV, which would give the impression that the first study is out of place. However, if in France they have had the need to use, at least temporarily, a single dose due to a lack of supply, this could occur in other geographical areas. The results show that, even in individuals with a good immunovirologic situation, with a single-dose vaccine, slightly over half of the patients seroreverted. I would ask the following questions: How many patients seroreverted with two doses? Would seroreversion be similar in HIV-negative individuals? The answer to the first question could be found in a recently published Andalusian retrospective study (NeukaM K, et al. J Acquir Immune Defic Syndr 2019). On the other hand, retrospective studies with HIV-positive patients have demonstrated that after being vaccinated against HAV, positive serology persists in 90% at 3 years and in 85% at 6-10 years, although the clinical meaning of this is unknown. For the authors of the HIV Clinic of Michigan, the alarm went off when, in the outbreak they are currently going through, 23% of the patients infected with HIV were theoretically immunised against HAV and, however, they presented acute hepatitis by HAV. The truth is that, apart from suggesting that vaccinated individuals are susceptible to HAV infection, little more can be deducted from this study; perhaps that it would be better to vaccinate them when HIV is suppressed. To sum up, we must be aware of the importance of having all our HIV-positive MSM patients immunized against HAV. To this end, the recommendation is to vaccinate them with two doses, separated by six months, and to do so when they have a good immunovirological situation; and perhaps the serologic tests should be repeated periodically (every 5 years?), in order to know whether they have seroreverted, in which case they would have to be vaccinated.

## 3. NEW THERAPIES: CABOTEGRAVIR

**Abstract 139**

**LONG-ACTING CABOTEGRAVIR + RILPIVIRINE AS MAINTENANCE THERAPY: ATLAS WEEK 48 RESULTS.**

Susan Swindells, University of Nebraska Medical Center, Omaha, NE, USA. Jaime-Federico Andrade-Villanueva University of Guadalajara, Guadalajara, Mexico. Gary J. Richmond, Broward Health Medical Center, Fort Lauderdale, FL, USA, et al.

**Design:** The Atlas study is a phase III, open, randomised and multi-centre clinical trial that was designed to establish the non-inferiority of a strategy of switching to two injectable, long-acting (LA) antiretrovirals, cabotegravir (CAB) with rilpivirine (RPV), in comparison with maintaining the previous antiretroviral treatment. The inclusion criteria were the following: adults, undetectable viral load in the last six months with an ART based on 2 NRTI + 1 INSTI, NNRTI, or PI. The patients were randomised (1:1) to continue with their usual ART (CONT) or change to CAB/RPV (LA). The participants assigned to the CAB/RPV group received the treatment orally every day for 4 weeks (CAB 30mg + RPV 25mg per day) to evaluate its safety. Then, they received IM (LA) CAB/RPV. The primary objective of the study was HIV-RNA ≥50 c/mL at 48 weeks of follow-up, using the snapshot algorithm of the FDA. The non-inferiority margin was established at 6%.
**Results:** The study included 616 participants (308 per group), of whom 33% were women. The basal regimen of the patients included: 2 NRTI + 1 NNTI (50%), INSTI (33%), or PI (17%). At 48 weeks of the study, 5 participants (1.6%) in the LA group and 3 (1.0%) in the CONT group had HIV1-RNA ≥50 c/mL, reaching the established criterion of non-inferiority. Similarly, the non-inferiority of LA with respect to CONT was also demonstrated in the secondary objective of achieving <50 c/mL (93% vs 95%, respectively) at 48 weeks. Three patients of the LA group and 4 of the CONT group had confirmed virologic failure in two consecutive samples. Two patients of the LA group had resistance mutations in the domains of retrotranscriptase and integrase. Both were from Russia and were infected with genotype 1-A HIV. There were no differences in adverse events between the two groups of the study. Only one patient passed away (CONT). In the LA group, 98% of the

patients were more satisfied with the new treatment than with the previous oral treatment.

**Abstract 140**

**LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV MAINTENANCE: FLAIR WEEK 48 RESULTS.**

Chloe Orkin, Queen Mary University of London, London, UK. Keikawus Arasteh, EPIMED GmbH, Berlin, Germany. Miguel Górgolas Hernández-Mora, Fundacion Jimenez Diaz, Madrid, Spain.

