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Cure for hepatitis C achieved, but what about HIV?

It is likely that within a few years we will be able to cure the vast majority of patients with hepatitis C by administering 3 to 6 months of interferon-free antiviral therapy (see H. Wedemeyer’s article on page 21). This is a quite remarkable prospect which, if it comes true (and most data speak in its favor) will change the perception of the disease and maybe even make it possible to fully eradicate the disease. However, several challenges still remain including some difficult economical considerations. In the long run, it is likely that an affordable regimen will be widely available since many effective new drugs seem to be heading to market in the near future.

An HIV cure is a tougher task. A few weeks ago I took part in the excellent Nobel Forum Conference “Towards a Cure for HIV” organized by the Center for HIV research at Karolinska Institutet in Stockholm and was impressed by the outstanding work being done by many different groups worldwide. While there are certainly several obstacles that have to be overcome, progress in the field is moving quickly. There is also at least one documented case, the famous Berlin patient, who was not only cured of leukemia, but of HIV as well after treatment with a hematopoietic stem cell transplant. Following the transplant, the patient’s antiretroviral therapy was discontinued, and he has now been off therapy for more than five years with no viral rebound, declining HIV-antibody levels, and largely absent HIV-specific T-cell response. Although not a universal way to treat the disease, the case shows that HIV is possible to cure. A sterilizing cure could not yet be proven in this case; a few viral particles may remain somewhere in the patient’s body, but nevertheless – and more importantly – he has most probably been functionally cured. While a sterilizing cure could be defined as the complete eradication of all replication-competent forms of HIV from the entire body, a functional cure can be considered the permanent viral suppression in the absence of therapy to levels that prevent immunodeficiency and transmission (Eiselle & Siliciano, Immunity 2012;37:337).

Most researchers and observers have ascribed the favourable outcome in this case to the fact that the patient received stem cells transplanted from a donor whose cells lacked the CCR5 co-receptor required for HIV to infect cells. A recent report of two additional patients with HIV and lymphomas (the Boston patients), who decreased their HIV DNA load to undetectable levels in PBMC after hematopoietic stem cell transplants with cells from donors with wild type CCR5 (Henrich et al, J Infect Dis 2013;207:1694) has questioned this assumption and suggested that other factors may have contributed, such as anti-T cell chemotherapy and graft-versus-host effect. Also while those two patients had discontinued their antiretroviral treatment they have not been followed for long enough after treatment cessation to draw any firm conclusions (Henrich et al. 7th IAS Conference, Kuala Lumpur 2013, Abstract WELBA05).

Some other promising studies and findings suggest that early treatment during primary infection may prevent seeding of latent reservoirs in long-lived central memory T-cells. The Mississippi baby, born to a mother diagnosed with HIV at delivery, was placed on antiretroviral treatment 31 hours after birth. Treatment was discontinued at the age of 18 months at which time the baby was lost to follow-up. When he returned to care after 6 months without treatment, his plasma viral load and total HIV DNA in PBMC were negative and no HIV-specific T-cell responses to HIV-Gag and -Nef peptide pools could be detected (Persaud et al. 20th CROI, Atlanta 2013, Abstract 48LB). It has been questioned whether this baby was actually infected or if this may have been a case of preventing transmission rather than cure (McCarty, BMJ 2013;346:f1599). However, the initial viral load of 19,800 copies/mL that subsequently decreased gradually to undetectable levels within the first month of treatment reassures me that an ongoing viral replication was present and that the baby was intrauterinely infected. In line with this, five other perinatally HIV-infected adolescents who began treatment soon after birth have been reported with undetectable HIV-specific antibodies, CD8+ T-cell responses, and residual plasma viremia. Moreover, it was impossible to isolate replication-competent virus from any of those patients, although proviral DNA was detectable at a low levels in resting CD4+ T-cells (Luzuriaga et al. 20th CROI, Atlanta 2013, Abstract 171LB). Longer term follow-up of those and other similar cases would be of great interest.

The immune system of infants is immature and so results cannot be directly translated into adult patients. A study from Thailand (Ananworanich et al. 20th CROI, Atlanta 2013, Abstract 47) and the French Visconti Cohort (Sáez-Cirión et al. PLoS Pathog 2013;9:e1003221) indicate that treatment during the acute phase of infection can decrease the size of the latent reservoir and in some cases establish post-treatment control (see C. Katlama’s article on page 17).

Current research is expanding our knowledge in the field and raising hope for the possibility of a cure for the disease. It is, however, important to remember that a kind of “functional cure” can already be achieved in almost all HIV-infected patients by using currently available antiretroviral treatment. This once fatal infection has been reduced to a chronic disease with a very favorable prognosis; a fact to be carefully considered when designing intervention-al cure studies. There must always be an acceptable risk-benefit balance for the individual patient.
In June, Professor Jan Gerstoft greeted a record number of 180 delegates welcome to Nordic Summer HIV Meeting in the Danish capital Copenhagen.

The day had two programmes – one for doctors and one for nurses. But the first Plenary Session was a joint session for both groups. It was titled Treatment as prevention (TasP).

Initiation of ART protects uninfected sexual partners from HIV infection – according to a study by HIV Prevention Trials network. It gives a 96% reduction in HIV transmission, said Prof Joep Lange from the Netherlands in the first talk.

– The incidence of HIV has come down from the peak in the mid-nineties, but the prevalence is still high. We need TasP, he continued.

Prof Lange added that he personally did not believe that TasP strategies by themselves will be sufficient to end the HIV epidemic.

– But it is clear that TasP should be scaled up in conjunction with other effective HIV interventions, and also clear that it is an essential component of the prevention package and should be rolled out as expeditiously as possible!

Benefits of starting ART early
TasP should start as early as possible. There is overwhelming evidence that this increases survival.

– In fact, when treatment is started early enough and the CD4+ cell count is kept above 500 mm³, life expectancy is similar to that of the non-HIV infected, Prof Lange continued.

An early start also reduces TB incidence.

– That is not so important in Scandinavia, but it is very important in sub-Saharan Africa.

There are also societal benefits of early treatment. It allows health systems to task-shift HIV treatment and care from specialized physicians to health officers, nurses and community health workers.

– This is not a trivial benefit if we consider the staggering health workforce shortages in many resource-poor settings.

This has also been recognised in treatment guidelines:

– The obvious benefits of early therapy for both individuals and society have led to recommendations in the latest US treatment guidelines to offer ART to all HIV-infected adults and adolescents – regardless of CD4+ cell count, Prof Lange said.

So can we see the end of AIDS on the horizon?

– We’re not there yet, but I think we can do a lot – including treatment for prevention, he ended his talk.
Experiences from Zambia
Prof Jeffery Stringer from USA gave a lecture on ART scale up in Africa – limited resources, unlimited possibilities. He began this by presenting data on worldwide HIV disease burden.
- In total there are 34 million people infected by HIV – of which adults are 30.7 million and children 3.3 million, he stated.

There has been an increase in the resources for HIV given by donor governments, and hence the number of people receiving ART in low- and middle-income countries has increased.
- This has led to that adult life expectancy in rural South Africa is increasing.

It has been shown in a study from 2013, Prof Stringer continued.

He presented data from his work in Zambia – a land-locked country slightly larger than Texas, with eight international borders and 14.2 million people.
- The prevalence for HIV in Zambia is 13.5% nationwide and 20% in the capital Lusaka. Life expectancy at birth is 51 years – it was 35 in 2001. Maternal mortality – which is a good indicator on how the health system works – is 440 per 100,000 (in Denmark 12) and infant mortality is 68 per 1000 (in Denmark it is 4.1).

