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The ISHEID welcomed in Marseilles, France, more than 1,000 attendees (70% non-French) from May 23 to May 25, 2012, with the aim of discussing recent advances in the field of HIV care. Page 4
Dear Colleagues,

Welcome to this issue of HIV & Virology News. The second of a four issue planned for 2012. An important clinical question is if patients diagnosed with HIV during primary infection should be recommended to start treatment immediately, or if initiating treatment in a later, more stable phase, is of no disadvantage. Christine Katlama is arguing for early intervention during acute infection, a standpoint that she shared with several other experts, see Alain Lafeuillade and colleagues’ report from ISHEID2012. More and more data supporting early treatment also in chronic infection with high CD4 cell counts are becoming available and the U.S. Department of Health and Human Services (DHHS) Panel recommend antiretroviral treatment regardless of CD4 cell count.

However, and unfortunately, no randomized control study that supports initiation of treatment in patients with high CD4 cell counts has been performed yet. The ongoing international randomized START (Strategic Timing of AntiRetroviral Therapy) study is looking into the matter whether starting antiretroviral therapy before the CD4 count drops to less that 500 cells/mm² reduces the occurrence of serious morbidity and mortality compared to waiting until the CD4 count drops to less than 350 cells/mm². Almost 2,500 patients have been enrolled so far. The enrollment goal is 4,000 subjects and despite the importance of this study, recruitment of subjects has been difficult in many countries as patients and doctors don’t want to wait until CD4 counts drop to less than 350 cells/mm² as required in the delayed arm. Another important obstacle, both for recruitment to START and to early treatment, is that a large proportion of HIV-infected patients are diagnosed late with low CD4 cell counts.

I was personally surprised by the high quality of presentations and discussions at the 2012 International Symposium on HIV & Emerging Infectious Diseases (ISHEID) that took place in Marseille, France, in late May. It was my first attendance to this meeting, but definitely not my last. Several interesting topics were discussed and some of those covered in the conference report in this issue of HIV & Virology News. One controversy that was discussed at ISHEID2012 was if neurological complications and neurocognitive impairment is something that we need to be cautious about also in patients on suppressive ART. My opinion and personal experience is that such complications are rare, but that neurological symptoms sometimes occur in patients on otherwise effective treatment, as has been reported by for example Canestri et al (Clin Infect Dis. 2010,50:773-8).

A lot of concerns have been raised about the effectiveness to prevent HIV replication in the CNS of new, and less conventional, drug combinations, such as PI/r monotherapy. We have only just published two cases with cerebrospinal fluid viral breakthrough on darunavir/r monotherapy maintenance (Scand J Infect Dis, in press) and recommended caution with protease inhibitor monotherapy until CNS results have been obtained from ongoing clinical studies. José Arribas who has an extensive experience in PI/r monotherapy usage contributes with a review and his view on the question whether an increased risk of neurocognitive impairment exists on PI/r monotherapy.

In cases of new-onset neurocognitive impairment or neurological symptoms, for example chronic headache, during treatment, a lumbar puncture is strongly recommended. To be able to interpret the results from cerebrospinal fluid measurements it is important to be familiar with the kinetics of CSF findings during asymptomatic HIV infection and we (Magnus Gisslén and Lars Hagberg) have reviewed some typical pattern of cerebrospinal fluid markers in asymptomatic HIV.

Graeme Moyle covers another issue of great clinical importance: chronic renal dysfunction related to ART and challenges regarding the assessment of renal function with new antiretroviral agents.

As has been reviewed in earlier issues of the journal, several new effective drugs for treatment of hepatitis C are under development and evaluation. The first step in the new hepatitis C treatment era was the release of the protease inhibitors boceprevir and telaprevir. Jean-Michel Pawlotsky gives his view on how those drugs should be used in hepatitis C mono-infected subjects. Significant interactions with NNRTIs and PIs limit their usage in HCV/HIV co-infected patients.

I hope that you will find this issue of interest, enjoy your reading!

US DHHS Panel recommendations for ART initiation in ART naive patients

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm³ (AI)
  - CD4 count 350 to 500 cells/mm³ (AII)
  - CD4 count >500 cells/mm³ (BIII)
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy (AI) (see perinatal guidelines for more detailed discussion)
  - History of an AIDS-defining illness (AI)
  - HIV-associated nephropathy (HIVAN) (AII)
  - HIV/hepatitis B virus (HBV) coinfection (AII)
- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (AI [heterosexuals] or AIII [other transmission risk groups]; see text for discussion).
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

MAGNUS GISSLÉN
Editor
Abstract:
This paper summarizes the presentations and debates that took place during the last ISHEID (International Symposium on HIV and Emerging Infectious diseases) in Marseilles, France, 23–25 May 2012. We have tried to point out advances and recommendations in 6 moving areas: Pre-exposure prophylaxis, antiretroviral strategies, acute HIV infection, HIV care, HIV/HCV co-infection management, HIV neuro-cognitive impairment. The statements made in this article are under the responsibility of their authors and do not necessarily reflect the views of speakers or their institutions, nor the view of companies that supported the ISHEID. Their aim is to move forward to a better and standardized care of HIV-infected patients.

Key words: HIV, HIV care, HCV, HCV care, ISHEID, guidelines, new drugs, HIV cure, HIV eradication, HDAC inhibitors, boceprevir, telaprevir, pre exposure prophylaxis, neuro-cognitive impairment, first line HIV therapy, acute HIV infection

Introduction
The ISHEID welcomed in Marseilles, France, more than 1,000 attendees (70% non-French) from May 23 to May 25, 2012, with the aim of discussing recent advances in the field of HIV care. The focus was – not only – on a potential French guidelines update, but also on potential worldwide recommendations according to current scientific knowledge. This report highlights the main topics that were discussed during this meeting with changes over the last 2 years, when the 2010 ISHEID was held.

Pre-exposure Prophylaxis (PrEP)
The ISHEID meeting took place only 2 weeks after the FDA voted with a large majority in favor of the use or Truvada® as pre-exposure prophylaxis against HIV. This topic was covered by a lecture from Mark Wainberg (Montreal, Canada) and a pros/cons debate that induced inflamed discussions [1].

In his presentation, Professor Wainberg recapped the current clinical trials addressing by diverse ways the issue of PrEP (Table 1). The main problem is the highly publicized IPrEx study [2] that, actually, failed its primary end points but was used by the firm to get open label extension (IPrEx-OLE).

IPrEx advocates argue that the efficacy is better if adherence is good, showing data with a 92 percent efficacy rate in the subset of patients with detectable levels of TDF/FTC in blood, i.e. with good adherence. The problem is that in this trial most patients were non-adherent in the view of overall results at a 42 percent efficacy rate, and also did not use condoms. This is worrisome in a controlled trial where participants have been monitored monthly with adherence and prevention messages. It precludes the catastrophe when Truvada® PrEP will be available outside clinical trials.

The IPrEX study tried to be reassuring in terms of resistance, although there were 2 patients already infected at baseline who developed a M184V mutation outside clinical trials.

The same arguments can be opposed to the lack of toxicity claimed by Truvada® PrEP advocates. Seven subjects discontinued Truvada® due to creatinine elevation and no long-term results in others. Actually, lack of resistance [3] may be underestimated (0/36: higher bound 95%CI: 9.5%).

Regarding the risk of sexual behaviour changes, it is exemplified by the obser-

### Table 1: Trials addressing the issue of PrEP in a scientific way (as on March 2012).

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Population</th>
<th>n</th>
<th>Drug tested</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004 South Africa</td>
<td>Women</td>
<td>889</td>
<td>TFV vaginal gel</td>
<td>39 %</td>
</tr>
<tr>
<td>iPrEx Brazil, Ecuador, Peru, South Africa, Thailand, USA</td>
<td>MSM</td>
<td>2 499</td>
<td>FTC/TDF p.o.</td>
<td>42 % at 144 weeks</td>
</tr>
<tr>
<td>TDF2 Botswana Men and women</td>
<td>1 200</td>
<td>FTC/TDF p.o.</td>
<td>62 %</td>
<td></td>
</tr>
<tr>
<td>Partners PrEP Kenya, Ouganda Heterosexual couples</td>
<td>4 758</td>
<td>FTC/TDF p.o.</td>
<td>67 %</td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP Kenya, South Africa, Tanzania Women</td>
<td>1 950</td>
<td>FTC/TDF p.o.</td>
<td>75 %</td>
<td></td>
</tr>
<tr>
<td>VOICE South Africa, Ouganda, Zimbabwe Women</td>
<td>5 029</td>
<td>TDF p.o. with TFV vaginal gel</td>
<td>60 %</td>
<td></td>
</tr>
<tr>
<td>Bangkok Tenofovirus Trial Thailand IVDA</td>
<td>2 400</td>
<td>TDF p.o. ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTS001 South Africa Women</td>
<td>2 200</td>
<td>TFV vaginal gel including</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This group of authors is mentioned as “the group” in the article.