**Desing:** The FLAIR study is a phase III, open, randomised and multi-centre clinical trial that was designed to establish the non-inferiority of a strategy of switching to long-acting (LA) cabotegravir (CAB) with rilpivirine (RPV), in comparison with maintaining (CONT) antiretroviral treatment with dolutegravir/abacavir/lamivudina (DTG/ABC/3TC). The study included naïve patients who received induction treatment for 20 weeks with DTG/ABC/3TC. Those with HIV-RNA < 50 cop/mL at 16 weeks of treatment were randomised (1:1) to continue with DTG/ABC/3TC or switch to CAB/RPV. The participants assigned to the CAB/RPV group received the treatment orally every day (CAB 30mg + RPV 25mg per day) for 4 weeks, in order to evaluate its safety. Then, IM CAB/RPV (LA) was administered. The primary objective of the study was HIV-RNA ≥50 c/mL at 48 weeks of follow-up, using the snapshot algorithm of the FDA. The non-inferiority margin was established at 6%.
**Results:** The study included 629 participants, of whom 566 reached HIV-RNA <50 cop/mL at 16 weeks and were randomised to receive CAB/RPV or continue the treatment with DTG/ABC/3TC (283 per group). At the beginning of the induction phase, the median of CD4+ lymphocytes was 444 cels/mL (7% <200 cels/mm) and the median of the viral load was 4.49 log10 c/mL (20% ≥100.000 c/mL). Of the total sample population, 22% were women. At 48 weeks of the study, 6 participants (2.1%) in the LA group and 7 (2.5%) in the DTG/ABC/3TC group had HIV1-RNA ≥50 c/mL, reaching the established criterion of non-inferiority. Similarly, the non-inferiority of LA with respect to DTG/ABC/3TC was also demonstrated in the secondary objective of achieving HIV-RNA <50 c/mL (LA 93.6% vs DTG/ABC/3TC 93.3%) at 48 weeks. Four patients of the LA group had confirmed virologic failure in two consecutive samples. Three of them (the other patient could not be tested) showed resistance mutations in the domains of retrotranscriptase and integrase. The three patients were from Russia and were infected with genotype 1-A HIV. Three patients of the DTG/ABC/3TC group had confirmed virologic failure in two consecutive samples. None of them showed resistance mutations in the integrase domain. There were no differences in adverse events between the two groups of participants. Only one patient passed away (CONT). In the LA group, 99% of the patients were more satisfied with the new treatment than with the previous oral treatment.

**COMMENT to abstracts 139 y 140:** Dr. Antonio Rivero
Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba

Cabotegravir is an integrase inhibitor with a long half-life (40 hours orally). Its long-acting formulation for intramuscular use allows increasing its half-life to 40 days. On the other hand, Rilpivirine is a non-nucleoside-analog reverse transcriptase inhibitor, currently commercialised for oral administration, with an approximate half-life of 50 days. Its long-acting formulation for intramuscular use allows increasing its half-life to 90 days. Therefore, the availability of both drugs allows creating an ART regimen that can be administered with very long inter-dose intervals. The LATTE-2 study demonstrated the high efficacy (< 50 cop/mL) of this combination in the long term administered every one or two months. The ATLAS and FLAIR studies are the fundamental trials that will allow registering this combination. Thus, the results of the primary objective of the study were much-anticipated and have caused great expectation. The results of the study have shown that the CAB/RPV combination is very efficient (non-inferior to the standard treatment with three antiretroviral drugs), well-tolerated and generates great satisfaction in the patients. The advantages of the LA CAB/RPV regimen in terms of convenience, adherence to treatment and satisfaction of the patients can play an important role in the creation of ART regimens in the near future. The only finding of this study that has caused some concern was the development of resistance mutations in the cases of confirmed virologic failure. These occurred in a very small number and percentage of patients, and especially in Russian patients with subtype 1-A. The possible implication of this finding is still unknown.

## 4. ANTIVIRAL TREATMENT IN PREGNANCY

**Abstract 757**

**POPULATION PK OF DOLUTEGRAVIR IN PLASMA, CORD, AND BREASTMILK: RESULTS FROM DOLPHIN-1.**

Laura Dickinson, University of Liverpool, Liverpool, UK. Kenneth Kintu, Infectious Disease Institute, Kampala, Uganda. Julie Anne Coombs, Desmond Tutu HIV Foundation, Cape Town, South Africa.

