VIRTUAL CROI
LIVESTREAM
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PROGRAMMA & ABSTRACTS

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**Livestream vanuit Seattle**

**Moderator:** Prof. dr. Jan Prins, AMC-UvA, Amsterdam

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Virtual CROI Livestream
26 februari 2015, Jaarbeurs Utrecht, Utrecht
**ABSTRACTS**

**Nieuwe inzichten in pathogenesis & cure**

Prof. dr. Charles Boucher
Erasmus MC, Rotterdam

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**108**

**Treatment With a TLR7 Agonist Induces Transient Viremia in SIV-Infected ART-Suppressed Monkeys**

James B. Whitney; So-Yon Lim; Christa E. Osuna; Sriram Anand; Tiffany L. Barnes; Peter T. Hraber; Tomas Cihlar; Romas Geleziunas; Joseph Hesselgesser; Beth Israel

**Background:** Latent reservoirs of replication competent HIV-1 persist in patients on antiretroviral therapy (ART) and represent the major obstacle to HIV eradication efforts. Considerable effort has been directed to identify pharmaceutical agents capable of safely reactivating latent HIV-1 in ART-suppressed patients.

**Methods:** A study was conducted in SIV-infected rhesus macaques (RM) on ART to determine if administration of an oral toll-like receptor 7 (TLR7) agonist would induce transient plasma viremia and reduce viral reservoirs. Ten RM were infected with SIVmac251 by rectal challenge. Plasma SIV RNA levels were measured by RT-PCR (limit of detection 50 copies/mL). The RM received ART at ~9 weeks post-infection (PI) and became virologically suppressed by 24 weeks PI; virologic suppression was maintained throughout week 45. At 45 weeks PI, 4 RM were administered 7 doses of the TLR7 agonist at twice monthly intervals, while on ART. The first 3 doses were 0.1, 0.2 and 0.3 mg/kg and the last 4 doses remained constant at 0.3 mg/kg. Total viral DNA was quantified in peripheral blood mononuclear cells (PBMC) and lymph node biopsies taken pre- and post-completion of TLR7 treatment. Two weeks after TLR7 dosing, ART was discontinued.

**Results:** The first 3 doses of TLR7 agonist administered to the SIV-infected ART-suppressed RM had limited effect on plasma viremia. However, doses 4 through 7 led to transient increases in plasma viral RNA (500 - 1000 SIV RNA copies/mL) in all treated RM with a return to < 50 copies/mL within 4-7 days of TLR7 dosing. After completion of the TLR7 regimen, SIV DNA levels were reduced by 56-75% in PBMCs and colon and lymphoid tissues. Viral DNA levels remained unchanged in the placebo control RM. To determine if these transient plasma virus blips and decreases in viral DNA content also reduced the size of the viral reservoir, ART was discontinued. While the plasma virus rebound kinetics in animals dosed with the TLR7 agonist were comparable to the placebo group after discontinuation of ART, the TLR7 treated animals showed a ~0.5 log10 reduction in plasma virus setpoint as compared to the placebo group.

**Conclusions:** Multiple oral administrations of a TLR7 agonist in SIV-infected ART-suppressed RM was safe, induced transient plasma viremia, reduced viral DNA content in PBMCs, colon and lymphoid tissues and established lower viral setpoint after ART cessation. These novel findings support clinical investigation of a TLR7 agonist in HIV-1 infected patients on ART.

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**103ALB**

**Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea**

Daouda Sissoko, Elin Folkesson, Mbile Abdoul, Abdoul Habib Beavogui, Stephan Gunther, Susan Shepherd, Christine Dansel, France Mentre, Xavier Anglaret, Denis Maloy

**Background:** The JIKI trial (Inserm C1463) assesses the benefits of high-dose favipiravir in reducing mortality and decreasing Ebola virus (EBOV) viral load in patients with Ebola virus disease (EVD).

**Methods:** JIKI is a phase II trial conducted in 2 Ebola treatment units run by MSF and ALIMA in Guinea. Inclusion criteria are: positive EBOV RT-PCR (Altona, crossing cycle threshold [CT] for positivity<40), age >1 year, ability to take oral drugs, and informed consent. Participants are prescribed oral favipiravir (adults: 6000mg Day [D]0 [H0 2400mg, H8 2400mg, H16 1200mg], and then 1200mg bid from D1 to 9). The primary endpoint is mortality. Mortality among participants is compared to mortality during the 3 month period preceding trial initiation in the same centers, as recorded in the MSF/EMLab database. On January 22, the DSMB recommended that the investigators present data on the first 69 adults and adolescents.

**Results:** from Dec 17, 2014 through January 20, 2015, 80 patients received favipiravir, including 69 adults and adolescents >14years (women 64%, age 38 years, median duration of illness 5 days). The baseline CT (BCT) was<20 in 42% and >20 in 58%; the baseline creatinine was >110 μM/L in 60% (BCT<20: 79%; BCT>20: 36%), including >300/μM in 27% (BCT<20: 43%; BCT>20: 10%); baseline ASAT level was >1000 IU in 38% (BCT<20: 77%; BCT>20: 17%); and baseline Creatine Kinase level >4000
IU in 18% (BCT<20: 24%; BCT>20: 8%). The figure shows the PCR CT values at baseline (D0) and at D2 and D4 following treatment initiation. Overall, 48% of participants died (BCT<20: 85%; BCT>20: 15%). The pre-trial mortality was 58% overall (p=0.15), 85% in patients with BCT<20 (p=0.26) and 30% in patients with BCT>20 (p=0.05). Mortality was 100% and 7% in patients with abnormal baseline creatinine values and BCT <20 or >20, respectively. The drug was well tolerated. Results of quantitative virology and PK tests will be available later.

Conclusions: In this non comparative proof of concept trial, most patients with CT < 20 had severe kidney failure and died, with no indication that favipiravir monotherapy improved survival. Patients with CT>20 had a lower mortality rate compared to pre-trial figures in the same settings. These preliminary data encourage continued testing of favipiravir with part

Panobinostat Broadly Activates Latent HIV-1 Proviruses in Patients

Kirston M. Barton; Thomas A. Rasmussen; Martin Tolstrup; Wei Shao; Bonnie Hiener; Ajantha Solomon; Lars Østergaard; Sharon R. Lewin; Ole Søgaard; Sarah E. Palmer

Background: To target the persistence of quiescent HIV-1 during ART, HDAC inhibitors have been used to induce viral transcription, which could potentially facilitate viral clearance. It is important that all replication competent proviruses are activated to fully purge infection. Therefore, we performed an in-depth analysis of the panobinostat clinical trial to determine whether the observed increases in unspliced cell-associated RNA (CA RNA) were due to transcription from a subset or a broad range of proviruses.

Methods: Panobinostat was administered to 15 patients on suppressive ART three times a week every other week for eight weeks (i.e., four cycles of drug). Cell-associated DNA (CA DNA) and RNA were extracted from PBMCs collected before, twice while receiving and four weeks after the final dose of panobinostat treatment. Additionally, plasma samples were collected prior to initiation of ART (nine patients) and during a post-panobinostat analytical treatment interruption (ATI, nine patients) to assess circulating HIV-1. Single-genome sequencing of the env region was used to characterise the virus from the cell-associated DNA and RNA and plasma RNA.

Results: The sequences obtained from the preART plasma reflected the infection status of the patient (acute vs. chronic). Phylogenetic analysis revealed that the panobinostatinduced viral RNA intermingled extensively with the CA DNA sequences from the equivalent time points, indicating that panobinostat activates transcription from a broad range of proviruses. The rebound virus from the ATI plasma was composed of expansions of homogenous sequences, and the sequences from this virus were genetically similar to the panobinostat-induced CA RNA sequences. Furthermore, CA DNA sequences that were identical to the rebound virus were detected. A significantly higher percentage of the sequences from the CA RNA were hypermutated compared to the CA DNA (p=0.04).