Call for task-shifting
ART in Zambia began with pilot projects in 1999, in order to find out if it was possible at all.
- The huge scale-up then began in April 2004. The shortage of doctors required use of non-physician clinicians such as nurses, clinical officers and pharmacy technicians, Prof Stringer explained.

The first problem they had to deal with was the absence of culture for good record-keeping. It was very episodic and careless.
- So we decided to “protocolize” the care and created a number of forms to guide local providers of care. We also adopted an IT-based journal and it was a great success.

However, an increasing number of people were lost to care.
- For every patient we add, we lose one. The capacity of the clinics is not enough. Once people started feeling better, they did not want to waste eight hours in order to see the doctors.

One technical solution to this problem is sending the patients SMS messages, which caused a significant increase in ART adherence.
- It is a cheap thing to do, to send a text message!

Prof Stringer also underlined the importance of task-shifting.
- Take tasks from doctors and give them to nurses. An RCT from 31 sites, published in 2013, shows that this system works well. The traditional facility model can’t cope with the influx of patients.

He concluded that huge progress have been made and now is not the time to slow down.
- And we need smarter support – with technology, but also with new care models.

HAART during pregnancy
Mother to child transmission (MTCT) is preventable, and the methods are well known, said Dr Terese Katzenstein from Denmark.

The first study that showed that prevention of MTCT is possible was published in New England Journal of Medicine in 1994 and concerned zidovudine.
- This was a very important study. It also proved a connection between the amount of virus in the mother and the risk of transmission – a high viral load gave a high risk for transmission, Dr Katzenstein said.

Another study then proved that the reason for efficacy also was due to the child receiving zidovudine via breast-milk.
She also referred to a later study that demonstrated a surprisingly high efficacy for nevirapine to prevent transmission.
- But with nevirapine the risk of resistance is higher.

Dr Katzenstein presented three options for prevention of MTCT programmes.
- In option B you go for HAART during pregnancy. The infant receives daily nevirapine or zidovudine from birth to age 4 – 6 weeks regardless of infant feeding method.

Need for monitoring
- There has been some confusion on recommendations regarding breast-feeding. We say that it should be avoided – if the mother and the child are in a safe setting, Dr Katzenstein continued.

A prospective cohort study on the influence of infant-feeding patterns from Durban, South Africa showed that exclusive breast-feeding is better than mixed feeding.
- Even though up to 40% of MTCT is due to transmission during breast-feeding, it means that most breastfed infants do not become infected with HIV – and why is that so? Is there a protective substance in breast milk? They have found a substance called tenacin C, but whether there are any clinical implications on tenacin C remains to be seen.

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different defects. Also they found an increased risk of congenital heart defects.
Is that reason to worry? I don’t know, but monitoring is necessary, because more infants will be exposed to these drugs.

In her summary Dr Katzenstein also called for monitoring for resistance development.
- The development in preventing MTCT is positive, despite many problems. More women are treated, and more transmissions are averted. I hope that this also leads to a decrease in stigmatisation, she finished her talk.

Need for testing
Why don’t physicians test for HIV? The question was asked by Prof Yazdan Yazdanpanah, and he presented a study on missed opportunities for HIV testing in newly diagnosed HIV-infected patients in France.
- Out of 191 MSM (men who have sex with men) 91 (48%) stated that they were MSM. Of these, only 41 (45%) were proposed a HIV test at the first contact. 50 (55%) were not. This means that in total only 25% of 191 had a test. That is a missed opportunity, he explained.

Of 588 patients with a HIV related symptom 82% (!) were not proposed a HIV test.

Hence the question on why physicians do not test for HIV.

A literature study in the US found eight barriers: Insufficient time, a burdensome consent process, lack of knowledge and training, lack of patient acceptance, pre-test counselling requirements, competing priorities and inadequate reimbursement.
- Whatever the next hottest, scientifically proven HIV treatment or prevention such as PrEP or TasP are, they will share a common denominator for implementation: The HIV test. They all begin with learning one’s HIV status!

We must also work on linkage to care. A positive test that doesn’t is useless, Prof Yazdanpanah summarised.
- IV drug abusers are often tested, but not linked to care, he added.

Two major challenges
In the Doctors Session that followed, Prof Douglas Richman from USA talked about HIV latency and eradication. He started this by pointing out some major challenges facing the HIV field.

HIV chemotherapy has been a major medical accomplishment over the past two decades and has dramatically reduced the morbidity and mortality to those with access to care, he said.
- I see two major scientific challenges for the future of management of HIV, neither of which may be achievable: To develop a vaccine for HIV uninfected people, and for the infected to develop approaches to cure the latent reservoir, Prof Richman said.

Why should we do this, when treatment is so effective? According to him, there are several reasons.
- To reduce drug costs, drug toxicity, the morbidity and mortality associated with viral persistence and immune activation. But also to reduce drug resistance and transmission.

He described the regulation of HIV basal transcription by integration site factors and T-cell activating factors. Strategies for a cure include eliminating residual virus replication and then eliminate latently infected cells and enhancing HIV-specific immunity.
- Gene therapy is needed to make cells “resistant” to HIV, or to excise or inactivate the provirus.

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“A long and challenging effort”
Patients on HAART are viremic, although below the level of detection (50 copies per ml).
- What is the source of this HIV RNA, he asked and presented two opposing theories on the subject:

The first is that there is ongoing replication despite apparently suppressive therapy. The second is that there is virus production by long-lived cells that fail to undergo lytic cell death, despite infection.

What the field needs are more sensitive and precise assays, said Prof Richman.
- Proposed assays require validation with characterization of sensitivity, specificity, accuracy, precision and reproducibility etc. Standards would make interpretation better. Sharing of protocols, reagents and specimens would permit more rigor and interpretability.

The search for a cure will be prolonged and challenging. In fact, it may not be possible; nevertheless, like the search for a vaccine, the challenge should not preclude the effort, he stated.
- Achieving a cure would have a dramatic impact, and the effort – regardless of the ultimate outcome – will yield significant insights into latency and reservoirs. Success, should it be possible, will take more than a decade, Prof Richman summarised.

The importance of dialogue between the lab and the clinic
Low level viraemia during HAART: What is the significance and how should it be managed was the title of Prof Anna Maria Geretti’s, UK, lecture.

She first talked on viral load (VL). Upon defining virologic failure, Prof Geretti called it a “grey zone”. ☺
- VL suppression under 50 copies is well validated as a target, she established.

A VL higher than 400 copies during ART impacts on clinical outcomes. But blips ranging from 50 to 400 copies are not associated with VL rebound.

- Larger blips or confirmed viraemia 50–400 copies are however associated with risk of greater VL rebound, she said and underlined that resistance is only one of the potential outcomes of viraemia.

The introduction of third generation VL assays has created dilemmas about interpretation.

- With RealTime and ArtusHIV 50 copies are still 50 copies. But with TacMan version 2, 100 copies is the new 50 copies. This underlines the importance of dialogue between the lab and the clinic.

Does HIV continue to replicate during seemingly suppressive ART? Prof Geretti said the issue remains controversial.

- Persistent detection of HIV-1 RNA has been reported in patients receiving long-term ART, although treatment regimens and definitions of virologic suppression varied considerably in previous studies.

**Implications for clinical care**

Technical factors affect VL assay performance.

- Assays that use extraction platforms capturing both RNA and DNA are more prone to showing low-level viraemia.