The aim of the study was to determine whether the physiological alterations produced in women during the third trimester of pregnancy can significantly affect the PK of DTG. It was a substudy of the DolPHIN-1 clinical trial (NCT02245022), which compared the efficacy and safety of dolutegravir (DTG) vs efavirenz (EFV) in pregnant women who began with ART in late pregnancy (from 28 weeks). This article evaluates the pharmacokinetics (PK) of DTG. The PK of DTG (0-24h) was determined 14 days after the beginning of the treatment, during the third trimester of pregnancy (T3) and in the first two weeks of postpartum (PP). Additionally, the authors determined the levels of DTG in breastmilk (BM) 2-6 and 24 hours after the dose. The study included 28 women. There were no significant differences in the PK of the DTG between T3 and PP. Furthermore, the area under the curve of DTG in BM was 1.13mg·h/L, which corresponds to 3% of the plasma.

**COMMENT:** Dr. Antonio Rivero
Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba.

The PK of the DTG is not significantly affected during the third trimester of pregnancy compared to the postpartum period. The study is of great importance, since it demonstrates that the physiological alterations produced in women during the third trimester of pregnancy do not significantly affect the PK of DTG and, therefore, it would not be necessary to make adjustments to the dosage.

**Abstract 39**

**RANDOMIZED TRIAL OF RALTEGRAVIR-ART VS EFAVIRENZ- ART WHEN INITIATED DURING PREGNANCY.**

Mark Mirochnick, Boston University, Boston, MA, US. David E. Shapiro, Harvard T.H. Chan School of Public Health, Boston, MA, USA. Leavitt Morrison, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

The NICHD P1081 study is an open, phase IV clinical trial that included women at over 20 weeks of pregnancy who were randomised (1:1) to initiate an antiretroviral treatment with raltagravir (RAL) vs efavirenz (EFV), plus two nucleoside analog reverse transcriptase inhibitors (2NRTIs). The study was carried out in Africa (Uganda and South Africa). The primary efficacy objective of the study was to reach HIV-RNA <200 cop/ml at the time of delivery. The tolerability objective was to remain in the assigned group at the time of delivery and the safety objective was the development of grade 3-4 adverse events (AE) in mother and child. The randomization was stratified by gestational age. The study included 408 women (206 RAL and 202 EFV) from Africa, South America and Thailand (only 7 women were from the U.S.A.). There were no basal differences between the two groups. In the primary objective of efficacy, a larger proportion of women in the RAL group reached HIV-RAN <200 copies / ml at delivery with respect to EFV (94% vs. 84%; p=.001), mainly between those with more than 28 weeks of pregnancy (Table 1). The decrease rate of the viral load was greater in the RAL group. The median time until reaching HIV-RNA below 200 cop/mL was 8 days in RAL and 15 days in EFV. Both regimens were well-tolerated and there were no differences between the two groups in the frequency of grade 3-4 adverse events (mothers and newborns), nor in the proportion of stillborn or preterm babies. One child of the RAL group and 4 of the EFV group were infected with HIV (p> 0.05).

**COMMENT:** Dr. Antonio Rivero
Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba.

The purpose of ART is to achieve and maintain HIV-RNA undetectable for the longest gestation time possible, especially in the third trimester and at the time of delivery. The latest guidelines of Gesida/PNS (2019) recommend the combination of TDF or ABC + 3TC or FTC with RAL, ATV/r or DRV/r as the ART of choice in pregnancy. It has been demonstrated that the time to reach viral suppression varies between the different regimens of antiretroviral treatments. Thus, regimens based on integrase inhibitors have shown to take less time to suppress the replication of HIV than regimens based on protease inhibitors or non-nucleoside-analog reverse transcriptase inhibitors. In this context, the NICHD P1081 study is of great importance, since it confirms this evidence among pregnant women. An especially interesting fact is that the use of a regimen based on RAL in women with over 28 weeks of pregnancy reached the target HIV-RNA count at the time of delivery in 93% of these women, which are significantly higher values than those obtained for EFV in the clinical trial and presumably also higher than those that could be reached by regimens based on PI potentiated with ritonavir. Thus, the study provides enough evidence to consider regimens based on RAL as the only ART regimens selectable for women with over 28 weeks of pregnancy.