Corresponding author: Alain Lafeuillade, MD, Email: alain.lafeuillade@ch-toulon.fr
Vation of more than 500 cases of syphilis in each arm, corresponding to a 40% incidence.

Finally, Truvada® as PrEP is not even cost effective:
- Ipxer showed that it was needed to treat 44 subjects during one year to prevent 1 HIV-infection;
- The cost of 44 years of TDF/FTC would not be so different from 44 years of TDF/FTC/EFV in a 30-year old MSM who will become infected despite PrEP;
- Truvada® PrEP means take 1 pill a day to prevent the use of 1 pill a day.

And, finally, no one knows who will pay for PrEp.

In an interactive session where participants voted against or for the concept of Truvada® PrEP, Mark Nelson (London, UK) further nailed it down by calculating that Truvada® PrEP will increase by 75 billion dollars health care related costs for a tiny effect. He finished his presentation by saying: “To do a double-blind test, give the new drug to rich patients and a placebo to the poor. No sense getting their hopes up. They could not afford it even if it worked”.

When the audience vote was cast, 72 percent expressed their negative position for Truvada® PrEP.

Consequently, the group stated that:
- We currently have to treat all HIV-infected patients, not HIV negative, with ART;
- There is a significant risk of long-term toxicity and resistance selection with this approach, which will impact the future efficacy of Truvada® in HIV-infected patients;
- If PrEP should be developed, it should never use drugs prescribed in HIV-infected patients;
- The lobbying for Truvada® use as PrEP corresponds to non-scientific positions and financial interests.

New ARV Drugs and ARV Strategies
Roy Trip Gulick [4] presented the pipeline of new ARVs. He argued that despite the availability of more than 25 ARV drugs we still need more molecules to improve convenience and increase tolerability of our regimens.

He then focused on some of these new ARVs.

GS-7340 has been shown capable in a 14-day monotherapy trial to decrease plasma HIV viremia of more than 1 log. The lower circulating level of TDF produced by this prodrug is expected to decrease renal toxicity of TDF. However, there is currently no clinical proof of this assumption and the 40 fold cellular increase in intracellular TDF concentrations at the 40 mg dose could also lead to even more renal toxicity.

Elvitegravir in combination with TDF/FTC and cobicistat has been shown to be equivalent to TDF/FTC/EFV at 48 weeks.

Cobicistat is believed to be the next pharmacological booster replacing ritonavir. However, it induces increases in creatinine levels after initiation that could be difficult to manage for a physician. Even if it does not correspond to perturbations in creatine clearance, it will be difficult in routine practice to interpret it with just a plasma creatine measurement.

Dolutegravir is a strand transfer integrase inhibitor with a half-life of 15 hours allowing OD administration without boosting. It shows an interesting resistance profile compared toRaltegravir (RAL) or Elvitegravir (ELV). In phase Ila trials it showed up to 2.5 log drop in viremia after 11 days. In the SPRING-1 trial no resistance mutation was observed through 96 weeks when administered with ABC/3TC. In the SPRING-2 trial, it was shown to be non-inferior to RAL.

Véronique Andrieu (Marseille, France) presented the current evidence supporting the use of ARV generics to treat HIV infection [4]. In the European Union several ARVs have already lost their patent (ZDV, 3TC, EFV, NVP, ritonavir). If there are not many ARV generics in the EU, there are many in Asia and Africa. Even more, pharmaceutical companies in these regions shut down the prices, market new combos and begin to invest in the research and development of new molecules.

Mark Nelson (London, UK) showed data on new NRTI-sparing strategies. An increasing number of seniors are now living with HIV, meaning that ARV pharmacological interaction with treatments of other diseases they have is a major issue. Analyzing trials already performed, Nelson showed that the best NRTI sparing regimens were combinations of integrase inhibitors with a boosted PI. However, studies are still in progress to generate long-term data.

Consequently, the group stated that:
- The new produrg of TDF carries question marks and will be challenged by the firm strategy of widespread use of TDF in PrEP;
- Cobicistat does not add advantages to ritonavir;
- The aging population implies the use of combos with the lowest drug interactions;
- EFV is an outdated drug due to its side effects and interactions;
- RAL is currently a valuable option but it is given BID, needs strict compliance due to its low genetic barrier to resistance and has an unacceptable high price;
- Dolutegravir will be the best third or second agent in a combination if the firm practices prices lower than RAL;
- A single tablet of ABC/3TC/Dolutegravir could be the best first line option keeping open several salvage possibilities. Furthermore, unlike TDF, ABC has a good CNS penetration;
- Dual combos of an integrase inhibitor plus a boosted PI will certainly move in the front row when more long-term data will be available;
- Generics are equivalent to original brands. The widespread use of Indian generics would help treating every HIV-infected patient worldwide, due to the slashing down of prices they practice compared to Western World firms most worried by their shareholders than the HIV pandemic.
Advertisement
Acute HIV Infection
Cécile Goujard (Paris, France) presented data [6] from the French Primo cohort (ANRS CO6) that began to include subjects in 1996 and still includes around 100 patients per year. It currently contains 1,450 patients (December 2011). The median time from PHI to inclusion is 31 days. Concerning HIV serology at inclusion, 95% had an incomplete Western blot with 26% being seroconverters (acute infection, < 2 bands). The population characteristic is: 84% men (83% MSM), median age, 35 years (range, 15-79). At the time of inclusion, 88% were symptomatic. Overall, 52% initiated ART at acute infection. Over time, an increased frequency in non-B subtype among MSM and Caucasian women was observed. The CD4 count was < 350/mm³ in 17% of patients at inclusion. In untreated patients, a rapid progression to CD4 < 350/mm³ was observed with a median time to progression of 44 months. CD4 count and HIV DNA were independent predictors of progression. Long term continuous early ART led to high immune restoration and a high virological response rate. The results of CD4 counts and HIV RNA in treated patients at 5 years are shown in Table 3.

There was a rapid and parallel decrease in HIV RNA levels, cellular activation and HIV-specific CD8+ responses in patients that initiated ART. A low impact of transient ART on viral set-point was observed. However, compared to untreated patients (ANRS SEROCO Cohort), acutely infected patients with < 350 CD4/mm³ receiving a transient ART course, remained 49 months longer off ART. Viral control is a rare phenomenon previously reported either spontaneously or after ART interruption in treated patients (the first “Berliner” patient). This status is currently analyzed in an ANRS study and named the “VISCONTI” patients (Viro Immunological Sustained Control of HIV after Treatment Interruption) led by Christine Rouzioux in Paris (7).

Jean-Pierre Routy (Montreal, Canada) presented additional data (8) in favour of an early ART intervention. There is a clear effect of the CD4 nadir on subsequent immune recovery on ART. Initiating ART at acute infection also reduces the size of the HIV reservoir. For patients coming to care with already a low CD4 count, recombinant IL-7 has been shown capable of increasing gut-associated lymphoid tissue CD4 repopulation. Doctor Routy concluded by saying “do not condemn a patient to a life-long treatment, start early to stop early”.

Consequently, the group stated that:
• There is a virological and immunological benefit of treating HIV at acute infection;
• Therapy at this disease stage must be part of clinical trials each time it is possible;
• There is a need for a huge information and alert of GPs about acute HIV infection in order to diagnose more cases at this stage.

The Search for an HIV Cure
The second day of the meeting was devoted to HIV reservoirs and the search for a cure. Carine Van Lint (Gosselies, Belgium) updated the participants’ knowledge on the mechanisms involved in keeping HIV latent [9].

Mario Stevenson (Miami, USA) demonstrated that the measurement of episomal DNA demonstrates that a cryptic reservoir of HIV replication persists during ART [10]. In most cases HIV continues to replicate in lymphoid tissues due to insufficient drug penetration or metabolism. Designing future therapeutic strategies, he used the faucet/drain analogy: it will be necessary to control the faucet with better ARVs and act at the drain by acting on efflux pumps.