During long-term, seemingly suppressive ART, HIV-1 RNA remains detectable in plasma at levels around 3 copies. This implies that VL “undetectability” is not an achievable target.

- The plateau of HIV-1 RNA detection may be higher in some patients, perhaps reflecting larger HIV-1 DNA reservoirs, Prof Geretti continued.

Among the implications for clinical care is the need to understand and address technicalities of VL testing.

- Support adherence and address factors influencing it. Review ART potency and tolerability – and change ART regimens based upon considerations of VL, drug potency, genetic barrier, penetration and tolerability and lifestyle, were among Prof Geretti’s advice.

**Mortality for HCV higher than for HIV**

Prof Raymond Schinazi from USA talked about HCV eradication – a task he named “mission possible”.

- I think we all know that there are 170 million people infected with HCV worldwide. In USA there are 2.7 to 3.9 million, he said.

Today’s standard of care is ribavirin + pegylated interferon-α + protease inhibitors.

- Nucleoside analog inhibitors (NAI) are best in class: They have high potency, are pan-genotypic, have a high barrier to resistance and carry a low pill burden and are orally bioavailable.

Since 2007 more Americans die from HCV than HIV infection, and the situation is similar in Europe. HCV related illness is expected to increase significantly in the coming years, Prof Schinazi said.

- In the absence of novel treatments it is going to be a tsunami of HCV related liver failure, transplant, death and an increased financial burden. Hepatitis C infection is at least five times more prevalent as HIV infection in the US, yet funding lags far behind.

**New drugs for HCV**

But the market will see an influx of new drugs over the next few years, and Prof Schinazi presented an overview of what is in the pipeline. He pointed out sofosbuvir as a very promising drug and estimated that it will be approved for all genotypes.

DAPN prodrug 1 and 2 represent new investigational compounds against HCV. It is potent and non-toxic in several cell culture systems.

By using a map of the world incidence of HCV, he underlined the need for affordable drugs.

- We must meet the silence of HCV’s forward march with resonant opposition! Also increase awareness through universal screening to unmask “silent” infections, education that empowers – and with care for prisoners, drug addicts, children and the poor.

- But the ultimate benefit of cures for HCV will not be measured by the cost they avoid – but by the lives they save, was Prof Schinazi’s conclusion.

**HIV and HCV drug interactions**

The last Speaker in Copenhagen was Prof Saye Khoo from UK. He talked about HIV – HCV drug interactions.

- While many drug-drug interactions (DDI) are unavoidable, most are manageable, he initially stated.

These DDIs may be anticipated, unanticipated but explainable – and unanticipated and unexplainable. Most potential interactions will remain unstudied, according to Prof Khoo.

- DDIs may also differ between patients, he said.

HCV treatment is complex.

- There are dosing schedules and stopping rules – and issues on adherence and toxicity and resistance to be addressed. They concern special populations, such as people with cirrhosis, post liver transplantation and with multiple co-morbidities and co-medications.

Prof Khoo therefore finished his talk by pointing out the need to configure health systems appropriately – with co-infection specialists and their advice, and with DDI resources.

Then the Meeting was over. Prof Gerstoft thanked all speakers and delegates and Gilead for their support.

- Next year the Nordic Summer Meeting will be held in Stockholm, on June 12. So save that date, he said.
pediatric programs have long been a lower priority due to the lack of commercial viability of pediatric antiretrovirals in the developed world, the need for special formulations and the low prevalence of new infections thanks to the success of antenatal testing and treatment programs. The WHO 2013 Guidelines prioritising treatment in children under 5 years of age with HIV underlines the paucity of options available to children in poorer regions of the world. Generic manufacturers seem unlikely to step up to the challenge of paediatric formulation development, pharmacokinetic and safety testing, leaving this group with a large unmet and unaddressed need.

The drug development process, in its earliest stages at least, is biased towards investigation in young males. For reasonable safety reasons, specifically with regards pregnancy, men are used in early phase drug development. The need to have no concomitant illnesses or co-medications excludes older individuals. Indeed the phase 1 single and multiple ascending doses (SAD and MAD) studies for safety and pharmacokinetic assessment of new potential medications are typically called ‘entry into man’. The dose finding pharmacokinetic/pharmacodynamic phase 2a and 2b studies similarly tend to also have multiple safety and concomitant medication related exclusion criteria that limit the likelihood that women or older individuals, say over 50s, will participate.

Thus when drugs enter the large phase 3 programs required for approval they are likely to have had little or no exposure in women or in older individuals nor any information about specific variation in pharmacology across these groups.

The pharmacokinetics of many medications is different in women to men, in part due to the impact on female menstrual hormones on metabolising enzymes, which will vary across the course of each cycle, but also differing fat mass and volume of distribution in women compared with men. Indeed the likely two-way interactions between antiretrovirals and

Women and Children last
Is drug development leaving the most in need behind?

When a disaster strikes at sea, priority for rescue is traditionally given to women and children, as most famously played out in the sinking of the Titanic. In more recent times this code of conduct has extended to include helping the most vulnerable to leave the scene first, this list may include the sick, disabled, elderly and young children. However, the antiretroviral drug development process seems to be neglecting these groups more than ever, with many recent approvals based almost entirely on data in young males, mostly with low viral loads.
the normal female menstrual cycle is are under- or really un-investigated. Interactions between administered oestrogens and progestogens and many antiretrovirals are well established, and make administration of hormone based contraception a challenge. Amongst new preparations, Strobil significantly decreases ethinyl oestradiol and increases administered progestrone by 126% [1]. Dolutegravir does not have any impact on oral contraceptives containing norgestimate and ethinyl oestradiol [2]. Drugs which increase administered progestogens are likely to also raise natural progesterone potentially leading to intensification of pre-menstrual symptoms. Two reports (at IAS 2013 in Kuala Lumpur) of breast pain in women commencing Stribi [3] may be potentially explained by the effect of this antiretroviral combination (presumably the cobicistat component) on natural progesterone. Even some NRTIs such as abacavir different in PK between men and women, with women having higher plasma exposure of abacavir and intracellular exposure of the active metabolite carbocavir triphosphate [4]. This may provide a partial explanation as to why women with high viral loads randomised to abacavir/ lamivudine in ACTG 5202 did not see an underperformance in virological efficacy relative to tenoforv DF/emtricitabine, unlike the comparison in men [5].

Similarly, age impacts drug metabolism due to declining expression of metabolising enzymes and of renal function as well as changes in body composition and gut function with age. The increasing number of medications for concomitant conditions received by older individuals also contributes to interactions many of which are uninvestigated at the time new antiretrovirals are approved, and indeed may never be in investigated. Typically two-way interaction studies are done (in young male volunteers) while 3 or more way interactions are more probable in clinical practice. For example, calcium channel blockers are rarely the subject of investigation despite being CYP3A metabolised and widely recommended as first or second line antihypertensives. Amongst the commonly used PI/r regimens there is a dose adjustment for dilitazem with atazanavir/r but no interaction study with darunavir/r. Amongst the INSTIs, a study of amiodipine and raltegravir has completed but no studies with Stribi or dolutegravir reported.

The higher rate of adverse events reported in older individuals in clinical studies (that in part makes them unattractive trials subjects despite often better virological outcomes) may be related to higher exposure of medication due to two main factors; better adherence in older subjects and diminished drug metabolism.