**Abstract 40**

## RCT OF DOLUTEGRAVIR VS EFAVIRENZ-BASED THERAPY INITIATED IN LATE PREGNANCY: DOLPHIN-2.

Kenneth Kintu, Infectious Disease Institute, Kampala, Uganda. Thoko Malaba, University of Cape Town, Cape Town, South Africa. Jesca Nakibuka, University of Cape Town, Cape Town, South Africa, et al.

The DolPHIN-2 study (NCT03249181) is an open clinical trial that included women at over 28 weeks of pregnancy who were randomised (1:1) to initiate an antiretroviral treatment with dolutegravir (DTG) vs efavirenz (EFV), plus two nucleoside analog reverse transcriptase inhibitors (2NRTIs). The study was carried out in Africa (Uganda and South Africa). The primary efficacy objective of the study was to reach undetectable HIV-RNA at the time of delivery (efficacy) and the development of toxicity to drugs in mother or child (safety). The study included 268 women. There were no basal differences between the two groups in terms of gestation time (31 weeks), viral load (4.4 vs 4.5 log10 cop/mL), or CD4 (464 vs 412 cels/µL). At delivery, the number of women who reached the primary efficacy end point (HIV-RNA < 50 cop/mL) was higher in the DTG group (90/122, 74%) than in the EFV group (49/115, 43%), with a risk ratio of 1.66 (1.32-2.09). These differences remained constant with independence of the basal viral load, CD4 count and gestation time. The proportion of women who reached HIV-RNA 1000 cop/mL at delivery was also higher in the DTG group than in the EFV group (93% vs 83%), with a risk ratio of 1.11 (1.00-1.23). Moreover, DTG was well-tolerated during gestation, with no differences with EFV in terms of adverse events. Likewise, there were no differences between DTG and EFV in gestation time at delivery (39.9 weeks in each group), or prematurity (16.67% vs 15.38%). There were congenital defects in 17 children (DTG 8, EFV 9). There were no defects of the neural tube. However, there were 4 stillborn babies, all from the DTG group. There were also 3 cases of HIV transmission, all in the DTG group.

**COMMENT:** Dr. Antonio Rivero

Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba.

The late initiation of the antiretroviral treatment during pregnancy is associated with a lower probability of reaching the suppression of HIV replication at the end of it and, thereby, a greater risk of vertical transmission of HIV. It has been demonstrated that the time to reach viral suppression varies between the different regimens of antiretroviral treatments. Thus, regimens based on integrase inhibitors have shown to take less time to suppress the replication of HIV than regimens based on protease inhibitors or non-nucleoside-analog reverse transcriptase inhibitors. Therefore, choosing an antiretroviral regimen to be initiated during late pregnancy may be crucial to the aim of preventing the vertical transmission of HIV. The use of DTG is not recommended during pregnancy due to its apparent relationship with defects of the neural tube in newborns whose mothers received DTG during the beginning of their pregnancy. The DolPHIN-2 clinical trial demonstrates that regimens based on DTG in pregnant women who initiate ART from 28 weeks of pregnancy are associated with a greater probability of reaching the suppression of the viral load at delivery. However, this was not associated with a decrease in the vertical transmission of HIV. In fact, all the cases of vertical transmission of HIV occurred in the DTG group. On the other hand, it is important to clarify the greater number of cases of stillborn babies in the DTG group (the 4 stillborn babies in the study were from the DTG group). Until these facts are not clarified, the use of DTG must be considered with great caution, even in late pregnancy.

**Abstract 87**

## A PHASE 1 STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS.

Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge. Magee–Womens Research Institute, Pittsburgh, PA, USA, et al.

*"Screening in every woman of fertile age and at risk of HCV infection"*.

Do pregnant women transmit HCV? Well, around 5.8%. With this percentage it can be reasonable to cure hepatitis C in pregnancy. This is a phase I clinical trial of SOF/LDV in pregnant women infected with genotype 1 HCV. The study includes 9 women, 8 of them with RSV and the other one pending. There were no infections in the fetus or safety problems in the participants.