Conclusions: Panobinostat non-selectively activates transcription from quiescent proviruses in patients on suppressive ART, supporting its ability to activate HIV-1 from latency. Furthermore, panobinostat activated virus that was genetically similar to that observed during ATI, indicating that it targets virus that drives rebound following treatment discontinuation. The high percentage of hypermutated HIV CA RNA that was detected stresses the need for assays that measure replication competent virus when assessing latency reverting agents.
The Size of the Active HIV Reservoir Predicts Timing of Viral Rebound

Behzad Etemad; Hayat Ahmed; Evgenia Aga; Ronald Bosch; John W. Mellors; Daniel Kuritzkes; Michael Para; Rajesh T. Gandhi; Jonathan Li

Background: Strategies to achieve sustained ART-free HIV remission will require validation in analytic treatment interruption (ATI) trials. Identifying virologic biomarkers that can predict time to viral rebound could accelerate the development of such therapeutics. We examined the association of pre-ATI cell-associated RNA (CA-RNA), DNA (CA-DNA), and residual viremia (RV) with timing of viral rebound during ATI.

Methods: We performed a retrospective combined analysis of participants from 5 ACTG studies who were virologically suppressed on ART and received no immunologic intervention prior to undergoing ATI. The timing of viral rebound was evaluated at either (1) confirmed viral load ≥200 HIV RNA copies/mL or (2) single viral load ≥1,000 HIV RNA copies/mL. Unspliced CA-RNA and CA-DNA were quantified using qPCR, and RV by the single-copy assay.

Results: Participants who initiated ART during acute/early infection (n=20) had lower levels of pre-ATI CA-RNA than those treated during chronic infection (n=104) [median <1.58 vs. 1.83 log10 HIV-1 RNA copies/10⁶ PBMCs, P<0.01]. No significant differences were seen in pre-ATI levels of CA-DNA or RV between those treated during acute/early vs. chronic infection. There were no significant differences by ART regimen (NNRTI vs. PI-based) in pre-ATI CA-RNA, CA-DNA, or RV. Higher pre-ATI CA-RNA levels were significantly associated with shorter time to viral rebound using a threshold of either 200 HIV-1 RNA copies/mL ≤4 wks [N=75] vs. 5-8 wks [N=35] vs. ≥8 wks [N=14]: 1.83 vs. 1.68 vs. <1.58 log10 HIV-1 RNA copies/10⁶ PBMCs, Kruskal-Wallis P<0.01] or 1,000 HIV-1 RNA copies/mL (1.83 vs. 1.69 vs. <1.58 log10 HIV-1 RNA copies/10⁶ PBMCs, P=0.01). The proportion of participants with detectable RV ≥1 copy/mL was significantly higher in those with shorter time to ≥200 HIV-1 RNA copies/mL ≤4 wks vs. 5-8 wks vs. ≥8 wks: 47% vs. 29% vs. 8%, Fisher’s P=0.02]. No significant association was seen between CA-DNA levels and timing of viral rebound. A modest correlation was detected between levels of pre-ATI CA-RNA and CA-DNA (Spearman r=0.16, P=0.08).

Conclusions: The size of the active HIV reservoir, as reflected by levels of CA-RNA and RV, is associated with the time to viral rebound after interrupting ART. CA-RNA and RV have the potential to serve as biomarkers of efficacy for therapies aiming to achieve sustained ART-free HIV remission.
**ABSTRACTS**

**22LB**

**Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study**

Sheena McCormack; David Dunn; On behalf of the PROUD Study Group

Background: Randomised placebo-controlled trials have clearly demonstrated that tenofovir/emtricitabine (TDF/FTC), when taken regularly as PrEP, reduces the risk of HIV infection. However, there are concerns that this benefit might be counteracted by users of PrEP engaging in riskier sexual practices, increasing their chance of exposure to HIV and other STIs. This supports the need for pragmatic open-label randomised studies which mimic real-life clinical practice.

Methods: The PROUD study enrolled MSM from 13 sexual health clinics in England between 27Nov2012 and 30Apr2014. Eligibility criteria included a negative HIV test in the previous 4 weeks and reported condomless anal intercourse in the previous 90 days. MSM were randomised 1:1 to receive open-label daily TDF/FTC either immediately (IMM) or after a deferral (DEF) period of 12 months, and followed quarterly. Based on early demonstration of efficacy, the TSC/IDMC recommended on 13Oct2014 that all MSM in the deferral period be offered PrEP. All analyses are modified ITT (excluding 3 MSM with a reactive HIV test at baseline) based on person-years (PY) to the first HIV test after 48 weeks or after 13Oct2014, whichever was earlier.

Results: 545 MSM were randomised (276 IMM, 269 DEF). At baseline, median(IQR) age was 35(30-43) and 81% were white; median(IQR) number of anal sex partners in the previous 90 days was 10(4-20); 64% reported a diagnosed STI in the previous 12 months. 20 MSM (5 IMM, 15 DEF) had no HIV test after baseline; completeness of follow-up for HIV incidence was 91% (237/261 PY) for IMM and 89% (216/242 PY) for DEF. Three HIV infections were observed in IMM (1.3/100 PY); 19 infections were observed in DEF (8.9/100 PY) despite 174 prescriptions of post-exposure prophylaxis (PEP). This yields a rate difference of 7.6/100 PY (90%CI 4.1-11.2) and a relative reduction of 86% (62-96%; P=0.0002). The proportion with a confirmed STI indicative of condomless anal intercourse (rectal chlamydia/gonorrhoea) was similar in IMM (29%) and DEF (27%) (P=0.50).

Conclusions: In this high incidence cohort, daily TDF/FTC conferred impressive protection against HIV, and higher than the levels previously observed in the placebo-controlled trials. Concerns that effectiveness would be undermined in a real-world setting were unfounded. There was no evidence of an increase in STIs in this population, although they were frequently reported in the year before enrolment. This result strongly supports the use of PrEP among MSM who are at risk of HIV infection.

**23LB**

**On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial**

Jean-Michel Molina; Catherine Capitant; Bruno Spire; Gilles Pialoux; Christian Chidiac; Isabelle Charreau; Cécile Tremblay; Laurence Meyer; Jean-François Delfraissy and the ANRS Ipergay Study Group

Background: Daily PrEP with oral TDF-FTC can reduce the risk of HIV infection in high risk individuals but long term adherence to a daily regimen remains challenging and explains the discordant results reported across trials. We wished to assess the efficacy of “on demand” PrEP in high risk MSM.

Methods: High risk adult MSM who reported condomless anal sex and had a creatinine clearance > 60 mL/mn were enrolled in this prospective randomized double-blind placebo-controlled study. Participants (pts) were asked to take two pills of TDF-FTC (300mg/200mg per pill) or placebo 2 to 24h before each sexual intercourse, then another pill 24h later and a fourth pill 48h after the first drug intake. All subjects received risk-reduction counseling, condoms, HBV and HAV vaccines when needed, were informed about post-exposure prophylaxis and were regularly tested for HIV and other sexually transmitted infections (STIs). The primary study objective was to demonstrate a reduction in HIV incidence with on demand PrEP. In November 2014, following the DSMB recommendation, the placebo arm was discontinued and on demand PrEP was offered to all participants.

Results: From February 2012 to November 2014, 414 pts were randomized and 400 without HIV-infection were enrolled. After a median follow-up of 8.8 months (IQR: 4.3 to 20.5), the incidence of HIV-infection was 6.75 per 100 pt-years in the placebo arm and 0.94 per 100 pt-years in the TDF-FTC arm indicating a relative reduction of 86% in the incidence of HIV with on demand PrEP (95%CI: 39.4-98.5%, P=0.002). Sixteen pts acquired HIV-infection after enrollment, 14 in the placebo arm and 2 in the TDF-FTC arm. Pts used a median of 14 pills/month (IQR: 8-20). Overall, 34% of pts acquired a new STIs. Safety was good with only one pt discontinuing TDF-FTC because of suspected drug-drug interaction. The rate of serious adverse events was low (9%) and similar.
across the study arms. Drug-related gastrointestinal adverse events (nausea, diarrhea, abdominal pain) were reported more frequently with TDF-FTC than with placebo (13% vs 6%, p=0.02). Only 2 pts (1%) in the TDF-FTC arm had transient decreases in creatinine clearance < 60 mL/min.