Tae-Wook Chun (Bethesda, USA) stressed the fact that ongoing viral propagation from cell to cell is a major mechanism of viral persistence during ART [11]. Expanding the discussion on therapeutic strategies aimed at reducing the reservoir, he first developed arguments for anti-latency agents like Histone Deacetylase (HDACi). However, an immune complementary approach to kill these cells where HIV was reactivated will probably be needed. Clinical trials addressing HIV cure will need to include ART discontinuation as an end point.

Romas Geleziunas (Foster City) presented the large Gilead pipeline [12] of potent molecules aimed at getting an HIV cure. He also mentioned Romidepsin, an HDACi, which is now off label and has low toxicity. Romidepsin is - 1000 fold more potent than SAHA at inducing latent HIV and at much lower doses than used in cancer, which is its current indication. Gilead also develops GS-9620, a potent TLR7 Agonist, which has the potential of enhancing immunity to eliminate HIV-infected cells.

Alain Lefeuillade (Toulon, France) presented a review of anti-latency [13] agents on behalf of Santiago Moreno (Madrid, Spain). The two trials using SAHA have shown an increase in unspliced HIV RNA in circulating CD4 T cells but no blip in viremia. Bryolat is a clinical trial ready to start using Bryostatin, a PKC agonist/inhibitor. Moreno’s group also recently showed that Maraviroc acted both like an ARV agent and an anti-latency agent.

Gero Hüttner (Heidelberg, Germany) together with the “Berlin patient” (San Francisco, USA) gave a coordinated lecture on gene therapy strategies to cure HIV [14].

Consequently, the group stated that:
• ART is not hard enough and ongoing viral replication/propagation persists, leading to develop better drugs;
• There is compelling evidence that a functional HIV cure can be achieved in a couple of years in a substantial proportion of patients;
• A closer collaboration between pharmaceutical companies and governmental research agencies is needed;
• Several compounds have to move quickly into clinical trials.

<table>
<thead>
<tr>
<th>ART</th>
<th>CD4 after 5 years of cART*</th>
<th>Undetectable HIV RNA at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>At acute</td>
<td>Continuous</td>
<td>766 (608-970)</td>
</tr>
<tr>
<td>At acute</td>
<td>Discontinued</td>
<td>510 (406-712)</td>
</tr>
<tr>
<td>Differed</td>
<td>Continuous</td>
<td>683 (402-773)</td>
</tr>
</tbody>
</table>

* Median (IQR)

Table 3: CD4 and plasma viremia levels at 5 years of ART in the Primo ANRS cohort.
Managing HIV/HCV coinfection
Several sessions addressed this issue [15-18]. In particular, talks given by Jean-Michel Pawlotsky (Paris, France), Vincente Soriano (Madrid, Spain) and Jürgen Rockstroh (Bonn, Germany).

HCV therapy is indeed a fast moving field with the recent development of directly acting antiviral agents against HCV (DAA). For a few months, the inclusion of NS3/4A Protease Inhibitors in the regimen is a new option for HCV-infected patients. Telaprevir is administered in these new regimes for a period of 12 weeks (total duration of the whole therapy with interferon and ribavirin: 48 to 72 weeks according to early virologic response at weeks 4 and 12) in genotype 1 HCV. Main side effects are rashes, in more than half of cases, leading to drug discontinuation in 2.6 percent of cases. There are 11 cases of DRESS syndrome and 2 of Steven Johnson syndrome already reported in trials conducted in mono-infected patients. Cytopenia, including anemia, are also found with Telaprevir. Serious adverse events occur in 48 percent of patients. Cytopenia, including anemia, are also found with Telaprevir. Serious adverse events occur in 48 percent of patients with cirrhosis. Boceprevir is given after one month leading phase with Interferon and ribavirin, during 24 to 44 weeks according to patients' status (naive, non-responder, F4). The main side effects are cytopenia.

Other HCV protease inhibitors are in the pipeline (Table 4). There is also a large number of nucleoside/nucleotide analogue inhibitors (Table 5), non-nucleoside inhibitors (Table 6), NS5A inhibitors (Table 7) and cyclophilins inhibitors (Table 8) that act not on HCV itself but on cellular genes. Nucleoside/nucleotide analogue inhibitors and cyclophilins inhibitors are the only classes with a high genetic barrier to resistance.

In HIV/HCV coinfected patients, there are several particularities like: a more elevated HCV load (more virological failures?), a risk of faster selection of drug resistance, drug-drug interactions, overlapping toxicities (rash & anemia), drug compliance issues with polymedication. These interactions are summarized in Table 9.

Consequently, the group stated that:

• The new standard-of-care treatment for HCV genotype 1 infection is the triple combination of pegIFNa, ribavirin and either telaprevir or boceprevir
• This new triple therapy yields higher cure rates, but with more side-effects and drug-drug interactions
• Boceprevir is far more manageable in terms of toxicity than Telaprevir in co-infected patients;
• IL28B testing remains important to predict DAA response. All hepatitis C patients must be tested;
• HCV subtype 1a responds less than 1b;
• DAA resistance might be important at baseline for some drugs (but no matter after failure);
• Shorter treatment durations (3 to 6 months) and more convenient regimens (QD) will replace current triple combinations based on first-generation DAA within 2 years;
• Combinations using IFN-free oral drugs are coming and is the way to go.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Median/mean log HCV RNA reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (Janssen)</td>
<td>Approved</td>
<td>750 mg q8h</td>
<td>14 days</td>
<td>-4.4</td>
</tr>
<tr>
<td>Boceprevir (Merck)</td>
<td>Approved</td>
<td>400 mg tid</td>
<td>7 days</td>
<td>-1.6</td>
</tr>
<tr>
<td>Danoprevir (Roche)</td>
<td>III</td>
<td>200 mg q6h</td>
<td>7 days</td>
<td>-3.8</td>
</tr>
<tr>
<td>Vaniprevir (Merck)</td>
<td>II</td>
<td>700 mg bid</td>
<td>8 days</td>
<td>-4.7</td>
</tr>
<tr>
<td>BI201335 (BI)</td>
<td>II</td>
<td>240 mg qd</td>
<td>14 days</td>
<td>-4.0</td>
</tr>
<tr>
<td>Nlaraprevir (Merck)</td>
<td>II</td>
<td>400 mg bid</td>
<td>7 days</td>
<td>-3.2</td>
</tr>
<tr>
<td>Asunaprevir (BMS)</td>
<td>II</td>
<td>300 mg bid</td>
<td>3 days</td>
<td>-3.3</td>
</tr>
<tr>
<td>ABT-450/350 (Abbott)</td>
<td>II</td>
<td>200 mg qd</td>
<td>3 days</td>
<td>-4.1</td>
</tr>
<tr>
<td>GS-9451 (Gilead)</td>
<td>I</td>
<td>400 mg qd</td>
<td>3 days</td>
<td>-3.5</td>
</tr>
<tr>
<td>MK-5772 (Merck)</td>
<td>I</td>
<td>400 mg qd</td>
<td>7 days</td>
<td>-5.4</td>
</tr>
</tbody>
</table>

Table 4: HCV Protease Inhibitors in development.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Median/mean log HCV RNA reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mericitabine (Roche)</td>
<td>II</td>
<td>1500 mg bid</td>
<td>14 days</td>
<td>-2.7</td>
</tr>
<tr>
<td>GS-7977 (Gilead)</td>
<td>II</td>
<td>400 mg qd</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
<tr>
<td>INX-189 (Inhibitex)</td>
<td>II</td>
<td>100 mg qd</td>
<td>7 days</td>
<td>-2.5</td>
</tr>
<tr>
<td>IDX184 (Idenix)</td>
<td>II</td>
<td>100 mg qd</td>
<td>3 days</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

Table 5: nucleoside/nucleotide HCV inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Median/mean log HCV RNA reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegobuvir (Gilead)</td>
<td>II</td>
<td>40 mg bid</td>
<td>8 days</td>
<td>-1.4</td>
</tr>
<tr>
<td>Filibuvir (Pfizer)</td>
<td>II</td>
<td>300 mg bid</td>
<td>8 days</td>
<td>-2.1</td>
</tr>
<tr>
<td>Seterobuvir (Roche)</td>
<td>II</td>
<td>800 mg bid</td>
<td>3 days</td>
<td>-2.9</td>
</tr>
<tr>
<td>BI207127 (BI)</td>
<td>II</td>
<td>800 mg q8h</td>
<td>3 days</td>
<td>-3.1</td>
</tr>
<tr>
<td>ABT-333 (Abbott)</td>
<td>II</td>
<td>600 mg bid</td>
<td>2 days</td>
<td>-1.5</td>
</tr>
<tr>
<td>ABT-072 (Abbott)</td>
<td>II</td>
<td>600 mg qd</td>
<td>3 days</td>
<td>-1.6</td>
</tr>
<tr>
<td>VX-222 (Vertex)</td>
<td>II</td>
<td>750 mg bid</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
</tbody>
</table>