**COMENTARIO:** Dr. Jesús Santos González

UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

very small N. Non-pan-genotypic treatment, currently not in use. From an epidemiological point of view, pregnancy could be another "opportunity" for diagnosis and treatment in women at high risk of transmission and/or loss after the follow-up, but it is better to perform a *"screening in every woman of fertile age and at risk of HCV infection"*.

## 5. TRANSMISSION CLUSTERS

**Abstract 68**

**HUGGING PHYLOGENETIC TREES: USE OF MOLECULAR ANALYSIS FOR PUBLIC HEALTH INTERVENTION.**

Alexandra M. Oster, CDC, Atlanta, GA, USA.

New computer tools have made it possible to identify HIV transmission clusters through the analysis of molecular data. Although these analyses were carried out in recent years, most of them were retrospective. Currently, public health agencies are beginning to use these data, which are gathered routinely from the sequences obtained from resistance studies. It is important to prospectively identify the transmission clusters, with the aim of strengthening the prevention strategies and ensure that people with HIV and those who are at risk of being infected with it can have access to the services they need (diagnosis, treatment and prevention programs). Tests of resistance to antiretroviral drugs are fundamental for both guiding the treatment and preventing the transmission of HIV

**Abstract 856**

**INCIDENT INFECTION IN HIGH- PRIORITY HIV MOLECULAR TRANSMISSION CLUSTERS.**

Joel O. Wertheim, University of California San Diego, San Diego, CA, USA. Nivedha Panneer, CDC, Atlanta, GA, USA. Anne Marie France, ICF International, Atlanta, GA, USA, et al.

The CDCs of Atlanta routinely analyse HIV sequences in order to analyse the clusters that show a rapid and recent transmission. Using the sequences of HIV-1 pol gene sent to the US National HIV Surveillance System, they identified 116 clusters among the cases diagnosed in 2010 and 2012, and the new infections that appeared in the period of 2013-2017. The authors highlighted the importance of keeping the viral load suppressed, as well as notifying the partners of the patients and the possible contacts to intervene with priority and prevent the development of transmission clusters.

**Abstract 857**

**MOLECULAR SURVEILLANCE AS A MEANS TO EXPAND AN OUTBREAK INVESTIGATION: MA 2015-2018.**

Betsey John, Massachusetts Department of Public Health, Boston, MA, USA. Nivedha Panneer, CDC, Atlanta, GA, USA.. Matthew Tumpney, Massachusetts Department of Public Health, Boston, MA, USA, et al.

In 2016, the Public Health Department of Massachusetts detected an increase of new diagnoses of HIV among parenteral drug users. With the help of the CDCs, they started a research in 2018 to characterise the outbreak. The diagnoses occurred between 01/2015 and 05/2018 were considered linked to the study. The cases that were molecularly and epidemiologically related were mainly men, under 40 years of age, non-Hispanic white and parenteral drug users. The use of molecular data increased the number of people linked to the outbreak and improved the prevention activities, which highlights again the importance of the molecular surveillance of clusters.

**Abstract 876**

**HIV MOLECULAR SURVEILLANCE AND PRETREATMENT DRUG RESISTANCE IN MEXICO CITY.**

Antoine Chaillon, University of California San Diego, La Jolla, CA, USA. Margarita Matías-Florentino, National Institute of Respiratory Diseases, Mexico City, Mexico. Santiago Avila-Rios, National Institute of Respiratory Diseases, Mexico City, Mexico, et al.

The authors analysed the sequences of over 2000 new diagnoses in Mexico City in the period 2016-2018. Globally, the transmission of resistance mutations was 14%, highlighting the resistance to non-analogs with 9.6%. Of the total sample, 40% of the patients were grouped in 99 clusters, mostly young men from the metropolitan area; 18% of the patients in clusters had resistance mutations, with 103N/S being the most frequent one. The presence of resistance mutations associated with transmission clusters compromises first-line treatments in different situations. Although they are less frequent in our

environment, they continue to be important in areas with lower economic resources and, due to migratory movement, they can become a cluster of rapid transmission that we must detect in order to prevent its expansion.

**Abstract 867**
**CLUSTER SURVEILLANCE OF FRENCH PRIMARY INFECTIONS: TOWARD A MORE VIRULENT CRF02_AG?**
Benoit Visseaux, INSERM, Paris, France. Lambert Assoumou, INSERM, Paris, France. Mary Anne Trabaud, CHU de Lyon, Lyon, France, et al.