Conclusions: On demand PrEP with oral TDF-FTC is highly effective to reduce the incidence of HIV-infection in high risk MSM and has a good safety profile.

Near Elimination of HIV Transmission in a Demonstration Project of PrEP and ART

Jared Baeten; Renee Heffron; Lara Kidoguchi; Nelly Mugo; Elly Katabira; Elizabeth Bukusi; Stephen Asimwe; Jessica Haberer; Deborah Donnell; Connie Celum

Background: Antiretroviral-based HIV prevention interventions, including pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART), showed high efficacy for HIV protection in clinical trials among African HIV serodiscordant couples. Assessing the effectiveness of these interventions, and their ability to complement one another, in implementation settings is a priority.

Methods: We are conducting the Partners Demonstration Project, an open-label, prospective study of PrEP and ART delivery among antiretroviral-naïve high-risk heterosexual HIV serodiscordant couples in Kenya and Uganda. High-risk couples are defined by a validated risk scoring tool (Kahle et al., JAIDS 2013). PrEP is offered as a ‘bridge’ to ART in the partnership – i.e., until ART initiation by the HIV-infected partner and for the first 6 months after ART is started; ART is recommended following national ART guidelines – initially CD4 <350 cells/mL but more recently all HIV serodiscordant couples regardless of CD4 count. To assess the impact of the PrEP as a bridge to ART strategy on HIV transmission, we compared observed HIV incidence to a counterfactual simulation model, using bootstrapping methods and constructed with data from a prior prospective study of HIV serodiscordant couples (the Partners PrEP Study, placebo arm), sampled selecting for a subset with an identical distribution of risk scores and duration of follow-up.

Results: Enrollment in the Partners Demonstration Project began in November 2012 and completed in August 2014, with a final sample size of 1013 couples. Given the risk score distribution of the study population, the counterfactual simulations predicted 21.7 HIV infections would be expected to date in this population (incidence 5.3 per 100 person-years, 95% CI 3.2-7.6). However, through July 2014, only one incident HIV infection has been observed during 440 person-years of follow-up, for an observed HIV incidence of 0.2 per 100 person-years (95% CI 0.0-1.3, p<0.0001 versus predicted) (Figure). PrEP was used during 47% of the 440 person-years of follow-up, ART 17%, both 25%, and neither 11%. The one transmission occurred in the absence of ART and with evidence of low PrEP adherence.

Conclusions: Early results from this demonstration project integrating time-limited PrEP and ART for HIV prevention in African couples show near elimination of HIV transmission, with an observed HIV incidence <0.5% per year compared to an expected incidence >5% per year.

Urine Assay for Tenofovir to Monitor Adherence to Tenofovir-Emtricitabine as PrEP

Helen C. Koenig; Karam Mounier; Giffin W. Daughtridge; Caroline E. Sloan; Linden Lalley-Chareczko; Ganesh Moorthy; S. Caitlin Conyngham; Elizabeth Keitner; Luis J. Monlauer; Pablo Tebas

Background: Tenofovir-Emtricitabine (TDF/FTC) is approved for pre-exposure prophylaxis (PrEP) for HIV infection. Adherence is critical for the success of PrEP, but current adherence measurements (self-report) and plasma tenofovir (TFV) levels are inadequate tools for real-time adherence monitoring. Our goal was to develop and validate a urine assay for the measurement of TFV levels to objectively monitor adherence to PrEP.

Methods: We developed a semi-quantitative urine assay using liquid chromatography mass spectrometry with high sensitivity/specificity for TFV. This assay allowed us to determine TFV concentrations in log categories between <10 ng/ml to > 10,000 ng/ml. To clinically validate the assay we conducted 3 cohort studies: 1) A cross sectional study of 10 HIV positive subjects with undetectable HIV viral loads on a TFV-based regimen to evaluate the qualitative relationship of urine TFV levels to plasma TFV levels, 2) A single dose study of TDF/FTC in 10 healthy subjects to evaluate TFV clearance in plasma and urine over 7 days, 3) A 16 week study of 10 HIV negative subjects receiving daily PrEP to evaluate concordance between plasma and urine over time.

Results: Cohort 1 demonstrated 100% concordance between presence of TFV in plasma and urine (PPV 100%, 95% CI, 0.63-1.0; NPV 100%, 95%CI, 0.05-1.0). TFV concentration was 3-4 logs higher in urine than plasma. In cohort 2, TFV was detected for >7 days in urine and 2-4 days in plasma after a single dose of TDF/FTC. Urine TFV was cleared in a log-linear fashion, with a direct correlation of urine levels to time since last dose. The urine assay was 2 logs more sensitive than serum over 7 days. In cohort 3, TFV was detected in 93% of urine samples (concentration range: >10 to >10,000 ng/mL) and 74% of plasma samples (concentration range: >10 ng/ml to >100 ng/ml). Urine TFV concentration > 1000 ng/ml was highly predictive of presence of TFV
in plasma (>10 ng/ml) (PPV 0.88, 95% CI, 0.69-0.97; NPV 0.88, 95% CI, 0.47-0.99), suggesting that the urine assay could be used to distinguish between recent adherence as defined by a dose of TFV within 48 hours (>1000 ng/ml), low adherence (>10 to >100 ng/ml), and non-adherence as defined by last dose more than one week prior (<10 ng/ml).

Conclusions: We provide proof-of-concept that a semi-quantitative urine assay measuring levels of TFV could be further developed into a point of care test to monitor adherence to PrEP.
ABSTRACTS

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Antiretroviral Concentrations in Brain Tissue Are Similar to or Exceed Those in CSF.

Namandjé Bumpus; Qing Ma; David J. Moore; Brookie M. Best; Ronald J. Ellis; Cristian L. Achim; Melanie Crescini; Courtney Fletcher; Igor Grant; Scott Letendre

Background: Limited distribution of many antiretroviral therapy (ART) drugs into the central nervous system (CNS) results in much lower drug concentrations in cerebrospinal fluid (CSF) than in blood. Estimates of CSF distribution have been linked to HIV RNA levels in CSF and neurocognitive performance but results can be inconsistent. One possible reason for this inconsistency is that ART drug concentrations in CSF may not accurately reflect those in brain tissue. The objective of this analysis was to measure ART drug concentrations in brain tissue collected from adults dying with HIV disease.

Methods: 9 HIV+ adults were evaluated in the California NeuroAIDS Tissue Consortium (CNTN) within 6 months of death; reported taking ART at that antemortem visit; and had detectable concentrations of at least one ART drug in serum at autopsy. Autopsies were performed within 30 hours of death. Brain tissue was collected and stored at -80°C. Concentrations of 6 ART drugs [see Table] were measured in 3 brain tissue regions, globus pallidus (GP), cortical gray matter (CGM), and white matter (WM), by LC/MS with a lower limit of quantitation of 25 ng/mL.

Results: Subjects were mostly men (82%) with a mean age of 40.4 (SD 5.0). The most common cause of death was pneumonia. ART drug concentrations in brain tissue in ng/mL are summarized in the Table. Concentrations of ATV, EFV, FTC, and 3TC were similar to published concentrations of these drugs in CSF but concentrations of TDF were higher than reported values in CSF. LPV concentrations in brain tissue were also higher than reported in CSF but only in WM. Drug concentrations appeared to vary by brain region: Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test).

Conclusions: This is the first analysis of ART drug concentrations in human brain tissue. Concentrations of most drugs in this small analysis were similar to reported concentrations in CSF but TDF had higher concentrations than expected based on CSF reports. Regional variation in ART drug concentrations may be important for antiviral efficacy and toxicity.

85LB

Levonorgestrel Implant + EFV-Based ART: Unintended Pregnancies and Associated PK Data

Kimberly K. Scarsi; Kristin M. Darin; Shadia Nakalema; David Back; Pauline Byakika-Kibwika; Laura Else; Sujan Dilly-Penchala; Susan Cohn; Concepta Merry; Mohammed Lamorde

Background: The subdermal levonorgestrel (LNG) implant is recommended for long-acting, reversible contraception with high efficacy (expected failure rate <1%). Efavirenz (EFV)-based antiretroviral therapy (ART) may decrease LNG pharmacokinetic (PK) exposure via cytochrome P450 mediated drug-interactions. A priori, we hypothesized that over 1 year of combined use, EFV would reduce LNG exposure, but not below the proposed threshold for contraceptive efficacy (180 pg/mL).