Table 6: non-nucleoside HCV inhibitors.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Median/mean log HCV RNA reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir (BMS)</td>
<td>II</td>
<td>10 mg qd</td>
<td>1 day</td>
<td>-3.2</td>
</tr>
<tr>
<td>PPI-461 (Presidio)</td>
<td>Ib</td>
<td>100 mg qd</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
<tr>
<td>GS-5885 (Gilead)</td>
<td>Ib</td>
<td>30 mg qd</td>
<td>3 days</td>
<td>-3.3</td>
</tr>
</tbody>
</table>

**Table 7:** NSSA HIV inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Median/mean log HCV RNA reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alisporivir (DEBIO-025)</td>
<td>II</td>
<td>1200 mg bid</td>
<td>14 days</td>
<td>-3.6</td>
</tr>
<tr>
<td>SCY-465</td>
<td>Ib</td>
<td>900 mg qd</td>
<td>15 days</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

**Table 8:** Cyclophilin inhibitors.

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>=</td>
<td>↑30%*</td>
</tr>
<tr>
<td>EFV</td>
<td>↓25% (tid)</td>
<td>↓10% (tid)</td>
</tr>
<tr>
<td></td>
<td>↓48% (bid)</td>
<td>↑10% (bid)</td>
</tr>
<tr>
<td></td>
<td>↓40%</td>
<td>↑20%*</td>
</tr>
<tr>
<td>ATV/r</td>
<td>↓15%</td>
<td>↑85%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>↓32%</td>
<td>↓42%</td>
</tr>
<tr>
<td></td>
<td>↓32%*</td>
<td>↓59%</td>
</tr>
<tr>
<td>FPV/r</td>
<td>↓30%</td>
<td>↓56%</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>LPV/r</td>
<td>↓52%</td>
<td>↑14%</td>
</tr>
<tr>
<td></td>
<td>↓45%*</td>
<td>↓43%</td>
</tr>
<tr>
<td>RTV (low dose)</td>
<td>↓32-75%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>↓19%*</td>
<td>--</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td></td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Methadone</td>
<td>=</td>
<td>↓31-40%</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Midazolam</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>↑5.3-fold*</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>--</td>
<td>↓42%</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>=</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Contraceptives (estrog./progest.)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>↑21%*</td>
<td>--</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.3-fold*</td>
</tr>
</tbody>
</table>

**Table 9:** pharmacological interactions with boceprevir or telaprevir.
Neurocognitive Impairment in the ART Era
A “hot debate” was organized to define whether neurocognitive impairment is a past or still a current problem in HIV care. Hans-Jürgen Stellbrink (Hamburg, Germany) argued that several confounding factors were responsible of the fact that some people think CNS disease is still an issue. He concluded that, first HIV encephalopathy may still occur in late presernters or non-adoherent patients, but essentially is a problem of the past. Then, lesser degrees of neurocognitive impairment may be a consequence of events preceding ART. With earlier treatment, true HIV-related neurocognitive impairment will most likely be a problem of the past. Lastly, modern ART regimens generally have sufficient neuropenetration, so the consideration of neuropenetration is essentially a problem of the past.

Magnus Gisslén (Gothenburg, Sweden) demonstrated that mild neurocognitive impairment concerns 39 percent of patients in the ART era. New onset cognitive impairment or neurological problems ever occur during effective ART. High CSF viral load with HIV encephalitis has been described in patients despite undetectable plasma viremia. The speaker’s advice was to pay attention to new-onset CNS symptoms also in patients on effective ART, especially if there is sub-optimal adherence and drugs with low CNS-penetrating ability. We also have to keep awareness with new, less studied drug combinations that can make the CNS an even more important sanctuary site for HIV.

When the audience vote was cast, 81 percent expressed their belief that neuro-cognitive impairment is still a current problem.

Consequently, the group stated that:
- Neuropsychological screening is not necessary in asymptomatic patients, but asking for symptoms and complaints is a simple way to detect patients that need further tests;
- Including ARVs with good CNS penetration is important since first line therapy.

Conclusion
The 2012 ISHEID allowed both to update knowledge and share experience. This summary shows that this meeting has the potential to update HIV care recommendations. The next ISHEID edition is scheduled in Marseilles, May 2014.

Conflict of interests: Alain Lafeuillade: research grants from Abbott, Merck, Roche. Advisory boards of Boehringer Ingelheim and ViV Healthcare.
Emilie Hoppe-Rapp: none.
Assi Assi: none
Gilles Hittinger: none
Cécile Poggi: none

References:

The 2012 ISHEID allowed both to update knowledge and share experience. This summary shows that this meeting has the potential to update HIV care recommendations.
HIV and Virology News is also available on the web. Here you can read the latest issue of the new Newsletter for everyone with an interest in HIV and Hepatitis. Previous issues will also be archived and accessible here.

The website offers direct access to the latest articles published in the Newsletter, and a Calendar detailing upcoming events of interest.

If you’re not on the distribution list already – this is where you can sign up in order to receive the magazine, free of charge, and you can also register for an electronic Newsletter.

The content on the website can also be viewed in a Smartphone. Directly after summer 2011, a Web App will be available for free download. This enables the user to access the content directly.

Go to www.hivvirology.com in order to find out more.
How will the new protease inhibitors be used in the treatment of chronic hepatitis C?

A new standard-of-care treatment has been approved in 2011 in Europe and the United States for treatment-naïve and treatment-experienced patients infected with hepatitis C virus (HCV) genotype 1, the most frequent HCV genotype worldwide. This new treatment is based on the combination of pegylated interferon (IFN)-α, ribavirin, and a protease inhibitor, either telaprevir or boceprevir.

How must telaprevir and boceprevir be prescribed?
Telaprevir and boceprevir can be administered with either pegylated IFN-α2a, 180 mg/week, or pegylated IFN-α2b, 1.5 mg/kg/week, and weight-based dosed ribavirin. Telaprevir must be administered at the dose of 750 mg every 7–9 hours with fatty food (1-3), boceprevir at the dose of 800 mg every 7–9 hours with food (4, 5).

Telaprevir administration starts at day 0 of therapy. HCV RNA level must be measured at baseline, week 4, 12 and 24. In treatment-naïve patients and re-treaters a prior course of pegylated IFN-α and ribavirin, telaprevir must be administered in combination with pegylated IFN-α and ribavirin for 12 weeks. If the patient achieves an extended virological response (eRVR), defined as an undetectable HCV RNA at weeks 4 and 12, pegylated IFN-α and ribavirin should be continued without telaprevir until week 24. In patients without an eRVR, pegylated IFN-α and ribavirin must be continued until week 48 (2). If HCV RNA is >1000 IU/mL at weeks 4 or 12 or detectable at week 24, treatment should be stopped, as the patient has no chance to achieve a sustained virological response (SVR) (1, 3). This was recently confirmed in a post-hoc analysis of Phase III clinical trials. In this study, all patients with an HCV RNA level >1000 IU/mL at week 4 or 12 had initially responded but subsequently broken through, and none of them achieved an SVR (6).

In contrast to telaprevir, boceprevir must be administered after a lead-in phase of 4 weeks with pegylated IFN-α and ribavirin alone, as a result of the design of Phase III clinical trials (4, 5). HCV RNA level must be measured at baseline, week 8 (i.e. week 4 of boceprevir administration), week 12 and week 24. In the European label, three groups of patients must be considered. Non-cirrhotic treatment-naïve patients must start boceprevir after the 4-week lead-in phase and continue with the triple combination until week 28 if their HCV RNA is undetectable at week 8; if HCV RNA is still detectable at week 8, the triple combination must be continued until week 36, followed by pegylated IFN-α and ribavirin without boceprevir until week 48. Non-cirrhotic treatment-experienced patients (excluding null responders) must receive the triple combination until week 36 and continue with pegylated IFN-α and ribavirin alone until week 48. Null responders to a first course of pegylated IFN-α and ribavirin and all cirrhotic patients must be treated with the triple combination of pegylated IFN-α, ribavirin and boceprevir until week 48. If HCV RNA is ≥100 IU/mL at week 12 or detectable at week 24, treatment should be stopped because the patients have no chance to achieve an SVR (4, 5).