A study of around 1000 patients diagnosed in France in the period 2014-2016. Most were French MSM and a small proportion were Sub-Saharan. Greater proportion of B subtypes and 20% of CRF02_AG. The latter subtype is related to non-MSM patients with higher viral loads and lower CD4 counts, suggesting a greater virulence than B subtypes. The authors concluded that the increase of transmission clusters makes it necessary to increase the epidemiological surveillance, in order to identify and stop these local outbreaks.

**COMMENT to abstracts 68, 856, 857, 876 y 867:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

The detection of clusters is critical to stop the HIV epidemic. First, we must carry out early diagnoses, detect clusters of rapid transmission, treat quickly to reach sustained virologic response, and protect the susceptible population with PrEP in order to prevent new infections. Pathogen transmission surveillance in real time is a field of great interest for Public Health agencies, at both local and national level. Phylogenetics, which is the study of the relationship between homologous genetic sequences, is a fundamental part of virology research. Factors such as geographical location, the moment of viral transmission and risky behaviours, also influence the parameters of a phylogenetic tree. When these are combined with epidemiological data, the analyses of clusters can provide information about what epidemiological factors are associated with a greater transmission of the virus. Therefore, the hypotheses about direct transmission only make sense when the analysis of the sequences is combined with the study of contacts. However, few studies contain data of contacts and of the sequence of HIV, and those that do are too small to provide information about the factors responsible for the propagation of HIV. Lastly, a global-network approach would allow researchers to determine whether the recently isolated HIV sequences are among known transmission clusters, thus carrying out a real-time surveillance of recent and growing local epidemics. A larger number of sequences introduced in the public databases would improve the precision and resolution of this approach.

## 6. RESISTANCE STUDY

**Abstract 143**
**SYSTEMATIC DETERMINATION OF IN VITRO HIV-1 INTEGRASE RESISTANCE FROM CLINICAL SAMPLES.**
Aniqa Shahid, Vincent Montoya, Wendy W. Zhang, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada.

The data of phenotypic resistance are relatively scarce for the new HIV integrase inhibitors: Dolutegravir (DTG), Bictegravir (BIC) and Cabotegravir (CAB). This study analyses the phenotypic susceptibility of a large panel of recombinant viruses derived from subtype B, selected to maximise the variation of the in vivo sequence. The results confirmed great cross-resistance between DTG, BIC and CAB and identified new mutation patterns that decrease sensitivity to integrase inhibitors, especially the sensitivity to Cabotegravir. These studies must be also extended to variants with non-B subtypes.

**AUTORA:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

**Abstract 144**
**DTG VS LPV/R (DAWNING): EFFICACY BY BASELINE NRTI RESISTANCE AND SECOND-LINE NRTI USE.**
Dannae Brown, ViiV Healthcare, Abbotsford, Australia. Ruolan Wang, ViiV Healthcare, Research Triangle Park, NC, USA. Mark Underwood, ViiV Healthcare, Research Triangle Park, NC, USA.

Dawning is a non-inferiority study that compared DTG + 2 NRTI with Lopinavir + 2 NRTI in HIV-positive patients with medium and low income, in whom a first therapeutic regimen had failed. Of the DTG and LPV groups, 84% and 70%, respectively, reached <50 copies/mL at 48 weeks of treatment. This was independent of baseline NRTI resistance, which was present in 90% of patients: 184I/V (86%), 65R (30%) and >1 TAMS (24%).The results of this study show the superiority of Dolutegravir with respect to Lopinavir/ritonavir in terms of efficacy in the second-line treatment of people with medium and low income. The selection of second-line treatment is a particularly important fact in these countries, where the therapeutic options are usually inferior compared to other regions.

**AUTOR:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

## 7. PRE-EXPOSURE PROPHYLAXIS (PREP)

**Abstract 846**
**RISK FACTORS FOR HIV INFECTION AMONG MSM IN THE ANRS IPERGAY PREP TRIAL.**
Marine Pillet, INSERM, Villejuif, France. Eric Cua, CHU de Nice, Nice, France.. Catherine Capitant, INSERM, Villejuif, France, et al.