Given the proportions of women (>50% of the global burden of infections) and older individuals (>30% of patients are over 50 years old in many larger US and EU clinics) that make up the pool of infected subjects the representation of these groups have been woefully lacking in recent phase 3 clinical trials. While figures for the proportion of subjects over 50 years of age are lacking, the median age was mid-30 in the Stribi and dolutegravir treatment naive programs. The proportion of women in the Stribi and Dolutegravir Phase 3 studies was typically around 15% of the total enrolment, meaning that about 100 women have been exposed to these agents for 96 weeks at the time of approval. Clearly this number is insufficiently low to assess whether safety and efficacy of these agents is different in female subjects, altering the risk-benefit consideration when deciding whether to use these drugs in females. Some newer studies currently recruiting are endeavouring to prioritise female recruitment and the FDA is making companies do female only studies as part of post approval commitments to redress, a little belatedly, this imbalance. Specific studies in older individuals are not planned although I am aware of a single PK study of raltegravir in over 60, beyond cohort studies of older subjects, which largely focus on comorbidities in persons with HIV disease. The POPPY study (A Prospective, Observational Study to Examine the Effects of Ageing on the “Pharmacokinetic and Clinical Observations in People Over Fifty”), run by Imperial College in the UK with support from multiple pharmaceutical companies will endeavour to at least partially address these deficits. The study has recently commenced recruitment.

A further deficit exists in recent clinical trials; the lack of subjects with advanced disease as measured by low CD4 (especially <100 cells/mm³) and high viral load. While treatment naïve trials in the recent past, such as CASTLE and AR-TEMIS, typically included subjects with a mean CD4 count in the low 200s, and a high proportion of subjects with high viral loads and low CD4 counts (for example the Atazanavir/ r arm in CASTLE includes 225 (50%) subjects with viral loads >100,000 and 103 subjects with CD4 counts <100 and a further 106 subjects with CD4 counts 100–200 [8].)

More recent studies have typically had mean CD4 counts in the mid 300s and only a third of subjects with high viral load (for example in the pooled analysis of Stribi studies 102 and 103 31% of subjects had baseline viral loads >100,000

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<th>ATV/r+TVD (n=355)</th>
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<td>13%</td>
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<td>3% : 4%</td>
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From Reference 9: Gilead Studies 102 and 103 Baseline characteristics. These studies were the pivotal trials leading to Stribi’s approval.
Advertisement
Priority needs to be given in clinical trials, potentially via regulatory enforced stratification, to recruit a representative sample of women, older individuals and those with advanced disease to ensure adequate safety and efficacy information at the time of drug approval.

and just 3% of subjects had CD4 counts <50 and a further 11% with CD4 counts 50-200) [9]. These advanced patients have historically been the key stress tests of antiretroviral regimens that separate our best regimens from the ‘alternate’ regimens. For example: It was largely advanced patients that drove the advantages of atazanavir/r (in CASTLE), darunavir/r (in ARTEMIS) and Efavirenz (in ACTG 5142) over lopinavir/r both in terms of efficacy and tolerability. Advanced subjects had more adverse event related discontinuations as well as more viral failures in these studies. These advanced subjects also showed up the lower antiviral potency of rilpivirine relative efavirenz (in ECHO), Eviplera to Atripla (in STAR) and once daily raltegravir relative to twice daily dosing (in QDMRK).

So not having these patients well represented in clinical trials raises the concern that our new agents are not being pushed and tested as hard as drugs of the past. The improved baseline status of subjects in recent studies likely explains the exceptionally high success rates, in both the test and control arms, reported in these studies. The low rates of failure also mean these agents enter practice with a paucity of data on the consequences of failure both in their own class and in the NRTI backbone. This makes future regimen planning a potential challenge, albeit that most first line failures appear ‘salvageable’ by PI/r based regimens.

Why are so few advanced subjects entering trials? At first thought the obvious explanation is earlier diagnosis of HIV infection and the changes in guidelines to encourage more universal treatment are shifting the demographics of trial entrants. This may well be true albeit the prevalence of ‘late’ diagnosis of HIV (say CD4 <350 at diagnosis) remains high (at least 30% in most EU countries) and is especially so amongst women. A second key bias in recent studies with INSTIs has been the insistence by the sponsoring companies on the use of Monogram Biosciences assays for resistance assessments. While most local services we use on a day-to-day basis may turn a viral sequence around in less than a week, including the integrase region, the sample processing time via this single site laboratory near San Francisco is often more than 3 weeks and sometimes up to 5 weeks. Sample failures commonly mean further delays and rescreening (or more often exclusion) of subjects. While the use of this central laboratory has been repeatedly flagged by investigators as a logistic problem and an obstacle to recruitment the sponsoring companies persist in its use. The explanation may be that the necessity of a long screening period facilitates the exclusion of more advanced subjects, making the study population one of predominately ‘easy’ to treat subjects, resulting in exceptional outcomes both in terms of safety and efficacy. Thus, new combinations looks better that those of the past, we can congratulate ourselves on making better and better therapies for HIV and set wholly unrealistic expectations on what may actually happen in clinical practice. The guys in marketing must love it.

In conclusion, there are concerns that the drug development process in HIV is losing sight of priority populations that make up a significant proportion of future potential recipients. Priority needs to be given in clinical trials, potentially via regulatory enforced stratification, to recruit a representative sample of women, older individuals and those with advanced disease to ensure adequate safety and efficacy information at the time of drug approval. Until we see more data in specific populations, we can only be confident that some of our new combinations work exceptionally well in young males with good CD4 cell counts.

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.

References:
Combination of HBV-DNA- and HBsAg levels to predict HCC risk

It has been shown that the HBV-DNA level in HBeAg negative chronic hepatitis B infection predicts the risk of hepatocellular cancer (HCC) if HBV-DNA is greater than 2,000 IU/ml. In those with HBV-DNA less than 2,000 a higher level of HBsAg (>1,000 IU/ml) is associated with increased risk of HCC. In a study from Taipei 2,165 chronically infected non cirrhotic HBsAg negative carriers were followed for almost 15 years. The combined predictive value of the two biomarkers HBV-DNA and HBsAg level was analyzed. In summary it was shown that in those with intermediate HBV-DNA levels of 2,000 – 20,000 IU/ml a significant correlation between HBsAg levels and the risk of HCC was demonstrated. In those with higher HBV-DNA (>20,000 IU/ml) the HBsAg level had no independent predictive value.

Tseng et al, JID 2013:208:594-93

Comment: Using the combined biomarkers may be useful in identifying patients at risk that are candidates for antiviral therapy.

HCV reinfection in HIV-positive MSM

In a retrospective analysis of HIV/HCV coinfected MSM between 2004 and 2012 in London the reinfection rate in patients who had been successfully treated or had cleared HCV spontaneously was studied. None of the participants had a history of injection drug use. More than two thirds were infected with genotype 1. 191 patients were followed for 562 person years. In those who had been treated the reinfection rate was 9.6/100 person years and in those who had cleared HCV spontaneously the reinfection rate was 4.2 (p=0.15). For those who were reinfected 20% cleared the virus spontaneously.

Martin et al; IAS Kuala Lumpur 2013, abstract TUAB0101

Comment: The reinfection rate was higher in those who were treated for HCV compared to those who cleared HCV spontaneously. One might speculate that this may indicate that spontaneous clearance confers some kind of partial immunity. The true reinfection rate may be even higher as a number of reinfections may have cleared spontaneously before they were diagnosed.