What is the utility of the lead-in phase?
The lead-in phase with pegylated IFN-α and ribavirin for 4 weeks does not provide any benefit in terms of SVR, as shown by the REALIZE trial in treatment-experienced patients receiving telaprevir (3). Nevertheless, the virological response to pegylated IFN-α and ribavirin during the 4-week lead-in phase is a strong predictor of the final outcome of triple combination therapy in both treatment-naive and -experienced patients receiving telaprevir or boceprevir. Indeed, the SVR rates are of the order of 80% in patients who achieve a more than 1-log HCV RNA drop during the lead-in phase, versus approximately 35% in those with an HCV RNA decrease <1 log (3-5). Thus, a lead-in phase of 4 weeks with pegylated IFN-α and ribavirin can be used with either boceprevir or (off-label) telaprevir, especially in treatment-experienced patients, to assess the tolerance of therapy and predict the likelihood of a subsequent SVR if the protease inhibitor is added in order to inform the treatment decision.

How must adverse events be managed?
With telaprevir, the most frequent adverse events are cutaneous, including pruritus, rectal burning and/or rash in more than half of cases (7). Anemia is also more frequent than in patients who do not receive telaprevir (1-3). Rash must be evaluated by an experienced dermatologist, who will prescribe topical corticosteroids when necessary, or will decide to stop telaprevir or all drugs in presence of a severe form. Indeed, out of approximately 3,500 patients treated with telaprevir in clinical trials worldwide, 11 drug rash reactions with eosinophilia and systemic symptoms (DRESS syndrome) and 3 Stevens-Johnson syndromes have been reported (7). In a recent report of French real-life patients with cirrhosis who failed on a first course of pegylated IFN-α and ribavirin and were retreated with a triple combination including telaprevir, serious adverse events were observed in approximately 50% of cases (8).
Figure 1. Treatment indication for the combination of pegylated IFN-α, ribavirin and telaprevir in treatment-naïve and treatment-experienced patients. TVR: telaprevir; PegIFN: pegylated IFN-α; RBV: ribavirin, eRVR: extended rapid virological response.

Figure 2. Treatment indication for the combination of pegylated IFN-α, ribavirin and boceprevir in treatment-naïve and treatment-experienced patients. BOC: boceprevir; PegIFN: pegylated IFN-α; RBV: ribavirin.
The death rate was 2%, essentially due to sepsis or hepatic decompensation. Anemia was frequent and often severe. Blood transfusions were required in 15% of patients, due to the poor response to erythropoietin in cirrhotics (8).

With boceprevir, the most frequent adverse events are anemia and dysgeusia (4, 5, 8). A recent large-scale randomized trial has shown no difference in SVR when ribavirin dose reduction or administration of erythropoietin was used to control anemia in patients receiving a triple combination containing boceprevir (9). In French real-life patients with cirrhosis who failed on a first course of pegylated IFN-α, ribavirin and boceprevir, serious adverse events were observed in nearly 40% of cases (8). The death rate was 1.3%, essentially due to sepsis. Severe anemia was frequent and required blood transfusions in 11% of patients (8).

What are the causes and consequences of treatment failures?

Failure to achieve an SVR with the triple combination of pegylated IFN-α, ribavirin and a protease inhibitor is due to an inadequate response to IFN-α, which results in the uncontrolled outgrowth of resistant HCV variants selected by the protease inhibitor (10). Thus, HCV resistance to protease inhibitors is not the cause but the consequence of treatment failure when these drugs are used in combination with pegylated IFN-α and ribavirin. At the time of treatment failure (viral breakthrough or relapse), 50% to 70% of patients harbor a dominant protease inhibitor-resistant HCV population (11). In the remaining patients, wild-type, sensitive viruses are still dominant, but the protease inhibitor-resistant population has also considerably expanded (12). After the protease inhibitor is withdrawn, the resistant viral population progressively returns to its pretreatment level, while the wild-type virus becomes dominant again within 1 to 2 years (11).

HCV resistance testing should not be performed before therapy because all patients harbor pre-existing viruses that are resistant to protease inhibitors, even if these variants are not detected by the poorly sensitive available methods. In case of viral breakthrough or relapse, HCV resistance testing is not useful, because its result has no impact on subsequent clinical decisions.

What alternative treatment options will be available in the next few years?

There are currently four options for future HCV therapies: (i) a triple combination of pegylated IFN-α, ribavirin and a direct-acting antiviral drug with a low barrier to resistance; (ii) a triple combination of pegylated IFN-α, ribavirin and a direct-acting antiviral or a host-targeted agent with a high barrier to resistance; (iii) a quadruple combination of pegylated IFN-α, ribavirin and two direct-acting antiviral and/or host-targeted drugs; (iv) an all-oral, IFN-free drug regimen. The efficiency of IFN-containing regimens depends on the individual patient’s responsiveness to IFN, itself under the control of a number of parameters among which the genetic background appears to be key. However, the effect of IFN responsiveness appears to be attenuated when a drug with a high barrier to resistance is used or with quadruple combinations. The results of IFN-free drug regimens depend on three parameters: the antiviral potency of the drug combination, its barrier to resistance, and the duration of therapy, which can be shortened when ribavirin is used. Recent findings suggest that the future of HCV therapy will be IFN-free. The ideal all-oral drug cocktail and its treatment: patient management in different groups of patients.

Conflict of interest disclosure:
The author has received research grants from Gilead and Roche. He has served as an advisor for Abbott, Achillion, Anadys, Biotica, Boehringer-Ingelheim, Bristol-Myers Squibb, DebioPharm, Gen-Probe, Gilead, Glaxo-SmithKline, Idenix, Inhibex, Janssen-Cilag, Madaus-Rottapharm, Sanofi-Aventis, Schering-Plough/Merck, Novartis, Pfizer, Roche, Vertex and Virco.

References:

HIV is a neurotropic virus and it is possible that in an aging HIV-infected population the Central Nervous System (CNS) damage caused by HIV might not be completely avoided by the use of HAART. In keeping with this concern, current EACS guidelines [1] have a specific section dealing with how to diagnose and manage HAND. The prevailing theory is that optimal neuropenetration of antiretrovirals could be an important factor to prevent the deleterious effects caused by HIV in the brain. One popular way of estimating the neuropenetration of antiretrovirals is the CNS Penetration Effectiveness (CPE) score [2].

Boosted protease inhibitor (bPI) monotherapy with Lopinavir/ritonavir or Darunavir/ritonavir for maintenance of viral suppression is a therapeutic strategy that has received considerable attention during the past decade [3]. This strategy has the advantage of treating HIV infection with just one antiretroviral, avoiding the cost and the toxicity associated with other drugs such as nucleosides. A recent metaanalysis [4] has shown that bPI monotherapy is slightly less efficacious than triple-drug HAART but is not associated with an increased risk of losing therapeutic options. bPI monotherapy is recommended as a possible therapeutic option in the EACS guidelines but not in the DHHS or IAS guidelines [3].

The CPE score of bPI monotherapy is considerably lower than that of triple-drug HAART (typically is 3 versus 7–9). Given this large difference in neuropenetration it is logical that one of the main concerns about bPI monotherapy is its inability to adequately protect against CNS disease caused by HIV. The low CPE score of bPI monotherapy would translate into a higher risk of CSF viral escape (HIV-1 RNA above levels of detection of standard assays in CSF despite having undetectable levels in blood) and consequently a higher risk of HAND.

Is bPI monotherapy a risk factor for CSF viral escape?
We still don’t know. Viral escape has been well described in patients receiving triple-drug HAART. We do not have a large randomized clinical trial with a systematic evaluation of CSF viral escape. The accumulated evidence is so far contradictory with a number of studies supporting that there is no increased risk of CSF viral escape in patients receiving bPI monotherapy while others report an increased risk [5]. The most recent study was presented at the 19th CROI. In a non-randomized study, investigators from Barcelona [6] reported CSF viral escape in 3 of 17 patients receiving Lopinavir/ritonavir monotherapy and in 1 of 17 receiving Lopinavir/ritonavir plus two nucleosides. In this study an ultrasensitive HIV
PCR assay with a limit of detection of 1 HIV RNA copy/mL was used.