*"Let's stop wasting time"*
The researchers of IPERGAY aim to identify which individuals will benefit more from PrEP. To this end, they analyse the group that was randomised as placebo. The infection rate was 7.5 infections per 100 people per year (CI95%: 4.3-12.2). There were no surprises; the ones who became infected were those who had receptive anal sex without a condom, contact with multiple partners, encounters in dark rooms and recreational drugs (especially GHB), and attended sex clubs and private parties. We know who we have to offer PrEP to.

**AUTOR:** Dr. Jesús Santos González
UGC E. Infecciosas, Microbiología Clínica y Medicina PreventivaHospital Universitario Virgen de la Victoria. Málaga.

**Abstract 960**
**CHANGES IN KIDNEY FUNCTION AMONG MSM INITIATION DEMAND TDF/FTC FOR HIV PREP.**
Geoffroy Liegeon, Hôpital Saint-Louis, Paris, France. Guillemette Antoni, INSERM, Villejuif, France. Gilles Pialoux, Tenon Hospital, Paris, France, et al.

*"Let's not be doubtful on the use of PrEP"*
More data of IPERGAY. It compares kidney safety in those individuals that were randomised to TDF/FTC vs placebo. There were no differences between the two groups, even in patients with higher risk of developing kidney problems. The lower global exposure, since it was an intermittent treatment, with an average dose of 15-18 pills per month, can explain the kidney safety profile of PrEP on demand.

**AUTOR:** Dr. Jesús Santos González
UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

**Abstract 48**
**PREPARING FOR PREP IN ENGLAND: PREVALENCE AND INCIDENCE OF HIV AND BACTERIAL STIS.**
Dana Ogaz, Ada R. Miltz, Sarika Desai,Public Health England, London, UK, et al.

*"We're still different".*
STIs epidemic in the West. This study presents the data of the decrease in HIV infection rate from 2012 in sexual health clinics of England. VIH decreases (from 3.7% of individuals per year in MSM with high risk to 1.6% in 2017); however, the rest of STIs increase (syphilis, gonorrhea and chlamydia). Is PrEP responsible for this rise in STIs? Curiously, Spain maintains the same rate of HIV and the same increase of STIs without PrEP.

**AUTOR:** Dr. Jesús Santos González
UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

**Abstract 104**
**THE PHASE 3 DISCOVER STUDY: DAILY F/ TAF OR F/TDF FOR HIV PRE-EXPOSURE PROPHYLAXIS.**
Charles B. Hare, University of California San Francisco, San Francisco, CA, USA. Josep Coll, Hospital Germans Trias i Pujol, Barcelona, Spain. Peter Ruane, Peter J Ruane, MD Inc, Los Angeles, CA, USA, et al.

*"Now what?"*
Discover: randomised, double-blinded, phase III clinical trial in which TAF/FTC vs TDF/FTC demonstrated non-inferiority in the prevention of HIV infection in individuals at risk. Clinical studies with over 4000 patients per group. Good tolerability of both treatments, although TAF/FTC showed better kidney profile and bone safety. Nothing we would not expect.

**AUTOR:** Dr. Jesús Santos González
UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

**Abstract 107**
**IMPACT OF PREP ON DRUG RESISTANCE AND ACUTE HIV INFECTION, NEW YORK CITY, 2015-2017.**
Kavita Misra, Jamie Huang, Demetre C. Daskalakis, New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, et al.

In a study with recently diagnosed patients in NYC, those with PrEP use before the diagnosis showed higher frequency of 3TC/FTC resistance mutations. Mutation 184V/I was more frequent among PrEP users (26% vs 2%). There was no selection of mutations related to Tenofovir (K65R). Moreover, more diagnoses were carried out at the time of acute infection (33% vs 9%). This is due to the fact that these patients are controlled more frequently. These screenings are very important to avoid initiating PrEP during the HIV infection window and to reduce the risk of resistance selection.

**AUTORA:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

## 8. ERADICATION OF THE EPIDEMIC AND A CURE FOR HIV INFECTION

**UPDATE ON HIV CURE**
Workshop W-1. Workshop for new investigators and trainees. Katharine J. Bar. University of Pennsylvania, Philadelphia, PA, USA.