Methods: We present the final, 48-week results of a longitudinal, parallel group, PK evaluation of HIV-infected, Ugandan women desiring an implant for contraception. A standard dose LNG implant was inserted at entry in two groups: (1) subjects not yet eligible for ART (control group; n=17); (2) subjects with undetectable HIV-RNA on tenofovir/ emtricitabine efavirenz (EFV group; n=20). At each visit, subjects were counseled on condom use and a pregnancy test was performed. Blood was collected at 1, 4, 12, 24, 36, and 48 weeks after entry and plasma LNG concentrations were analyzed by a validated LC-MS/MS method, with an assay calibration range of 50-1500 pg/mL. Demographic data were analyzed with a T-test or chi-square, as appropriate. PK data were reported as geometric means (GM) and GM ratio.
Results: All women were Black African with a mean age of 31 years. Subjects in the EFV group were on EFV for a median of 10 (range 5-66) months prior to entry. PK data are presented in the Table and reveal a 45-57% reduction in LNG concentrations beginning at week 1 and persisting through week 48. Unexpectedly, 3 women in the EFV group became pregnant between weeks 36 and 48. No pregnancy occurred in the control group. At the last study visit, 15 subjects (75%) in the EFV group, but no subjects in the control group, had LNG concentrations below 303 pg/mL (the highest concentration at which a pregnancy was observed; p<0.001).

Conclusions: Contraceptive failures (15%) were seen among HIV-infected women on EFV-based ART within a year of receiving an LNG implant, and LNG exposure was markedly reduced. In addition, the proposed threshold for LNG efficacy (180 pg/mL) was inadequate in our study population. Alternative contraception should be offered to women on EFV-based ART plus LNG implant, but studies of novel implant dosing strategies should be pursued.

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Data presented as pg/mL and geometric mean (GM) with 90% confidence intervals, unless indicated. * n=11; excludes 3 pregnant patients and 6 subjects who did not reach the week 48 endpoint due to study arm closure.

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ART Choice Impacts Antimalarial Exposure and Treatment Outcomes in Ugandan Children

Sunil Parikh; Norah Mwebaza; Richard Kayubi; Joshua Ssebuliba; Sylvia Kiconco; Liusheng Huang; Qin Gao; Abel Kakuru; Jane Achan; Francesca T. Aweeka

Background: Treatment guidelines for HIV and malaria co-infected children are not developed despite concern that drug interactions impact malaria outcomes. Artemether-lumefantrine (AR-LR), contains long-acting LR with a predominant impact on reinfection rates. Previously, HIV-infected children, managed with lopinavir/ritonavir (LPV/r)-based ART, had lower risk for malaria compared to those on efavirenz (EFV) or nevirapine (NVP)-based ART. The pharmacological basis for these distinctions has not been fully addressed.

Methods: Using intensive and population methods, we investigated the pharmacokinetics (PK) and pharmacodynamics (PD) of AR-LR as treatment, in the context of varying ART in HIV infected children 0.5 to 8yrs in the highly endemic region of Tororo. HIV-uninfected children served as controls (C). Intensive (area under the concentration-time curve, AUC) and sparse PK were done over 21d with clinical and parasitological response followed for 42 d. AR, active dihydroartemisinin (DHA), and LR were measured by LC tandem MS.

Results: 130 children had intensive PK (n=30LPV/r; 19EFV; 30NVP and 51C); 89 children had sparse PK (n=26LPV/r; 7EFV; 18NVP and 38C). Lower AR AUC was seen with EFV and NVP compared with C [GMR; EFV:0.41 (p=0.0003); NVP:0.36 (p=0.001)]; DHA was reduced only with EFV [GMR 0.29 (p<0.0001)]. Notably, LPV/r and EFV had dramatic and converse effects on LR AUC; LPV/r and EFV resulted in 2 fold higher and 3 fold lower AUC, respectively. Nearly all EFV children exhibited undetectable LR day 14 and 21 levels (Table). Cumulative 28d risk of parasitologic failure was 11, 44 and 32%, for children on LPV/r, EFV and NVP, respectively. Children on EFV vs. LPV/r had a 4.4 fold higher risk of parasitologic failure at 28d (p=0.007). Recurrent parasitemia risk at 28d was linked with LR AUC (p=0.03) and day 7 levels (HR 0.55, p=0.001). Day 7 <175 ng/mL, a key threshold for clinical outcomes, was linked with 2.5-fold higher risk of recurrent parasitemia (p=0.012) with 9, 89, and 10% of LPV/r, EFV and NVP children below this threshold.

Conclusions: Based on PK for 219 malaria episodes, EFV-based ART results in clinically significant reductions in AR and LR exposure. LR exposure is strongly linked to parasitological failure and 89% of EFV children had day 7 LR <175 ng/mL. In the face of emerging resistance, optimum AR-LR dosing is critical. Low exposure to both AR and LR with EFV-based ART suggests need for improved dosing guidelines in children.
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EFV but Not ATV/r Significantly Reduces Atovaquone Concentrations in HIV+ Subjects

Monica M. Calderon; Joseph A. Kovacs; Alice K. Pau; Maryellen McManus; Raul Allaro; Parag Kumar; Scott R. Penzak

Background: Atovaquone is an alternative agent for prophylaxis and treatment of PCP and toxoplasmosis. Previous studies have shown that average steady state atovaquone concentrations (Cavg) ≥14 μg/mL and ≥18.5 μg/mL are predictive of successful treatment of PCP and toxoplasmosis, respectively. In a recent study, atovaquone exposure following a single dose of atovaquone/proguanil was reduced by 46-75% in HIV+ patients receiving EFV, LPV/r or ATV/r compared to HIV- controls receiving no ART. The current study was conducted to determine if similar pharmacokinetic (PK) interactions occur in HIV+ subjects receiving atovaquone oral suspension at doses used in the treatment of PCP or toxoplasmosis.

Methods: 30 HIV+ volunteers were recruited, 10 each taking EFV-based ART, ATV/r-based ART, or no ART. Subjects were randomly assigned to atovaquone 750 mg BID with food for 14 days (Phase 1) followed (after a washout period) by atovaquone 1500 mg BID with food for 14 days (Phase 2), or vice versa. On day 14 of each phase, blood samples were collected over 12 hrs to determine atovaquone PK parameter values including area under the concentration-time curve [AUCt] and Cavg using non-compartmental methods. PK parameter values from the EFV and ATV/r arms were compared to the no ART arm using an unpaired t-test.

Results: 29 of 30 subjects (25 males; mean age: 42±11 yrs) completed both dosing cohorts. HIV-RNA was < 50 copies/mL in all subjects in the EFV and ATV/r-based ART groups. Median (range) HIV-RNA in the no ART group was 1224 (<40-26,743) copies/mL. Median (range) C4+ counts in the EFV, ATV/r, and no ART-based groups were 602 (212-1321), 616 (357-916), and 585 (412-912) cells/mm3, respectively. Geometric means with 90% CIs are presented for AUCt and Cavg. Geometric mean ratios (GMR) are also included for EFV vs. no ART, and ATV/r vs. no ART.

Conclusions: Subjects on EFV-based ART had 47% and 44% lower atovaquone exposure than no ART subjects at atovaquone doses of 750 mg BID and 1500 mg BID, respectively (P<0.01 for each). Moreover, 4 of 10 subjects (40%) on EFV-based ART + atovaquone 750 mg BID had an atovaquone Cavg <14 μg/mL – the concentration associated with successful PCP treatment. In contrast, ATV/r PK parameter values did not differ significantly from control group values at either of the studied doses. These data suggest that the current recommended dose of atovaquone 750 mg BID for PCP treatment may not be adequate in all patients receiving concurrent EFV.