Is bPI monotherapy associated with increased risk of CNS adverse events in clinical trials?

Probably not. The MONET, MONOI and OK04 [5] clinical trials have not shown a significant increase in the incidence of CNS adverse events in patients receiving Darunavir/ritonavir or Lopinavir/ritonavir monotherapy for maintenance of virological suppression. It should be noted that CNS adverse events are a very insensitive way of evaluating CNS function and the sample size on these trials was relatively small. In MONOI there were two patients in the Darunavir/ritonavir monotherapy group who suffered mild neurological transient symptoms in the setting of CSF viral escape.

Is bPI monotherapy a protective factor for HAND?

We still don’t know. Current standard for diagnosis of HAND relies on detailed neuropsychological testing. This kind of testing has not been performed in the larger trials of bPI monotherapy. In the MOST clinical trial [7], which evaluated Lopinavir/ritonavir monotherapy, changes in neuropsychiatric tests results did not differ between patients who had detectable HIV-RNA in CSF vs. those with suppressed RNA in CSF. In the MONET clinical trial [8] there were no significant differences between the treatment arms (Darunavir/ritonavir monotherapy or Darunavir/ritonavir and two nucleosides) for any of the Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) scores on cognitive function during 96 weeks of follow up. Finally in the small study by Santos and colleagues [6] presented at last CROI the rate of neuropsychological impairment (in this case evaluated by complete neuropsychological testing) was 59% in patients receiving Lopinavir/ritonavir and two nucleosides and 41% in patients receiving for at least two years Lopinavir/ritonavir monotherapy.

Is bPI monotherapy a protective factor for HAND?

We still don’t know. This question appears provocative. However there is one study suggesting that interruption of HAART is associated with an improvement in some psychophysiological tests [9]. In addition another study has shown that drugs with higher neuropenetrance might be associated with worse neuropsychological function [10]. Finally, in vitro testing has suggested that penetration of antiretrovirals into the brain at concentrations sufficient to suppress viral synthesis will carry some risk of neuronal damage [11]. Paradoxically in some scenarios bPI monotherapy could decrease the risk of neurocognitive dysfunction due to its lower associated neurotoxicity.

Are there more studies evaluating neurocognitive function in patients receiving bPI monotherapy?

Yes. The PIVOT trial [12] has randomized 587 patients to triple drug HAART or bPI monotherapy. Detailed neuropsychological testing and CSF exams are part of the protocol. The PROTEA clinical trial (ClinicalTrials.gov Identifier: NCT01448707) is currently enrolling patients. In PROTEA patients with suppressed HIV replication are randomized to Darunavir/ritonavir monotherapy or Darunavir/ritonavir plus two nucleosides. PROTEA secondary endpoints include to evaluate the correlation of plasma HIV-1 RNA, CSF HIV-1 RNA, and neurocognitive function.

In summary we still don’t know if bPI monotherapy is a risk factor for HAND. Current evidence is quite limited. However in the near future we are going to see results that would probably offer more definitive answers. Since bPI monotherapy CPE score is so radically different from triple drug HAART the results of these ongoing studies would tell us a lot about the merits of the current paradigm of better neuropenetrance = less viral CSF escape = better neurocognitive function.

Conflict of Interests

Dr Arribas has received advisory fees, speaker fees and grant support from Tibotec, Janssen, Abbott, BMS, Gilead, MSD. He has received advisory fees and speaker fees from Viiv.

References:

6. Santos JR, Muñoz-Moreno1, Moltó J et al. Long-Term Monotherapy With Lopinavir/ritonavir (>2 years) is not Associated with Greater HIV-Associated Neurocognitive Impairment. CROI 2012. Abstract #E-117

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Cerebrospinal fluid (CSF) laboratory findings in HIV-infected patients with various neurological or neurocognitive symptoms raise many questions. Could the CSF laboratory results be ascribed to some pathological event such as opportunistic infections, or signs of HIV dementia, or are they in line with what is normally found in asymptomatic HIV-infected subjects? To be able to answer such questions it is necessary to know the kinetics of CSF findings during HIV infection with or without treatment.

HIV RNA

HIV RNA is almost always detectable in the CSF in untreated HIV, irrespective of disease stage. The levels are often 0.5–1 log lower in CSF than in plasma, (figure 4), but 10–20% of asymptomatic patients have higher levels in CSF than in blood, (figure 5).

Like in blood, viral load decrease fast (within months) to undetectable levels also in the CSF. However, slightly increased CSF HIV RNA levels (50–500 copies/mL) could be found in approximately 10% of samples from asymptomatic patients on treatment with plasma viral load <50 copies/mL [3]. Those CSF viral breakthroughs are associated with increased CNS immunoactivation, but the significance is unknown, and they might represent CSF viral blips, similar to plasma viral blips. In rare cases, CSF viral escape can be associated with development of neurological or cognitive symptoms in patients on antiretroviral treatment and suppressed plasma viral load [4, 5]. Measurement of CSF HIV RNA is strongly recommended as part of the evaluation of patients presenting with new neurological symptoms and signs while on treatment.

Neopterin and beta-2 microglobulin

Neopterin is a biochemical product of the guanosine triphosphate pathway that is both cell-restricted and inducible by immune-inflammatory stimuli. It is produced primarily in monocyte/macrophage and related cells and the most important stimuli are interferons, especially Th1-type cytokine interferon-γ (IFN-γ). Beta-2 microglobulin, a portion of the major histocompatibility complex class I antigen is another marker of immune stimulation and both markers are increased in the vast majority of untreated HIV-infected patients, also in early asymptomatic stages [9], (figure 6). Despite suppression of plasma and CSF HIV RNA by antiretroviral treatment to below the detection limits of clinical assays, CSF neopterin often remains mildly elevated, indicating persistent low-level intrathecal immune activation.

Patients with HIV-associated dementia exhibit particularly high CSF neopterin concentrations and also often high CSF viral loads, (figure 7). As earlier mentioned, increased CSF/plasma albumin ratio is common in patients with HIV-associated dementia while CSF WBC count usually is low.
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In summary, a mild inflammatory reaction measured as increased number of lymphocytic cells (3–30/µL) and HIV count 0.5–1 log lower than in blood is a common CSF finding in untreated asymptomatic HIV infected patients. This is important to take into account when HIV patients are examined for suspected opportunistic infections or HI-associated dementia, but also for doctors in general care when patients with unknown HIV status have unexpected CSF pathology.

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References:

Figure 1. CSF WBC counts in 198 untreated neuro-asymptomatic HIV-infected subjects with different CD4-cell counts. Median and interquartile range indicated, dotted line represent upper normal limit 3 cells/mL (data on file).

Figure 2. CSF WBC counts in 59 HIV-infected subjects on suppressive ART and no CSF escape. Median and interquartile range indicated, dotted line represent upper normal limit 3 cells/mL.

Figure 3. CSF/plasma albumin ratio and IgG index in 198 untreated neuroasymptomatic HIV-infected patients. Median and interquartile range indicated, dotted line represent upper normal limits (data on file).

Figure 4. Plasma and CSF HIV RNA in 198 untreated neuroasymptomatic HIV-infected subjects (data on file).

Figure 5. Plasma vs CSF HIV RNA in 198 untreated neuroasymptomatic HIV-infected subjects. Higher viral load in CSF in 11% of patients (data on file).

Figure 6. CSF neopterin and beta-2 microglobulin in 198 untreated neuroasymptomatic HIV-infected subjects. Median and interquartile range indicated, dotted line represent upper normal limits (data on file).

Figure 7. CSF and plasma neopterin and HIV-RNA in untreated HIV-infected patients in different disease stages, from [9]. NA = neuroasymptomatic, ADC = AIDS dementia complex, Rx = antiretroviral treatment, OIs = CNS opportunistic infections.
News on HIV and Renal Function

Renal disease and monitoring of renal function remain key concerns for physicians managing people with HIV infection. While end-stage renal disease is rarely a contributor to death in persons with HIV, renal disease and dysfunction are common, prevalent events and a key contributor to or harbinger of other morbidities, notably cardiovascular disease (CVD).

Indeed there are considerable overlap in traditional risk factors for both renal and CVD including smoking, diabetes mellitus, hypertension, dyslipidemia, obesity, ethnicity and HIV factors including low CD4 count and active viral replication. Furthermore, various data indicate that reduced eGFR and markers of renal injury, such as proteinuria (+protein on dipstick testing, or microalbuminuria defined as spot urine albumin to creatinine ratio of >30 mg/g), predict progression to end stage renal disease, cardiovascular disease, AIDS events, and all-cause mortality in persons with HIV. Early intervention with antiretroviral therapy, universal therapy being now recommended in the US DHHS guidelines, may be valuable in the prevention of both CVD and HIV-associated nephropathy (HIVAN), one of the most common causes of renal disease in people with HIV.