Valacyclovir in HIV/HSV2 co-infection

To evaluate whether the addition of valacyclovir to suppressive ART therapy in HIV/HSV 2 co-infection would reduce markers of inflammation and immune activation sixty patients were included in a randomized study. Patients were randomised to placebo, 500 mg Valacyclovir BID or 1,000 mg BID. Treatment was given 12 weeks and patients were followed for a total of 18 weeks. The primary outcome measures were percentage of activated (CD38+HLADR+) CD8 T-cells in blood, highly sensitive C-reactive protein, interleukin-1 and soluble intercellular adhesion molecule-1 in plasma. A majority of the study participants were Caucasian MSM. Of eight patients with side effects five received placebo. Three patients in the placebo group, three in the low dose group and none in the high dose group had at least one outbreak of herpes. Neither high nor low dose of valacyclovir had any effect on the primary outcome parameters. In conclusion Valacyclovir had no effect on immune activation and inflammation.

Yi et al, Clin Infect Dis; Advance access published August 14 2013

Comment: Earlier studies with acyclovir have shown some minor effect. This has however been in the pre-ART era and in more recent studies in patients not yet on ART.

Does marijuana smoking accelerate the progression of liver disease in HIV-HCV coinfection?

690 coinfected Canadians without significant fibrosis or end stage liver disease were included in a study of the progression of liver disease and marijuana. 53% of the participants had smoked marijuana in the last 6 months. The average consumption was 7 joints per week and 40% smoked marijuana on a daily bases. No correlation between the number of joints per week and progression of liver disease was found.

Brunet et al, CID 2013:57:663-70

Comment: There may be many good arguments against smoking marijuana. Increased progression of liver disease in coinfected patients is however not one of those arguments.

HIV Type-1 Group O infection in Gabon

The HIV-1 pandemic is totally dominated by group M. A limited number of group O infections have been described in a few West African countries. In Cameroon it has been estimated that about 1% of the HIV infections belong to group O. To determine the prevalence of HIV-1 group O in Gabon and to characterize the genetic diversity samples from 1,176 HIV positive individuals were analyzed. 4/1,176 (0,3%) were diagnosed as group O. Of the 4 cases 1 died shortly after diagnoses and one was lost to follow up. The two remaining individuals both had CD4 count < 200 and viral loads of 100,000 and 10,000 during treatment with NNRTI containing regimens. The HIV1 group O however is naturally resistant to NNRTI as consequence of the presence of the Y181C mutation. In 1997 the rate of group O was estimated to be 0.9%. Given the very low numbers no firm statistical analyses could be performed but there are no indications that group O is becoming more prevalent.

Liègeois et al, AIDS Research and Human Retroviruses 29:2013:1085-1090

Comment: It is still unknown why the spread of HIV-1 group O has been so limited compared to group M.

Switching HIV treatment based on CD4 count versus viral load monitoring

In a prospective multicenter Thai study two different strategies to monitor HIV-infection were compared. 21 public hospitals participated in the study. The endpoint was 3 year clinical failure. Failure was defined as death, a new AIDS defining event or CD4 < 50. About 700 patients who started ART were randomized to either measurement of CD4 count only or CD4 count and viral load every three months. Viral load was actually measured in all patients but in the CD4 arm the results were not revealed. All patients were given first line NNRTI-based therapy together with two NRTIs. Patients were switched to second line PI therapy if viral load decreased less than 1 log after 3 months or viral load was above 400 thereafter. In the CD4 only arm therapy was switched to second line if CD4 declined more than 30%
from its peak value unless the CD4 count remained above 200. 14% (n=50) of the patients switched therapy to second line, 31 in the CD4 arm and 19 in the viral load arm. The median time to switch was shorter in the viral load arm. A total of 58 (30 in the viral load arm and 28 in the CD4 arm) patients reached the endpoint. 33 developed a new AIDS defining event and 22 died. At study conclusion there was no difference in viral load suppression, immune restoration or resistance development. The study was designed as a non-inferiority study and the result was that non-inferiority was confirmed.


Comment: In most resource limited settings viral load measurements are not performed routinely. Systematic monitoring with only CD4 may be an acceptable alternative.

Reduction of hepatocellular carcinoma with long-term antiviral therapy against hepatitis B

472 patients with chronic hepatitis B were treated with entecavir. They were compared to a historic cohort of 1,143 patients who did not receive any antiviral therapy for hepatitis B infection. All patients were monoinfected and followed for at least one year. Most patients who received entecavir had elevated ALT and HBV-DNA > 4 log copies/ml. The control group was recruited from 1973 to 1999. A second comparison was done with patients treated with lamivudine 1995 to 2007. Risk scores based on earlier publications on the natural course of Hepatitis B infection were applied. The ETV group was followed for an average of 3.2 years (1,561 person years) and the control group for 9.5 years (12,381 person years). During follow up 12 patients (2.54%) in the entecavir group and 144 (12.6%) in the controls developed HCC. The incidence was 76 and 116/10,000 patient years. 21 persons in the control group developed cirrhosis while no cases of cirrhosis were observed in the entecavir arm. To allow a comparison patients were matched according to risk factors and time. The cumulative HCC incidence in the ETV group was 0.7% at two years, 1.2% at three years, 2.5% at four years and 3.7% year five. The corresponding figures for the matched control group was 0.7% at two years, 1.2% at three years, 2.5% at four years and 3.7% year five. The corresponding figures for the matched control group was 0.7% at two years, 1.2% at three years, 2.5% at four years and 3.7% year five. The conclusion was that non-inferiority was confirmed.

Hosaka et al, Hepatology, July 2013;98-107

Comment: Antivirals are thought to reduce the incidence of HCC. For ethical and practical reasons it is however not possible to conduct a randomized placebo controlled study to confirm the protective effect of antiviral therapy. Thus this is a valuable study confirming the lower HCC incidence with antiviral therapy. It also confirms that lamivudine is less effective than entecavir in lowering the HCC incidence.

Reduced efavirenz dose?

The ENCORE1 study compared the standard dose of 600 mg efavirenz with a reduced dose of 400 mg in first line therapy. 636 treatment naïve HIV-positive persons from 13 countries were randomized to either 400 or 600 mg efavirenz in combination with two nucleoside/nucleotide reverse transcriptase inhibitors. The study was double blind. Average CD4 was 99 cells and one third had viral load greater than 100,000. Efavirenz was given as 200 mg pills with a matching placebo in the 400 mg arm. After 48 weeks 94 and 92% had viral load less than 200 copies/ml. The 200 copies cut off was used because some of the participating countries do not routinely use more sensitive viral load measurements. Among those with baseline viral load above 100,000 copies/ml 93 and 91% had viral load below 200 copies/ml. The overall number of side effects was similar in the two arms but central nervous system symptoms were significantly more common with the higher dose. The conclusion was that 400 mg efavirenz is non-inferior to 600 mg efavirenz in treatment naïve patients.

Puls et al. IAS Kuala Lumpur 2013, abstract WELBB02

Comment: A lower efavirenz dose would reduce both cost and CNS side effects. Can we expect a fixed dose combination pill with 400 mg efavirenz?

Updated guidelines for PEP after occupational HIV exposure

United States Public Health Service (USPHS) has published new guidelines for the management of occupational HIV exposure and the use of Post Exposure Prophylaxis (PEP). One change from the guidelines from 2005 is that a combination of three drugs should be given in all cases. According to the old guidelines an evaluation of the risk in each exposure should be done to estimate the optimal number of drugs. Several alternative drug combinations are recommended. If possible the HIV status of the exposure source patient should be determined. Treatment should start as soon as possible and continue for four weeks. Initiation of therapy should not be delayed pending expert opinion. It is not defined in the document when it is too late to start medication. Follow up appointment with counseling and testing should begin within 72 hours. Another change compared to the previous guidelines is that testing after 4 instead of 6 months is acceptable if a fourth generation HIV antibody/antigen test is used.