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Drug-Drug Interactions Between Anti-HCV Regimen Ledipasvir/Sofosbuvir and Antiretrovirals

Polina German; Kimberly Garrison; Phillip S. Pang; Luisa M. Stamm; Adrian S. Ray; Gong Shen; Marc Buacharern; Anita Mathias

Background: Use of some anti-HCV agents with antiretrovirals (ARVs) in coinfected patients may be complicated by drug-drug interactions (DDIs). A fixed-dose combination tablet composed of the NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. We conducted a Phase 1 study to evaluate the potential DDI between LDV/SOF and protease-inhibitor (PI)-containing ARV regimens: ritonavir [RTV, r] boosted atazanavir (ATV/r) or darunavir (DRV/r) plus emtricitabine/tenofovir DF (FTC/TDF; TVD).

Methods: This was a multiple-dose, randomized, cross-over study in healthy volunteers. In Part A (simultaneous dosing), subjects received LDV/SOF, ARVs (Cohort [CH] 1: ATV/r (300 mg/100 mg)+TVD (200 mg/300 mg); CH 2: DRV/r (800 mg/100 mg)+TVD), and LDV/SOF+ARVs each for 10 days. In Part B (CH 3 and CH4), an evaluation of staggered (12 hour) dosing of LDV/SOF and ARVs was conducted. LDV, SOF, GS-331007 (predominant circulating metabolite of SOF), and ARV plasma concentrations were analyzed and PK parameters were calculated. Results of 90% CIs for the geometric least squares means ratios (%; combination vs. alone) for analytes’ AUCtau, Cmax and Ctau were estimated by a linear mixed effect model and compared to lack of PK alteration boundaries of 70-143%. Safety assessments were conducted during the study.

Results: Ninety-five of 96 subjects (N=24/CH) completed the study; one CH 2 subject withdrew consent. Most adverse events (AEs) were Grade 1 or 2. Most commonly reported AEs were ocular icterus with ATV (22%, N=21; CH 1 and 3), headache (19%, N=18; all CH), and nausea (16%, N=17; all CH). One SAE of abdominal pain (Grade 3) was concluded related to ATV/r+TVD by the investigator. Modest increases in LDV and GS-331007 with ATV/r+TVD and a small reduction in SOF with DRV/r+TVD were observed. Increases in ATV and RTV were also observed, and TFV exposures were elevated with both ARV regimens, following either simultaneous or staggered administration of LDV/SOF.

Conclusions: Study treatments were generally well tolerated. LDV/SOF increases TFV exposure within RTV-boosted ATV- or DRV-based regimens. The safety of higher TFV concentrations in this setting has not been established. Consider alternative HCV or ARV therapy to avoid increases in TFV. Patients should be monitored for TFV-associated adverse reactions if coadministered.
Etravirine Pharmacokinetics During Pregnancy and Postpartum
Brookie M. Best; Angela Colbers; Jiajia Wang; Graham Taylor; Alice Stek; Marjo van Kasteren; Mark Mirochnick; David Burger

Background: Maintaining therapeutic concentrations of antiretrovirals (ARVs) throughout pregnancy is critical to prevent perinatal transmission and maternal resistance development. Physiological changes during pregnancy may alter the pharmacokinetics (PK) of prescribed medicines, particularly those metabolized by cytochrome (CYP) P450 enzymes. To date, no studies have reported etravirine (ETV) PK during pregnancy. ETV is metabolized by and inhibits or induces CYP 3A4, 2C9 and 2C19. The goal was to determine ETV PK parameters during the 2nd and 3rd trimesters compared to the same subjects postpartum and to historical non-pregnant controls.

Methods: P1026s is an ongoing, multi-center, multi-arm, prospective PK study of HIV-1 infected pregnant women on ARVs for routine care. This arm enrolled women on ETV 200 mg twice daily. The PANNA Study is a similar design, enrolling in European countries. Steady-state 12-hour ETV profiles were obtained in the 2nd and 3rd trimesters, and at 4-12 weeks postpartum. Maternal and cord blood samples were collected at delivery. The P1026s target steady-state ETV 12-hour AUC was 2.5 μg*hr/mL (10th percentile in nonpregnant historical controls). The 50th percentile AUC in non-pregnant controls is 4.2 μg*hr/mL, and a suggested minimum concentration from the GRACE trial is 0.16 mg/L. Paired PK parameters were compared with the Wilcoxon signed-rank test at a significance of p<0.05.

Results: Five, 12 and 8 women completed 2nd trimester, 3rd trimester, and postpartum PK evaluations. Median (range) age was 26 (19-43) years. Seven patients were black; 6 Hispanic; and 1 Caucasian. At delivery 9/10 patients had an HIV viral load <50 copies/mL. One subject took ETV 400 mg once daily; her oral clearance (CL/F), AUC0-12, and half-life values are included in the summary data, while individual concentrations were excluded. ETV PK parameters are presented below. The median (range) ratio of cord blood/maternal plasma concentrations (n=5) was 0.59 (0.19-4.25). Six children were HIV uninfected; for five children results are pending.

Conclusions: While 2nd trimester and postpartum ETV PK were similar to non-pregnant adult PK, 3rd trimester exposure was significantly higher than postpartum and historical controls. The metabolism of ETV is complex; pregnancy, ETV itself and other drugs alter the activity of these pathways. The increased 3rd trimester exposure may be due to decreases in CYP2C19 activity and ritonavir exposure. No ETV dose change is needed during pregnancy.

Pharmacokinetics of Etravirine in HIV-1–Infected Pregnant Women
M Ramgopal; O Osiyemi; C Zorrilla; HM Crauwels; R Ryan; K Brown; V Hillewaert; B Baugh

Background: Antiretroviral (ARV) therapy during pregnancy has dramatically reduced the risk of mother-to-child transmission. Physiologic changes during pregnancy can affect the PK of ARVs.

Methods: Phase IIIb study evaluating HIV-1–infected pregnant women (age ≥18 years), in the 2nd trimester of pregnancy, receiving ETR 200mg bid with other ARVs. ETR plasma concentrations were assessed predose and 1, 2, 3, 4, 6, 9 and 12 hours postdose during the 2nd and 3rd trimesters and (6-12 weeks) postpartum. ETR PK parameters were derived using non-compartmental analysis. Safety and efficacy were investigated at each visit and summarized using descriptive statistics.

Results: Fifteen women [11 black, 2 Hispanic, 2 white] were enrolled; 13 had evaluable PK. ETR AUC24h, Cmin and Cmax were higher by 46% (LS Means ratio, 90% CI: 1.46, 1.12-1.90), 131% (2.31, 1.26-4.22) and 39% (1.39, 1.15-1.67) during the 2nd trimester and by 28% (1.28, 0.98-1.69), 93% (1.93, 1.03-3.61) and 31% (1.31, 1.08-1.59) during the 3rd trimester, versus postpartum. ETR post-partum PK was comparable to historic controls in HIV-1 infected subjects [DUET]. Though mean ETR exposures during pregnancy were higher compared to post-partum, the observed exposures were still in range with those previously observed in HIV-1 infected subjects treated with ETR 200 mg bid. Unbound ETR PK will be explored. Median baseline (BL) viral load (V/L) was 49 copies/mL; for one woman, BL V/L was 54,000 copies/mL and remained detectable throughout the study. All other women had VL<400 copies/mL during pregnancy (>90% had VL<50 copies/mL). The median increases in CD4 from baseline were 29 and 45 cells/mm3 for the 2nd and 3rd trimester respectively, and were >100 cells/mm3 postpartum. Four subjects had serious adverse events (SAEs), none of which were at least possibly related to ETR (premature rupture of membranes; hypertension; headache; and one subject had 3 SAEs: pregnancy induced hypertension [twice] and premature labor). One subject had a treatment emergent adverse event (atopic dermatitis) that was at least possibly related to study drug. All infants were HIV-negative.