However, as we have seen with CVD antiretroviral agents may impact the tools and biomarkers we use for the assessment of risk of disease (e.g. lipids for CVD, estimated glomerular filtration rate for renal disease) and cumulative exposure to some antivirals may contribute to endpoint risk (myocardial infarction, chronic kidney disease, typically defined as an eGFR repeatedly <60 ml/min).

Renal disease and its monitoring have therefore become a ‘hot topic’ in HIV, with many unanswered questions, most notably about long term monitoring and timing of therapy modification.

Estimating glomerular filtration rate
There are 3 main estimation equations, the weight based Cockcroft-Gault (CG)
plus the Modified Diet in Renal Disease (MDRD) and its refinement the Chronic Kidney Disease Epidemiology (CKD-Epi) equations both of which each include age, sex and race but not weight. All 3 equations rely on creatinine in plasma. Removal of creatinine in the kidney is both a passive and active event so agents which effect active secretion of creatinine affect all the equations even if ‘true’ passive glomerular filtration (as measured by inulin or now more commonly iohexol filtration) is normal. Furthermore, factors such as muscle mass, faddish diets and training supplements such as creatine may also influence plasma creatinine. Clinical cohort data from Baltimore, presented at CROI 2012 suggested that the MDRD equation, the Cockcroft-Gault (CG) equation, and the CKD-EPI equation all performed relatively similarly, although CG was heavily biased by the body mass index of the patient studied (Abstract 863, Lucas). Renal function can then be graded by estimated creatinine clearance or eGFR (Table).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>II</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>III</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>IV</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>V</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
</tr>
</tbody>
</table>


New agents that impact eGFR
Several new agents recently approved (rilpivirine) or in advanced development (the pharmacoenhancer cobicistat and integrase inhibitor dolutegravir) impact active creatinine secretion in the kidney resulting in changes in calculated GFR. We have also learnt that ritonavir may also have this effect to some degree. This is a familiar phenomenon with older drugs in other therapeutic areas, such as cimetidine or probenicid. This problem that arises in persons with HIV is that the observed changes alter what our monitoring tools tell us, making the diagnosis of a drug toxicity or other renal disease more challenging. The change in active creatinine secretion is not a toxicity per se, but may mislead our interpretation of what is going on in the kidney. As these agents interfere with various tubular pumps, for dolutegravir the influx transporter Organic cation transporter (OCT)-2, for cobicistat (and probably ritonavir) the efflux pump Multidrug and toxin extrusion (MATE) protein-1, they may also influence the renal excretion of other drugs or, when efflux is inhibited, lead to accumulation of specific agents within renal tubular cells. Thus, they may influence the pharmacokinetics and safety profiles of concomitant medications. So until there is better understanding of these changes, physicians will be faced with dilemmas about whether observed changes in eGFR reflect simply a benign physiologic effect or an emergent toxicity. Education of colleagues about these effects (and the CYP3A interactions with cobicistat, many of which are pending investigation) in other medical specialties will be needed.

Two large phase 3 studies were presented at CROI 2012 using cobicistat as part of a combination tablet with the integrase inhibitor elvitegravir (EVG) plus tenofovir DF (TDF) and emtricitabine (FTC). Both studies excluded subjects with baseline eGFR <70mL/min. Sax et al (Abstract 101) presented the 48 week results of a double-blind, randomised trial comparing single tablet efavirenz (EFV)/FTC/TDF versus EVG/cobicistat/FTC/TDF in ART-naïve subjects. Serum creatinine increased by 0.14 mg/dL in the EVG/cobicistat/FTC/TDF arm compared to no changes in the EFV/FTC/TDF arm over...
In settings where there is an elevated risk of CKD HIV physicians will need to examine and define new tools to monitor for renal disease and educate other medical specialities about interpretation of routine renal assessment tools.

48 weeks. Most of this increase was seen by week 2 of the study. This increase in serum creatinine translated to a creatinine clearance reduction of 14.3 mL/min with the EVG/cobicistat/FTC/TDF compared to 3.0 mL/min with EFV/FTC/TDF by week 48. Drug discontinuations due to renal events were 1.4% vs. 0% in the EVG/cobicistat/FTC/TDF vs. EFV/FTC/TDF arm, respectively.

Similarly, DeJesus et al (Abstract 627) presented a trial assessing EVG/cobicistat/FTC/TDF versus atazanavir(ATV)/ritonavir(r)+FTC/TDF in a 48 week, double-blind, randomised trial in ART-naïve patients. Both groups saw modest increases in serum creatinine. However, the EVG/cobicistat/FTC/TDF treatment resulted in an average additional increase in serum creatinine of 0.04 mg/dL over that observed with FTC/TDF+ATV/r. This additional increase was again evident by week 2 and persisted to week 48. However, only 0.3% participants in each arm had their treatment discontinued due to renal adverse events. Only data on interquartile ranges were reported limiting the potential to understand the range of change that may be observed. Further details of proteinuria, glycosuria, and serum phosphate changes were not reported.

The effect of dolutegravir on renal function was reported by Stellbrink et al (Abstract 102LB) in the ART-naïve, double-blind, phase 2b, dose-finding, randomised trial exploring 3 different doses of dolutegravir relative to efavirenz (with either FTC/TDF or lamivudine (3TC)/abacavir (ABC) as the nucleoside analogue backbone). The highest dose, 50 mg of dolutegravir has been chosen for further development. Similar increases of 0.10–0.15 mg/dL of serum creatinine were seen across all dolutegravir arms and did not differ by whether FTC/TDF or 3TC/ABC used as the partner. Data for the complete range was shown, with all subjects seeing changes across a narrow range of variation. Increases in urine albumin-creatinine ratios were also small and similar across arms and no discontinuations for renal events were reported across this small 96 week study. More details from the phase 3 programme are expected in the coming year.

Drugs and the Kidney
The D:A:D cohort study reported data on declines in renal function by estimated creatinine clearance in patients originally with normal renal function, (defined as an estimated creatinine clearance of >90 mL/min using the Cockcroft-Gault equation) by drug use and traditional risk factors. (Ryom et al Abstract 865). Two definitions for endpoints were used, the development of either a confirmed creatinine clearance of ≤70 mL/min or ≤60 mL/min (‘chronic kidney disease’ or grade 3 changes). Recovery of creatinine clearance rates after drug discontinuation was also reported. Similar to data previously reported in the Eurosidia cohort, cumulative exposure to TDF, atazanavir/r, and lopinavir/r were each associated with declines in creatinine clearance to ≤70 mL/min. However, only lopinavir/r use was associated with creatinine clearance ≤60 mL/min. Data describing drug discontinuations indicated that, relative to subjects with normal renal function, discontinuations of TDF, but not other drugs increased once creatinine clearance fell below ≤70 mL/min and more markedly once below ≤60 mL/min. This increased discontinuation rate may offer an explanation for the lack of association with TDF and creatinine clearance ≤60 mL/min. After drug discontinuation, renal function appeared to improve slowly back towards although typically remained abnormal in the year following discontinuation. Similar data on slow recovery of renal function after TDF discontinuation were reported from a cohort in Spain (Bonjoch abstract 870).

Summary
Challenges regarding the assessment of renal function are emerging with new agents. As these agents will be used in partnership with other drugs, both antiretroviral and for other diseases, that may affect kidney function and in settings where there is an elevated risk of CKD (HIV per se, diabetes mellitus, CVD to name but a few) HIV physicians will need to examine and define new tools to monitor for renal disease and educate other medical specialities about interpretation of routine renal assessment tools in these settings.

Conflict of Interests
Dr Moyle has received research grants from Abbott, Ardea Biosciences, Bionor, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies and Tibotec.

He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, Tibotec and ViV Healthcare.

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HIV primary infection:
There is no reason to delay ART in primary/recent HIV infection anymore

One of the hottest topics in HIV in 2012 is the potential for an HIV cure and HIV disease remission. This has led researchers to focus both on a better understanding of HIV pathogenesis with a particular interest in viral reservoirs and the different ways set up by the virus to remain silent in long-lived memory cells [1].