Infect Control Hosp Epidemiol.2013;34:875-892

Comment: It is logical to use a three-drug regimen for all cases. What I find less logical is that many alternative drug regimens are recommended. To my understanding it would be much more manageable and practical to have only one single well tolerated drug combination for initial treatment. If for some reason the treatment needs to be modified that can easily be done. To shorten the follow up time to four months using a fourth generation HIV antibody/antigen test seems to be very reasonable taking the improved sensitivity of modern tests into account.

Conflict of Interests

Dr Flamholc has received honoraria as speaker and/or advisor from Abbott, Bioinvent, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Roche and Janssen.
Advertisement
Considerable interest and excitement has arisen over the last two years for a newly recognized population that has finally been dubbed “post treatment controllers” (PTC) more explicitly than the original Visconti patients. These patients with primary HIV infection have, in fact, been capable of controlling their viral replication without ART and apparently despite having no specific favorable genetic background to prevent HIV evolution.

They are thought to be potentially more “standard patients” for the functional cure concept than the Berlin patient or the Mississippi baby. If standard patients with certain characteristics and under circumstances that both have to be further explored can be “functionally cured”, it would represent a great deal of hope for the scientific and patient community.

After the SMART era, when our hopes of structured treatment interruption were swept away by the unequivocal message “Once you have started ART, you cannot discontinue it for any reasons”, we felt that we may at least still pursue our dream of HIV cure to the extent of disease remission [1–2]. We envisioned that some patients could go off treatment for prolonged periods of time, and that HIV could be defeated or made weak enough to bend its head and stop replicating without ART pressure.

Our enthusiasm has been justified when more data about the Visconti cohort was published earlier this year. There was very little interest when Hocqueloux and Rouzioux first reported these cases of patients with long term control of HIV replication following ART. Today, approximately 50 PTC patients have been described in the literature between 1999, when J. Lisziewicz reported the first Berlin patient to receive early treatment at PI and then remained undetectable for two years, until the last paper by Asier Saez Cirion on the French Visconti cohort [3–4].

Who are the Visconti PTC patients?
The initial Visconti study evaluated 18 patients diagnosed in the 2000s and treated after a median delay of 10 weeks following a symptomatic primary infection. ART was maintained for a median time of 2.4 years. All of those patients except one have remained off treatment for a median period of 9.3 years. One was restarted on ART because of a cancer while his viral load was still < 50 cp/ml. Fourteen have remained < 50 cp/ml up to the present, despite a partial rebound after treatment interruption (TI). Overall, 5 patients had at least one episode of residual viremia, defined as 2 values of VL > 50 cp/ml.

One of the remaining issues is to determine the factors that can be associated with PTC status.

- If one examines the viro-immune characteristics of PTC patients at the time of primary infection, their relatively standard profile shows a low CD4 count, a subnormal CD4/CD8 ratio, a high viral load, and a viral DNA in the range of values reported in this context.

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<td><strong>Median (IQR)</strong></td>
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<td>ADN-VIH, log cp/10⁶ PBMC</td>
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Looking in depth at their immunologic profiles, as reported by Asier Saez Cirion and Hocqueloux [4–5], PTCs are characterized by the following:

- A very weak HIV-specific CD8+ T-cell response during the viral control period, with weak suppressive capacity to inhibit HIV that is very similar to the CD8 response in ART-treated patients.
- A low T-cell activation status.
- Very low HIV reservoir levels that in some cases continue to decline for years after TI.

There also seems to be a difference in terms of distribution of HIV-DNA within resting memory cells. Whereas the reservoir is generally distributed mostly in the long-lived resting memory cells, these long-lived cells contribute minimally to the HIV reservoir in PTCs, the HIV-DNA being stored in cells with a shorter life span. This could explain why a slow decrease in DNA was observed over time, even after treatment was discontinued following a gradual shrinking of the reservoir.

**PTCs compared to HIV controllers**

If we consider whether these are unique subsets of patients, we see that HIV controllers, who spontaneously control HIV replication, mainly differ from PTCs in the way they regulate HIV replication (Figure 1). The two groups are similar with regard to HIV-DNA. However, PTCs have limited T-cell activation and a weak CD8 response, while HIV controllers regulate their HIV by a strong CD8 response due to a high level of protective genetic background. However, this takes place at the expense of a powerful CD8 CD4 T-cell activation that may not be optimal in the long run.

![Figure 1](image1.png)

**HIV controllers (HIC)**

Asymptomatic primary infection: low viral loads and high CD4 T-cell counts in PHI

- 80% HIC carry one protective HLA-class I allele

Generally strong HIV-specific T-cell responses with strong capacity to eliminate infected cells

Abnormal high levels of T-cell activation

Estimated frequency: 0.5% of HIV infected patients

**Post-Treatment Controllers (PTC)**

Symptomatic primary infection: high viral loads and low CD4 T-cell counts in PHI

- 57% PTC carry one HLA-class I allele associated with high viral loads

Generally very weak HIV-specific T-cell responses with poor capacity to eliminate infected cells

Low levels of T-cell activation

Estimated frequency: 5–15% of HIV infected patients interrupting a > 12 months-length treatment initiated in primary infection

**SALTO ANRS 116**

Treatment interruption in early treated patients with CD4 > 350 and VL < 50 000 cp/ml

- **95 patients**
  - Age 40 years (IQR: 36–45).
  - **Pre-cART values**
    - CD4: 454/mL (392–576)
    - VL: 4.3 log10 cp/mL (3.9–4.5)
    - CD4 nadir: 382/mL (340–392)
  - **Duration of cART**: 5.3 years (4.0–6.0)
  - **Baseline values**
    - CD4 cells: 813 cells/mL (695–988)
    - Total DNA: 206 copies/10⁶ PBMCs (IQR: 53–556)

- **12 months post TI**
  - 7/95 patients still had a VL < 400 cp/mL
    - (7.5%, CI: 3.7–14.6)
  - 4/7 kept a VL < 400 copies/mL up to 36 months
  - All had CD4 cell > 500/mm³
  - HIV DNA was the only significant predictor of maintaining VL < 400 cp/mL
    - med: < 10 vs 233 cp/10⁶ PBMCs

**Building an international cohort of PTCs**

The ANRS has recently announced in Kuala Lumpur their intent to build a large international cohort of PTCs in order to better understand the mechanisms underlyng viral control, i.e., HIV remission, and to identify predictive markers that are associated with viral control after TI. The main outcome is to identify patients in whom HAART could be safely interrupted.

For this purpose a definition of PTC has been established: a patient who has started ART at any time with a viral load > 2000 copies/mL and whose viral load has remained < 400 cp/mL for at least 12 months post ART interruption.

**More cases of PTC?**

- **A German case**
  - At IAS in July Jan van Lunzen reported the case of a 67-year-old man who had been treated with ART 3 months after HIV exposure and 1 month after seroconversion and remained undetectable for 5.5 years. Treatment was stopped in 2004 and up to the present (for 9 years) his plasma VL has remained < 20 cp/mL and DNA is undetectable [7].