Conclusions: ETR exposure increased during pregnancy; this was not associated with an increased occurrence of SAEs. The regimen was well tolerated. Virologic response was maintained throughout the study and there was no mother-to-child transmission. These data indicate ETR 200 mg bid could be a treatment option for HIV-1 infected pregnant women.
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**Sofosbuvir/Daclatasvir in HIV/HCV Co-infected Patients With Extensive Liver Fibrosis**

Alissa Naqvi; Francine Guillouet de Salvador; Isabelle Perbost; Brigitte Dunais; Aline Joulié; Rodolphe Garraffo; Pascal Pugliese; Jacques Durant; Pierre Marie Roger; Éric Rosenthal

**Background:** All-oral combination of sofosbuvir (SOF), a pan genotypic HCV NS5B inhibitor, plus daclatasvir (DCV), NS5A inhibitor, has been poorly evaluated in HIV/HCV coinfected. Interactions between this anti-HCV regimen and antiretroviral drugs (ART) have been poorly investigated. We evaluated the safety and efficacy of SOF plus DCV and plasmatic concentrations of antiviral drugs in HCV/HIV co-infected patients.

**Methods:** HCV patients with extensive liver fibrosis (METAVIR F3 and F4) and stable HIV disease received SOF 400 mg QD and DCV (30, 60 or 90 mg QD) for 24 weeks. Residual plasma concentrations of DCV, sofosbuvir’s metabolite (GS331007) and ongoing ART were determined on patient's blood samples 15 days after starting HCV treatment. The primary efficacy endpoint was sustained virologic response 12 weeks after treatment discontinuation (SVR12).

**Results:** Baseline characteristics of the 26 patients are shown in the table. HCV viral load under treatment was undetectable in 4/19 (21%) at Day (D)15, 7/14 (50%) at Week (W) 4, 11/12 (92%) at W8, 8/8 (100%) at W12 and 4/4 (100%) at W16. SVR12 results and pharmacological testing will be presented. During the first weeks of treatment, DCV plus SOF combination therapy was well tolerated with no grade 4 adverse events or drug discontinuation.

**Conclusions:** Interferon-free treatments for HCV are needed for HIV/HCV co-infected patients. Pharmacological testing of DCV and SOF is needed to assess drug interactions with HIV antiviral therapy. The preliminary data suggest that DCV plus SOF treatment is well-tolerated and safely co-administered with multiple ART regimens to patients with extensive liver fibrosis.

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**Simeprevir and Sofosbuvir Regimens for Hepatitis C: Decompensation and Serious AEs**

Ponni V. Perumalswami; Kian Bichoupan; Lawrence Ku; Neal M. Patel; Rachana Yalamanchili; Thomas Schiano; Mark Woodward; Douglas Dieterich; Andrea D. Branch

**Background:** New therapies for hepatitis C virus (HCV) were well-tolerated in registration trials; however, results in real world clinical practice can be different. We characterized hepatic decompensation and serious adverse events (SAEs) in patients receiving standard care at the Mount Sinai Medical Center.

**Methods:** All HCV infected patients treated with regimens that contained sofosbuvir (SOF) and/or simeprevir (SMV) were included. The Cases experienced at least one of the following: hepatic decompensation, indicated by new or increased jaundice, ascites, encephalopathy, or sepsis, or another SAE. There were two cohorts: Cohort 1 included 466 patients, Cohort 2 included 43 liver transplant (LT) patients. The incidence of decompensation/SAE was calculated for each cohort. Within each cohort, a matched Case-Control study was performed to identify risk factors for decompensation/SAE. For Cohort 1, up to five Controls were selected for each Case based on treatment regimen and duration. For Cohort 2, matching was 1:2. Cases and Controls were compared using matched conditional exact analysis.

**Results:** A total of 489 patients met the inclusion criteria: 466 in Cohort 1 (non-LT) and 43 in Cohort 2 (LT). There were 13 non-LT Cases (2.8%) and 8 LT Cases (19%), p < 0.01 for the comparison. In Cohort 1, most (62%) were on SOF/RBV, 15% were on SOF/PEG/RBV, and 23% were on SMV/SOF. Among 67 non-LT patients on PEG/RBV-free regimens, three decompensated/experienced an SAE [4%]. In Cohort 2, all were on SOF/ RBV. Treatment was discontinued in 4/13 (31%) of non-LT Cases and in 2/8 (25%) of LT Cases. Similar to registration trials, liver decompensation/SAE lead to treatment discontinuation in 1% [5/446] of the entire non-LT Cohort and in 5% [2/43] of the entire LT Cohort. Among non-LT patients, risk factors for SAE/decompensation included low baseline albumin, high INR, and high total bilirubin. In LT patients, lower hemoglobin, eGFR, ALT, AFP and higher serum creatinine were risk factors for SAE/decompensation.

**Conclusions:** This study identified subgroups of non-LT and LT patients who may require more intensive monitoring and additional interventions to successfully complete SMV/SOF-based treatment regimens. Patients with reduced hepatic biosynthetic function and LT patients were especially vulnerable to serious AEs and decompensation (DA031095, DK090317).
Utility of Hepatitis C Viral-Load Monitoring With Ledipasvir and Sofosbuvir Therapy

Sreetha Sidharthan; Anita Kohli; Anu Osinusi; Amy Nelson; Zayani Sims; Kerry S. Townsend; Lydia Tang; Michael Polis; Henry Masur; Shyam Kottilil

Background: Directly acting antivirals (DAA) are replacing interferon-based hepatitis C therapy. On interferon-based treatment, HCV RNA plasma levels were early predictors of treatment response and mainstays for response-guided therapy. However, the clinical utility of HCV RNA levels to guide duration of DAA therapy has not yet been determined. The aim of this study was to determine the ability of on-treatment plasma HCV RNA levels to predict treatment outcome in HCV mono-infected and HIV/HCV co-infected patients treated with ledipasvir and sofosbuvir.

Methods: In two NIAID clinical trials, SYNERGY A (HCV mono-infected, n=17) and ERADICATE (HIV/HCV co-infected, ARV naïve n=13, on cART n=37), subjects were treated with a fixed dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 weeks. In both trials, patients were treatment-naïve, non-cirrhotics, and infected with HCV genotype 1. Serial measurements of plasma HCV RNA were performed by the Roche COBAS TaqMan HCV test v1.0 and the Abbott real-time PCR assay. The positive predictive value and negative predictive value at week 4 and end of treatment (EOT) for both assays were calculated.

Results: By the Abbott assay on SYNERGY, 11/17 patients had detectable (6/17 quantifiable) HCV RNA at week 4 and 5/17 patients had detectable but unquantifiable HCV RNA at EOT (Figure 1a). All patients with undetectable HCV RNA at week 4 and EOT achieved SVR12, and none with detectable HCV RNA relapsed (PPV 100 and NPV 0). By the Roche assay (Figure 1b), all patients had undetectable HCV RNA at EOT and achieved SVR 12 (PPV 100). On ERADICATE, 32/50 patients had detectable (9/50 quantifiable) HCV RNA by the Abbott assay at week 4 (Figure 1a), 31 of whom achieved SVR4 (PPV 100 and NPV 3.1). At EOT, 7/49 patients had detectable but unquantifiable HCV RNA by the Abbott assay, all of whom achieved SVR4 (PPV 100 and NPV 0). By the Roche assay (Figure 1b), all 50 patients were undetectable at EOT and 1 relapsed (PPV 98).

Conclusions: Contrary to past experience with interferon-containing treatments, the presence of detectable HCV RNA levels at EOT is not predictive of relapse in these studies. The low negative predictive values at week 4 underscore the importance of continued therapy for patients who fail to achieve undetectable levels of HCV RNA early on during treatment because their chances of achieving SVR are still high.
Effect of HIV Coinfection on Adherence to a 12-Week Regimen of HCV Therapy With Ledipasvir/Sofosbuvir

Kerry S. Townsend; Tess L. Petersen; Lori A. Gordon; Amy Nelson; Cassie Seamon; Chloe Grass; Anu Osinusi; Michael A. Polis; Henry Masur; Shyam Kottilil

Background: The treatment of hepatitis C virus (HCV) infection is rapidly evolving to interferon (IFN) and ribavirin (RBV) free treatment with directly acting antiviral agents (DAAs). The impact of DAAs on HCV treatment adherence in HIV/HCV co-infected populations has not been extensively evaluated. We compared adherence rates of the IFN and RBV free DAA regimen of ledipasvir/sofosbuvir (LDV/SOF) between HCV mono-infected and HIV/HCV co-infected patients.