This should theoretically lead physicians to be more offensive in terms of anti-HIV therapy as soon as viral infection is diagnosed. Indeed, HIV physicians are still timid and hesitant to start ART as soon as HIV is diagnosed and in particular, when HIV is invading the human body in the acute phase of infection.

Optimal management of primary HIV infection (PHI) still remains controversial and the potential benefits and disadvantages of initiating antiretroviral therapy (ART) during acute infection is a subject of debate [2]. Indeed, such debate paralleled the question about when to start antiretroviral therapy in chronically infected patients. Most of the reasons put forward have been the asymptomatic status of HIV disease that could be further controlled, the tolerability and toxicity of cART, the risk of resistance and the cost of ART.

However, things have changed dramatically. We have to first of all keep in mind that HIV is deleterious at any time of HIV infection even in the so-called “early stage” of HIV infection, secondly that ART is much easier for long term intake with compact, simple and well tolerated regimens.

HIV primary infection is a devastating “tsunami” that severely and durably impacts the immune system. From the very early hours of its penetration into the body, HIV provokes a cascade of events that will set up the viral clock for the patient’s entire life [3].

Several factors are predictors of more rapid HIV disease progression including the severity of clinical symptoms, the intensity of viral replication at time of primary infection and the CD4 cell count. For example, in the ANRS PRIMO cohort, 75% of patients with CD4 cell count initially less than 500/mm³ at primary infection had, two years later, less than 350 CD4/mm³ [4]. In a more recent study of patients with recent HIV infection, 27% reached criteria for starting cART after 9 and 50% after 18 months [5].

The size of the reservoirs is determined in the very early stages of primary infection. Several factors are involved in driving the magnitude of the HIV reservoir size such as CD4 T cell nadir [6], viral replication which determines the size of the viral reservoir. The fact that HIV reservoirs remain relatively stable after prolonged therapy suggests that the harm caused by HIV to the immune system during untreated infection creates the immunological conditions that favour the survival and persistence of virus infected cells.

HIV primary infection carries a higher transmission risk
The very high level of HIV replication during PHI and the high activation of the immune system represent unfortunate optimal conditions to ensure HIV transmission from one individual to another. Worldwide, it is estimated that every year, nearly three million people become infected with HIV. Several studies have shown that about 50% of new infections were acquired through individuals who were acutely infected or recent seroconverters [7-8].

ART decreases risk of HIV transmission. One of the major arguments for “pro treatment defenders” in chronically infected patients, is the impressive results of the HPTN 052 study demonstrating an over 95% reduction rate of heterosexual transmission of HIV when the HIV-positive partner was treated with CD4 above 350 CD4/mm³ [3]. Controlling viral replication in blood from an infected to a non-infected person is one of the most effective ways to prevent viral transmission between them.

ART decreases severity of acute HIV disease.
The control of viral replication in acute HIV infection rapidly decreases HIV symptoms. In the case of HIV CNS involvement that should be looked for – it is highly recommended to initiate ART in order to limit the setting of HIV in the CNS compartment and probably wise to use drugs with optimal CNS and CSF penetration.

ART improves HIV disease markers and preserves immune functions.
Most studies have shown that the early initiation of ART delayed the progression of immune deficiency and that this benefit was maintained after treatment was discontinued.

AIDS rates were similar in early treatment groups compared to those in whom treatment has been deferred, however, the death rate due to a non AIDS defining event was lower in the early treatment group [9-10].

This, again, reinforces the major finding from the SMART study that replication of HIV is deleterious through immune activation and inflammation.

Similarly, the SETPOINT study which aimed to compare 36 weeks of cART with deferred therapy in early HIV infection was prematurely stopped in June 2009 because of a higher rate of disease progression in the untreated group [5]. Main-
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taining ART in early treated patients [11-12] leads to an incremental increase of CD4 over years with values above 500 CD4/μl, the magic number to reach since it has been associated with a quasi normalized survival as well as a protective factor against development of non AIDS related cancer [13].

ART decreases HIV set point and HIV reservoir.

This hypothesis has been controversial in the past with discordant reported benefits of temporary early cART [14-16]. There are now more convincing data that support the benefit of early treatment on those key viral parameters that sound like the HIV clock. The very recently published Primo-SHM trial provides the strongest evidence to date of a clinical benefit of temporary cART initiated during PHI. Early cART transiently lowered the viral set point by 0.5–0.8 log10 copies/ml, increased the CD4 cell count, and deferred the need for initiation of ART during chronic HIV infection by 1.1–2.3 years [17].

Likely to be a consequence of the decreased viral set point, early treatment intervention is associated with a reduction in the size of the viral reservoir [3, 18-19] and the preservation of immune function by limiting systemic immune activation.

There is currently an enormous interest from the recent reports including during last CROI, of patients who had been treated at the time of primary HIV infection who for several years are able to maintain their viral replication at a minimal level after ART discontinuation [20-21]. Interestingly those patients are characterized by an excellent immune status and a very low reservoir similar to the Elite controllers but without the special favourable HLA genetic profile. This represents a situation of HIV remission or functional cure.

Conclusion

Early intervention to durably prevent any HIV replication is the only smart answer to oppose the frantic production of this highly deleterious virus. The paradigm has profoundly changed. There is no longer any reason to let this virus replicate and every good reason to believe that if one day there is a cure for HIV, the best candidates will be those who will have optimally controlled their HIV replication through ART initiation. Medical education should be provided to all physicians to ensure they do not miss the opportunity of diagnosing HIV early in its course and of referring patients to initiate therapy.

Conflict of Interests

Professor Katlama has received research grants from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Tibotec. She has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Tibotec and ViHJ Healthcare.

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1. Lewin SR, Rouzioux C. HIV cure and eradication: how will we get from the laboratory to effective clinical trials? AIDS. 2011 Apr 24;25(7):885-97
Topical Conferences in 2012

June 27–28
7th International Workshop on Clinical Pharmacology of Hepatitis Drugs
Cambridge, United States
http://www.virology-education.com

June 28–29
7th International Workshop on Hepatitis C – Resistance & New Compounds
Cambridge, United States
http://www.virology-education.com

July 19–20
7th International Workshop on HIV Transmission – Principles of Intervention
Washington DC, United States
http://www.virology-education.com

July 19–21
14th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV
Washington DC, United States
www.intmedpress.com/comorbidities/

July 20–21
“Towards an HIV Cure”: AIDS 2012 Pre-Conference Symposium
Washington DC, United States

July 20–21
4th International Workshop on HIV Pediatrics
Washington DC, United States
http://www.virology-education.com

July 22–25
19th Word AIDS Conference
Washington DC, USA
www.aids2012.org

August 20–22
2nd World Congress on Virology
Las Vegas, USA
http://omicsonline.org/virology2012/

September 6–8
27th European Congress of the International Society for Sexually Transmitted Infections
Antalya, Turkey
http://www.iusti2012turkey.org

September 7–9
The Viral Hepatitis Congress 2012
Frankfurt Germany
http://www.viral-hep.org/

September 9–12
AIDS Vaccine 2012
Boston, United States
www.hivvaccineenterprise.org/conference/2012

September 12
52nd ICAAC
San Francisco, United States
http://www.icaac.org/

September 12–14
The Focus of Bridging the Sciences: Changing Landscape for HCV Therapies (BTS)
Atlanta, United States

September 30 – October 3
2012 United States Conference on AIDS
Las Vegas, United States
www.nmac.org/technical-assistance-cba-programs/2012-us-conference-on-aids.html

October 10–12
8th Australasian Viral Hepatitis Conference
Auckland, New Zealand
www.hepatitis.org.au/

October 17–19
Australasian HIV/AIDS Conference 2012
Melbourne, Australia
http://hivaidsconference.com.au

October 26–27
21st Annual HIV Conference
Lake Buena Vista, United States
www.faetc.org/Conference

November 5–6
3rd International Workshop on HIV & Aging
Baltimore, United States
http://www.virology-education.com

November 11–15
Eleventh International Congress on Drug Therapy in HIV Infection
Glasgow, United Kingdom
http://www.hiv11.com

November 13
The 63rd annual meeting of the american association for the study of liver diseases (AASLD)
Boston, United States
http://www.aasld.org/Im2012

December 4–7
HIV DART 2012 – Frontiers in Drug Development for Antiretroviral Therapies
San Diego, California, United States
www.informedhorizons.com/hivdart2012

December 14–15
2nd Global Workshop on HCV Therapy Advances
Rome, Italy
http://www.virology-education.com