- **The Mississippi baby**
  - This is a convincing case that HIV can be defeated when attacked very early in its natural course post infection if an ART defense is set up immediately.
  - A baby was born at 35 weeks to a mother who had been diagnosed with HIV at the time of delivery. The mother had a low viral load with about 4000 HIV RNA infected cells and to identify predictive markers that
copies/ml. The baby was infected with positive HIV antibodies, a viral load of about 10,000 copies/ml, and a positive HIV-DNA. He was treated at the 35th hour post birth. His viral load was controlled with ART until 18 months of age. The parents then missed follow-ups for 6 months, during which the baby did not receive any treatment. The big surprise was to discover that there was no RNA viral replication, HIV antibodies were negative, total DNA could not be detected in PBMC, and there were no immunologic signatures of an active HIV replication.

Towards a “happy end”
Last July at IAS in Kuala Lumpur, Deborah Persaud and her colleagues confirmed that this baby, now a few months older, was still functionally cured. This undoubtedly means that, once again, very early initiation of ART can prevent establishment of a latent reservoir and achieve a cure in children [8].

If one baby can be functionally cured, why not others?

Are there chronically infected patients with a functional cure?
There are currently few data to suggest that chronically infected patients with a functional cure exist. However, puzzling results have been published in the ANRS Salto study (figure 2) [9]. This investigation was designed during the 2000s, at a time when we thought that TI might be an option. It was to evaluate the safety of ART TI in early treated chronically infected HIV patients with preART viral loads < 50,000 cp/ml and CD4 cells > 350/mm³. The study sought to identify baseline factors predictive of the time it would take to reach fixed criteria to resume therapy, i.e., CD4 cell count < 300/mm³ and/or a CDC stage B or C event. HIV-DNA was then the only predictive factor for a longer continuation of ART. Seven patients maintained viral loads < 400 cp/ml for at least 12 months.

The only predictive factor for maintaining control of HIV-RNA among the 7 PTCs differed, and for the 88 non-controllers patients was a low HIV DNA (< 10 cp/10⁶ in PTC versus 233 cp/10⁶).

Whether chronically infected patients who represent the vast majority of the HIV-infected population can be found with extremely low viral reservoirs, and whether a functional cure is achievable, remain major clinical research issues. Studies are underway.

In summary
There is mounting data to suggest that the reservoir is a key element in the cure approach. Beyond research on drugs and interventions to decrease viral reservoirs, there are strong indications that there is hope for a functional cure in patients being currently treated. We have undeniably entered a new era of research that should be an encouragement for potentially infected individuals to be tested early, and physicians to treat early, with the hope of achieving a remission of HIV infection.

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 ViIV Healthcare.

References:
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Late Breaker abstract submission opens:
August 1, 2013

Late Breaker abstract submission deadline:
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C/O SABA-ADAGP, 2012
The path towards IFN-free therapy of hepatitis C

Part 3: We need to be prepared.

How to ensure access to novel antiviral therapies against hepatitis C?

In the last two issues of the magazine, I summarized the enormous recent development on the path towards interferon-free therapy of hepatitis C. First phase III data for the HCV polymerase inhibitor sofosbuvir have been published in the New England Journal of Medicine [1, 2] and the drug may be approved by FDA and EMA within a few months. Shortly after this, two additional HCV protease inhibitors (simeprevir and thereafter faldaprevir) should reach the market in both Europe and North America. Several additional phase III studies on different IFN-free therapies are ongoing and thus treatment options for all genotypes will very likely improve during the next two years.

I expect that by the end of 2015 we should be able to cure the far majority of HCV genotype 1 and 2 infected individuals within 3 to mostly 6 months of antiviral therapy — if the respective health system in each country will enable access to the different drugs. Tolerability of treatment will likely be much better than any IFN-based therapy. Thus, considering this background we are now facing various questions and issues. Should we still start antiviral therapies now with “the old” triple therapy with boceprevir or telaprevir? Are we promising too much to our patients and what kind of problems may arise with the new “wonder-drugs”? And finally and maybe most importantly, are we prepared for the new era of hepatitis C therapy and can we ensure that all patients in need will get access to treatment?

To start now or to wait for novel IFN-free therapies?

Treatment decisions for any disease should be based on a careful risk-benefit assessment considering the individual risk to develop clinical complications, the potential side effects of therapies and the efficacy of treatment. In certain settings, costs and access to therapy may represent additional important issues. Regarding hepatitis C, a detailed work-up of the patients’ profile is nowadays extremely important. While individuals with mild liver disease may indeed have the time to wait for more effective and better tolerable therapies, the situation is more complex in patients with more advanced liver disease. Thus, an accurate staging of liver fibrosis by either non-invasive or invasive (biopsy) methods is absolutely mandatory to enable an appropriate risk assessment.

The annual risk to develop hepatocellular carcinoma in HCV-infected patients with liver cirrhosis can be as high as 4% and hepatobiliary cancers have been described even in hepatitis C patients without complete liver cirrhosis. Fibrosis progression is accelerated in older patients and males; additional co-factors to develop liver cirrhosis include smoking, alcohol consumption, diabetes mellitus and HIV coinfection. Unfortunately, most of these factors are not only associated with a worse clinical course of liver disease but also with lower response rates to interferon-based antiviral therapies. E.g., the chance to achieve a sustained virological response to PEG-IFNa/ribavirin/boceprevir or telaprevir therapy in a >60 year old male patient with liver cirrhosis who has failed a previous course of IFNa/ribavirin therapy will be lower than 15%. At an early stage of treatment HCV kinetics may improve the predictive values for treatment failure and response; thus a rational approach is frequently to start therapy and to monitor response and tolerability of therapy.

Treatment is even more challenging as side effects of triple therapy are more serious in patients with advanced liver cirrhosis. Various “real-world” cohorts (e.g. the French CUPIC study [3] or single center cohorts from Germany [4] and other countries) described SAEs rates between 20–40% in patients with liver cirrhosis and even deaths were reported. However, triple therapy was rather safe and comparable to the pivotal phase III studies in other large cohorts. Data of more than 1600 patients treated in the telaprevir early-access-program have been presented by Massimo Colombo and co-workers [5]. Remarkably, not only the safety profile but also early efficacy was very well in line with the findings from the registration studies. Thus and taken together, the option of triple therapy with telaprevir or boceprevir should still be explored in patients with hepatitis C, in particular in countries and settings where access to the novel drugs may be delayed or is uncertain. However, unnecessary exposure to side-effect-prone therapies should be avoided in individuals with very mild liver disease.
Possible problems when using novel IFN-free therapies?

How easy and safe will IFN-free therapy of hepatitis C be? Pill burden, requirement for additional diagnostics, on treatment HCV RNA monitoring, novel side effects, duration of therapy, drug-drug interactions, resistance and costs are potential concerns.

Currently, boceprevir and telaprevir have to be taken two or three times a day. In addition ribavirin adds significantly to the overall pill burden. A full 48 weeks course of boceprevir/PEG-IFNa/ribavirin therapy requires intake of >5000 capsules or tablets. The good news is that most of the new therapies in advanced clinical development consist of 1–2 daily dosings frequently with only 1 pill per dose. Even if 2–3 DAAs are combined, single-tablet formulations are developed. Considering the overall rather short duration of therapies, I do not think that the pill burden will be a major issue in the treatment of hepatitis C.

Host genetics play an important role for antiviral response to interferon alfa therapy. The IL28b genotype has been identified as a strong predictor for SVR. Of note, the IL28b genotype has still been associated with viral clearance in some IFN-free treatment trials indicating that the host's innate immune response is contributing to HCV clearance even in DAA combination therapies. During the last year it became evident that the importance of the IL28b genotype becomes smaller when more potent treatment regimens are applied. It remains to be established for each DAA combination if IL28 genotyping may identify patients who could clear HCV with a shorter treatment duration. However, the test could still be of major importance in resource-limited settings where patients could be identified who will clear HCV infection with the probably much cheaper old standard-of-care of PEG-IFNa and ribavirin.