Methods: Participants were representative of the urban Washington D.C. cohort and were HCV treatment naïve, genotype 1 study subjects from two National Institute of Allergy & Infectious Diseases (NIAID) phase 2 clinical trials (Synergy A: HCV mono-infected participants, n=20, and Eradicate: HIV/HCV co-infected participants, antiretroviral (ARV) naïve, n=13, on combination ARV therapy, n=37). Patients were treated with LDV (90 mg) + SOF (400 mg) as a fixed dose combination once daily for twelve weeks. Adherence was measured using three tools: MEMS (Medication Event Monitoring System) caps, pill counts, and patient report. Adherence over time was compared using Wilcoxon T test. Analyses were performed using PRISM 6.0 (Graphpad).

Results: Patients enrolled were predominately African American (83%) and male (73%), with a median age of 59 years. Patients in all three-treatment groups had prompt viral load decline associated with high adherence rates. Only twelve out of the sixty patients (20%) missed 4 or more pills. However, patient adherence significantly decreased from baseline - week 4 compared to week 8 - 12 in all three groups [HCV mono-infected (p=0.02), HIV/HCV ARV naive (p=0.01), and HIV/HCV ARV treated patients (p=0.01)].

Conclusions: Adherence to the single daily tablet of LDV/SOF in this urban population was high and coupled with complete HCV viral suppression. However, adherence significantly declined over the course of treatment, suggesting that shorter duration DAA therapies should be evaluated for HCV treatment efficacy in this patient population.

Drug-Drug Interactions Between Anti-HCV Regimen Ledipasvir/Sofosbuvir and Antiretrovirals

Polina German; Kimberly Garrison; Phillip S. Pang; Luisa M. Stamm; Adrian S. Ray; Gong Shen; Marc Buacharern; Anita Mathias

Background: Use of some anti-HCV agents with antiretrovirals (ARVs) in coinfected patients may be complicated by drug-drug interactions (DDIs). A fixed-dose combination tablet composed of the NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. We conducted a Phase 1 study to evaluate the potential DDI between LDV/SOF and protease-inhibitor (PI)-containing ARV regimens: ritonavir [RTV, r] boosted atazanavir [ATV/r] or darunavir [DRV/r] plus emtricitabine/tenofovir DF (FTC/TDF; TDF).

Methods: This was a multiple-dose, randomized, cross-over study in healthy volunteers. In Part A (simultaneous dosing), subjects received LDV/SOF, ARVs [Cohort (CH) 1: ATV/r (300 mg/100 mg)+TVD (200 mg/300 mg); CH 2: DRV/r (800 mg/100 mg)+TVD], and LDV/SOF+ARVs each for 10 days. In Part B (CH 3 and CH4), an evaluation of staggered (12 hour) dosing of LDV/SOF and ARVs was conducted. LDV, SOF, GS-331007 (predominant circulating metabolite of SOF), and ARV plasma concentrations were analyzed and PK parameters were calculated. 90% CIs for the geometric least squares means ratios (%; combination vs. alone) for analytes’ AUCtau, Cmax and Ctau were estimated by a linear mixed effect model and compared to lack of PK alteration boundaries of 70-143%. Safety assessments were conducted during the study.

Results: Ninety-five of 96 subjects (N=24/CH) completed the study; one CH 2 subject withdrew consent. Most adverse events (AEs) were Grade 1 or 2. Most commonly reported AEs were ocular icterus with ATV (22%, N=21; CH 1 and 3), headache (19%, N=18; all CH), and nausea (18%, N=17; all CH). One SAE of abdominal pain (Grade 3) was concluded related to ATV/r+TVD by the investigator. Modest increases in LDV and GS-331007 with ATV/r+TVD and a small reduction in SOF with DRV/r+TVD were observed. Increases in ATV and RTV were also observed, and TFV exposures were elevated with both ARV regimens, following either simultaneous or staggered administration of LDV/SOF.

Conclusions: Study treatments were generally well tolerated. LDV/SOF increases TFV exposure within RTV-boosted ATV- or DRV-based regimens. The safety of higher TFV concentrations in this setting has not been established. Consider alternative HCV or ARV therapy to avoid increases in TFV. Patients should be monitored for TFV-associated adverse reactions if coadministered.
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Tenofovir Alafenamide (TAF) in a Single-Tablet Regimen in Initial HIV-1 Therapy

David Wohl; Anton Pozniak; Melanie Thompson; Edwin DeJesus; Daniel Podzamczer; Jean-Michel Molina; Gordon Crofoot; Christian Callebaut; Hal Martin; Scott McCullister

Background: Tenofovir alafenamide (TAF) is a novel tenofovir (TFV) prodrug that, when administered in the single tablet regimen elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF), has >4-fold increase in intracellular TFV diphosphate and >90% lower plasma TFV levels compared to tenofovir disoproxil fumarate (TDF). Two Phase 3 studies of identical design were conducted in distinct geographic areas comparing 2 single tablet regimens, E/C/F/TAF and E/C/F/TDF, in treatment-naive HIV-1+ adults.

Methods: Patients were randomized 1:1 to receive a single tablet regimen of E/C/F/TAF or E/C/F/TDF once daily in two Phase 3 double blind studies. Primary endpoint was Week 48 virologic response by FDA Snapshot algorithm in a pre-specified analysis of the combined studies.

Results: 1,733 subjects were randomized and treated: 15% women, 43% non-White, 23% viral load ≥100,000 copies/mL. Median baseline characteristics were: age 34 yrs, VL 4.58 log10c/mL, and CD4 count 427 cells/mL. The primary objective was met, as E/C/F/TAF was non-inferior to E/C/F/TDF with 92% and 90%, respectively, having HIV RNA <50 copies/mL at week 48 (difference +2%, 95% CI -0.7% to +4.7%, p=0.13). The rates of virologic success between E/C/F/TAF and E/C/F/TDF were similar across subgroups according to age, sex, race, baseline HIV1 RNA level, baseline CD4 cell count, region (US versus exUS), and study drug adherence. Mean change in CD4 count at Week 48 was 230 cells/mL in the E/C/F/TAF arm vs. 211 cells/mL for E/C/F/TDF (p=0.02). Virologic failure with resistance occurred in 0.8% in the E/C/F/TAF arm and 0.6% on E/C/F/TDF. Treatment related SAEs were rare: E/C/F/TAF 0.3% (n=3), E/C/F/TDF 0.2% (n=2). There were no reports of proximal renal tubulopathy (including Fanconi Syndrome) in either arm. No single AE led to discontinuation of more than 1 subject on E/C/F/TAF. Grade 2, 3, or 4 AEs occurring in ≥ 2% were: diarrhea (3.3% vs. 2.5%), nausea (2.2% vs. 2.0%), headache (2.7% vs. 2.1%), and URI (3.6% vs. 3.1%) in the E/C/F/TAF and E/C/F/TDF arms, respectively.

Conclusions: Through 48 weeks of treatment, high virologic response rates were seen in patients receiving E/C/F/TAF or E/C/F/TDF, and similar responses were seen across subgroups evaluated. Drug resistance was <1%. Both regimens were well tolerated, and no unique AEs associated with TAF occurred. These data support the use of E/C/F/TAF, the first TAF-based single tablet regimen, as a potential new regimen for initial treatment of patients with HIV-1 infection.

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Antiviral Activity/Safety of a Second-Generation HIV-1 Maturation Inhibitor

Carey Hwang; Dirk Schürmann; Christian Sobotha; Heather Sevinsky; Palanikumar Ravindran; Hong Xiao; Neelanjana Ray; Mark Krystal; Ira B. Dicker; Max Lalaiладe

Background: BMS-955176 is a 2nd-generation HIV-1 maturation inhibitor (MI). A 1stgeneration MI (bevirimat) showed clinical efficacy in early-phase studies, but ~50% of subjects had reduced viral susceptibility associated with naturally occurring polymorphisms in Gag. We assessed BMS-955176 antiviral activity, safety, and exposure–response during 10 days of monotherapy in HIV-1, subtype B-infected subjects.