Dr. Bar reviewed our current knowledge on the persistence of HIV, highlighted the major obstacles for cure strategies and discussed the pre-clinical and clinical developments in the search for a functional or eradicating cure for HIV. She talked about studies which demonstrate that most viruses present in reservoirs are defective, and that one of the main mechanisms of the persistence of the reservoir is the clonal expansion of intact viruses from latently infected cells. The initial evidence of this persistence route came from the detection of multiple pro-viruses with the same integration sequence within the host cell. The latent reservoir is still an enigma. We need further knowledge of its size, clonal expansion and establishment time. The substantial, although incomplete, reductions of the reservoir provide valuable data about the fact that the early administration of the antiretroviral treatment is a priority in both children and adults. Greater immunity may be necessary to maintain a long-lasting suppression. There are new immunotherapies (Shock and Kill) that must first demonstrate their safety. Many new agents under development, such as LRA (Latency Reversal Agents) in combination with immunomodulators or with monoclonal antibodies, are very promising therapies for the near future.

**AUTORA:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

**Abstract 29.**
**SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOUS CCR5 DELTA 32 ALLOGENIC HSVT.**
Ravindra K. Gupta, Sultan Abduljawad, Laura McCoy, University College London, London, UK.

This was the case of the London patient who showed undetectable viral load of HIV after 18 months of terminating ART. The remission occurred after the patient received a transplant of stem cells from a donor who had two genetic mutations that remove CCR5 receptors from the CD4 T cell surface. This made him the second man in history, after the "Berlin patient", to achieve the remission of HIV after a transplant of this kind, and this opened a door to the possibility of curing HIV.
For Brown, it was leukemia; for the London Patient, it was Hodgkin lymphoma. These cancer treatments create a unique environment that can be hostile to HIV. First, chemotherapy and/or radiotherapy eliminate many of the reservoirs where the virus hides and, secondly, the new cells that do not express CCR5 receptors prevent HIV from propagating. However, it is very unlikely that this will lead to generalised transplants of stem cells for people infected with HIV; it is only one more step in the right direction.

**AUTORA:** Dra. Isabel Viciana
Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.

**Special presentation.**
**ENDING THE HIV EPIDEMIC: A PLAN FOR THE UNITED STATES.**
Anthony S. Fauci, National Institute of Allergy and Infectious Diseases, National Institute of Health, US Department of Health and Human Services, Bethesda, MD, USA.

*"No more excuses, we have the tools to end the epidemic".*
Fauci's plenary impressed all attendants. He did not talk about cures nor the elimination of the virus or vaccines. He talked about eradicating new infections in the U.S.A., reducing 75% of the infection rate in 5 years and 90% in 10 years. All the health administrations agree. And this is based on four pillars: diagnosing all the people infected as soon as possible, treating the infection quickly and effectively, offering PrEP to all the individuals at risk and giving a quick response to rapid-growth outbreaks.

**AUTOR:** Dr. Jesús Santos González
UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.

# THANKS



**THANKS:**

A los miembros del Grupo Andaluz para el Estudio del VIH (GAEVIH) de la SAEI que han hecho posible que este número salga adelante.

- Dra. Nuria Espinosa Aguilera. Presidenta de GAEVIH. UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen del Rocío. Sevilla.
- Dra. Inés Pérez Camacho. Secretaria de GAEVIH. UGC Medicina Interna. UMT Hospital de Poniente. Almería.
- Dra. Isabel A. Pérez Hernández. Servicio de Medicina Interna. Hospital Comarcal de Melilla.
- Dr. Antonio Rivero. Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba.
- Dr. Jesús Santos González. UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.
- Dra. Rosario Palacios Muñoz. UGC E. Infecciosas, Microbiología Clínica y Medicina Preventiva. Hospital Universitario Virgen de la Victoria. Málaga.
- Dra. Isabel Viciana Ramos. Servicio de Microbiología. Hospital Virgen de la Victoria. Málaga.



Protectings Partners: Abbvie Laboratories, Gilead, Janssen-Cilag, MSD
Special thanks to ANGELINI laboratories

**Andalusian Society of Infectious Diseases.** Avda. de la Aeronáutica 10, building Helios, 2nd floor, module 8.
Phone 954389553. Email: **secretariatecnica@saei.org**

Design and layout by José María Hidalgo Garrido (jmhidalgogarrido@gmail.com). Translated by Adrián Serrano Linares (adri_baggins@msn.com)