Methods: AI468002 (NCT01803074) is a Phase 2a, randomized, multi-part trial. Forty HIV-1, subtype B-infected subjects with HIV-1 RNA ≥5000 c/mL and CD4+ T-cell counts ≥200 cells/mL were randomized 1:1:1:1 to BMS-955176 dose groups of 5, 10, 20 or 40 mg, then 4:1 to receive an oral suspension of BMS-955176 or placebo once daily (QD) for 10 days. Twenty additional subjects were later randomized to 80 and 120 mg QD dose groups. The primary endpoint was change in HIV-1 RNA from baseline to Day 11; safety and exposure–response were secondary endpoints.

Results: Overall, 60 subjects were randomized to receive either BMS-955176 (n=48) or placebo (n=12). Median change in HIV-1 RNA from baseline to Day 11 ranged from −0.15 to −1.36 log10 c/mL and maximum median change between baseline and Day 24 (study discharge) ranged from −0.50 to −1.70 log10 c/mL across the BMS-955176 groups. An exposure–response relationship was observed; there was an increase in maximum median response over the range of 5–40 mg QD, which plateaued at −1.64 log10 c/mL at doses of 40–120 mg QD. Maximum median declines in HIV-1 RNA were similar for the 40–120 mg QD dose groups regardless of baseline Gag polymorphisms (positions evaluated: V362, Q369, V370, and T371). BMS-955176 was generally well tolerated, and no unique AEs associated with TAF occurred. These data support the use of E/C/F/TAF, the first TAF-based single tablet regimen, as a potential new regimen for initial treatment of patients with HIV-1 infection.
tolerated at all doses. There were no deaths, serious adverse events (SAEs), AEs leading to discontinuation, grade 3–4 related AEs or clinically relevant grade 2–4 laboratory abnormalities.

Conclusions: BMS-955176 achieved maximum median declines of >1 log10 c/mL in HIV-1 RNA at doses of 20–120 mg QD. Response increased with doses up to 40 mg QD, with a plateau of ~1.64 log10 c/mL observed at 40–120 mg QD. The greatest response achieved was a maximum median change of ~1.70 log10 c/mL in the 40 mg group. Unlike 1st generation MIs, in this proof-of-concept study BMS-955176 showed similar antiviral activity in subjects with wild-type HIV-1 or HIV-1 with Gag polymorphisms. BMS-955176 was generally well tolerated at all doses. Phase 2b studies for BMS-955176 will begin Q2, 2015.

554LB
Cabotegravir and Rilpivirine As 2-Drug Oral Maintenance Therapy: LATTE W96
Results
David A. Margolias; Cynthia C. Brinson; Graham H. Smith, Jerome de Vente, Debbie P. Hagens; Sandy K. Griffith; Marty H. St. Clair; Kimberly Y. Smith; Peter E. Williams; William R. Spreen

Background: Cabotegravir (CAB, GS744) is an HIV INSTI under development as both an oral and long-acting (LA) injectable. LATTE was designed to select an oral dose of CAB and to evaluate a two-drug ART regimen with rilpivirine (RPV), as suppressive maintenance therapy.

Methods: Phase 2b, multicentre, partially-blinded, dose-ranging study in ART-naïve HIV infected adults, randomized 1:1:1:1 to the induction regimen of once daily oral CAB 10 mg, 30 mg, 60 mg or efavirenz (EFV) 600 mg with TDF/FTC or ABC/3TC through Week (W) 24, followed by a two-drug oral maintenance regimen of CAB (blinded dose) + RPV 25 mg through W96. CAB patients (pts) with a VL <50 c/mL immediately prior to W24 discontinued NRTIs and began RPV 25 mg; no change was made for EFV + NRTIs pts (ITT Maintenance Exposed (IME)).

Results: 243 pts were randomized and treated (ITT-E): 96% male, 38% non-white, 14%>100,000 c/mL HIV-1 RNA, 61% TDF/FTC. Amongst pts who began CAB + RPV at W24, 86% had HIV-1 RNA <50 c/mL by snapshot at W96 overall, relative to 83% of pts continuing EFV (ITT-ME). Five protocol-defined virologic failures occurred during 72 weeks of Maintenance (CAB 10 mg [2], CAB 30 mg [1], EFV [2] including two on CAB + RPV with treatment emergent resistance [INI + NNRTI, NNRTI]). Drug-related AEs > Grade 2 were reported by 14% and 19% of CAB and EFV pts, respectively with 4% and 4% occurring during the 72W Maintenance phase. SAEs occurred in 10% of CAB pts (none drug related); and 6% EFV pts (one drug-related - suicide attempt). Fewer CAB pts withdrew due to AEs (3%), than EFV pts (15%), mostly prior to the Maintenance phase. Treatment-emergent lab abnormalities > Grade 3 occurred in 26% of CAB and 37% of EFV pts through W96, most commonly elevated creatine kinase. Rates of any graded ALT elevations were 20% with CAB and 21% with EFV.

Conclusions: When used as two-drug maintenance therapy in virologically suppressed pts, CAB + RPV provided similar antiviral activity to EFV+2 NRTIs through W96. CAB + RPV was well tolerated overall, with no SAEs considered drug related and few AEs leading to withdrawal. Considering all safety and efficacy data, oral CAB 30mg once-daily was selected for further development. Results support the selected dose regimens for the ongoing Ph2 LATTE-2 study with CAB LA + RPV LA as injectable two-drug maintenance therapy.
35LB

Early ART and Sustained Virological Suppression Limits HIV Proviral DNA Reservoir: CHER Evidence

Helen A. Payne; Sarah Watters; Marvin Hsaio; Robin Callard; Abdel Babiker; Mark F. Cotton; Kennedy Ot wormsbe; Avy Violari; Diana M. Gibb; Nigel J. Klein

Background: Improved understanding of HIV-1 proviral DNA latent reservoir formation and impact of ART-strategies on reservoir size can inform treatment strategies in paediatric HIV.

Methods: HIV-1 proviral DNA was measured from a substudy of 118 children from the Children with HIV Early Antiretroviral Therapy (CHER) trial where HIV-infected infants <12 weeks with CD4% ≥25% were randomised to early limited ART for 40 or 96 weeks or deferred ART. For infants on deferred ART or following ART interruption after 40/96 weeks ART was started/re-started for clinical progression (CDC severe stage B/C disease) or CD4% <20%. HIV-1 proviral DNA was measured by quantitative PCR using DNA extracted from 384 cryopreserved PBMC samples taken 12-weekly from 40 to 252 weeks after a minimum of 24 weeks of ART. The effects on proviral DNA decline of early versus deferred ART and ART-interruption were investigated. Predictive factors for reservoir decline were explored including ART duration, enrolment CD4 and CD4 at 96 weeks, HIV serostatus and quantitative HIV-antibody at 84 weeks, baseline CMV viraemia, immunological phenotypes, enrolment viral load, viral load 9–12 months prior to proviral DNA measurement and total weeks continuous suppression below 400 copies/ml. The profiles of 5 children with undetectable proviral DNA measurements were also described.

Results: After a minimum 24 weeks of ART, 73 children starting early ART showed a trend towards less HIV-1 proviral DNA compared with 45 children on deferred ART: median 27 [IQR 8 – 51] versus 100 [48 – 202] copies of provirus per 10^5 PBMCs, p=0.08. Overall, reduced reservoir size and probability of developing an undetectable reservoir were strongly associated with earlier ART-initiation and longer continuous virological suppression (p-values all <0.0001). However patterns of decline varied despite continuous ART and apparent virological suppression. ART-interruption only modestly increased levels of proviral DNA (p=0.03). HIV serostatus did not correlate with reservoir size (p=0.92) but higher CMV DNA levels at enrolment were associated with an increased HIV reservoir (p=0.02). Four children with undetectable proviral DNA underwent ART-interruption as per CHER randomisation and exhibited HIV-1 viral resurgence.

Conclusions: These findings inform the interplay between clinical, immunological or virological factors involved in reservoir dynamics, and support the view that early-initiation of ART and sustained virological suppression are key to reservoir reduction.
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