It will be absolutely crucial to investigate if novel IFN-free therapies will be really as safe as currently promised. Phase II data look very promising for most compounds but complete data sets of larger phase III trials are certainly needed. Transient early increases of bilirubin levels have been observed in several trials including novel protease inhibitors and other drugs. These bilirubin changes are not a sign of liver toxicity but can be explained by interactions with transporters and metabolizing enzymes. However, bilirubin increases can certainly be a concern in patients with liver cirrhosis and thus the differential diagnosis between liver decompensation and clinically irrelevant drug-reactions could become a challenge in single patients. Similarly, transient ALT elevations have been observed with some compounds that again could be a concern in patients with advanced liver disease. Photosensitivities and mild GI-symptoms occurred in other phase 2 trials but seem to be well manageable in most patients. Finally, ribavirin is still part of many regimens and certainly adds to the overall side-effect profile with hemolysis and anemia, itching and other skin reactions and dry cough. Ideally, future HCV therapy should therefore not only be IFN-free but also ribavirin-free.

Chronic HCV infection can be cured by IFN-free therapies within three months in the majority of cases. Thus, 12 weeks courses of DAA therapies are currently explored in the majority of trials. While 6–8 weeks of therapy may be sufficient for a proportion of patients, longer therapies of up to 24 weeks could increase response rates in individuals who otherwise would relapse after 12 weeks of treatment. Optimal treatment duration will need to be established during the coming years. However, as compared to previous treatment regimens used for the treatment of hepatitis C and also compared to most therapies in other chronic viral infection, duration of therapy will likely not become a major barrier to HCV therapy.

Drug-drug interactions are a potential challenge in the treatment of hepatitis C when telaprevir or boceprevir are used. While the potential for drug interactions may be lower for several novel compounds in clinical development, most HCV protease inhibitors and also drugs from other classes such as non-nucleosidic polymerase inhibitors and NS5A inhibitors are still metabolized via the cytochrome P450 3A4 or 3A5 enzymes. Importantly, studies investigating drug interactions should not only be performed in healthy volunteers but also in...
patients with advanced liver disease and in patients infected with hepatitis C, as drug levels may differ in patients as compared to non-infected individuals with a healthy liver.

More than $10^{12}$ HCV virions are produced every day. Thus, every possible resistant variant to antiviral drugs is present at any time in HCV infected patients, which could be selected during antiviral therapy. Subsequently, mono-therapies with the current 1st generation HCV protease inhibitors are not possible. The resistance profile and the resistance barrier obviously differ largely between compounds and different DAA classes. While non-nucleosidic polymerase inhibitors have a very low barrier to resistance, resistant variants to the nucleotide analogue sofosbuvir have not been selected yet in large phase 3 trials. Thus, the issue of potential treatment failure due to resistance will vary between different DAA regimens. HCV-resistant variants may persist for some time after treatment when the respective compound has been stopped – depending on the respective fitness of the specific HCV strain. Resistance testing may therefore be required in particular in patients who have failed a previous course of antiviral therapy if a drug from the same class with potential cross-resistance is used. I expect that resistance testing may initially play some role to select the optimal treatment regimen for each patient. However, in the long run with more different treatment approaches available, HCV resistance will very likely not represent a major problem in the treatment of hepatitis C.

How to ensure that all patients in need will get access to antiviral therapy?
The goal of HCV therapy must be to prevent liver-related morbidity and mortality in as many patients as possible and ideally to clear HCV from the entire population. To achieve this goal, it is not only required to increase the efficacy of antiviral therapies but even more importantly to ensure a high effectiveness on the population level. Effectiveness is determined by various factors including efficacy of a given therapy, screening rates, appropriate diagnostic procedures, initiation of therapy, access to therapy, and obviously adherence to treatment. Potential scenarios considering all these different factors are shown in the figure. It is quite obvious that it is now time to increase efforts for HCV screening, as

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**The best case scenario?**

\[
\text{Effectiveness} = 95\% \text{ Efficacy} \times 75\% \text{ Screening} \times 85\% \text{ Diagnosis} \times 85\% \text{ Initiation of treatment} \times 90\% \text{ Patient starts treatment} \times 90\% \text{ Adherence} = 42\%
\]

**A realistic goal**

\[
\text{Effectiveness} = 95\% \text{ Efficacy} \times 50\% \text{ Screening} \times 75\% \text{ Diagnosis} \times 80\% \text{ Initiation of treatment} \times 80\% \text{ Patient starts treatment} \times 80\% \text{ Adherence} = 18\%
\]

**Reality?**

\[
\text{Effectiveness} = 80\% \text{ Efficacy} \times 20\% \text{ Screening} \times 60\% \text{ Diagnosis} \times 50\% \text{ Initiation of treatment} \times 75\% \text{ Patient starts treatment} \times 60\% \text{ Long-term Adherence} = 2.2\%
\]
The kitchen table is more than a place for meals; it’s a place where families meet. But was the wood it’s made from harvested sustainably? Used to be hard to tell. Now shoppers can look for the Forest Stewardship Council (FSC) label to make sure wooden furniture and a variety of other products are forest-friendly. WWF helped start the FSC to ensure that the world’s forests are managed responsibly, and that people and wildlife who depend on forests can continue to do so long into the future. Help us look after the world where you live at panda.org/50
Therapies will very likely be available for almost every patient in the very near future, as IFN-related contraindications for therapy will no longer apply. And if general practitioners realize that treatment of hepatitis will become much easier and more successful, we could convince them that it is really worthwhile to test for HCV more frequently.

Concluding remarks
The era of IFN-free therapy of chronic hepatitis C will start already in 2014 for some genotypes and patients! By the end of 2015 we may be able to choose from several different treatment regimens and treatment of HCV genotype 1 and 2 infections should not be a major challenge any more. While various studies are ongoing to further improve response rates even in so called “difficult-to-treat” populations, we now need to make sure that all patients in need will get appropriate access to therapy.

Conflict of Interests
Honoraria for consulting or speaking (last 5 years): Abbott, Abvie, Biolex, BMS, Boehringer Ingelheim, Gilead, ITS, J/Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViV.

Research grants: Abbott, BMS, Gilead, Merck, Novartis, Roche, Roche Diagnostics, Siemens.

References:
2. Jacobson et al., Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options
5. Colombo et al., The telaprevir early access programme. EASL 2013 (abstract Journal of Hepatology)
When you posed this question to clinicians there used to be two main answers:

– Use a boosted protease inhibitor plus “recycled” TDF/FTC. Tenofovir would be “hyperactive” in the presence of M184V and together with a potent protease inhibitor might be enough to regain control of HIV replication. This has been my usual approach.

– Use a boosted protease inhibitor plus one antiretroviral from a new class of drugs – such as raltegravir – plus tenofovir. There might be other preferences regarding choice of the new class, for example Etravirine – not a new class but certainly a drug from a new generation of non-nucleoside reverse transcriptase inhibitor quite active against isolated K103N- or Maraviroc.

None of the supporters of these opinions could claim to have solid data to back their views. “Solid data” in medicine is synonymous of “clinical trial data”. Prior attempts to perform a clinical trial for rescue therapy of failed first-line non-nucleoside reverse transcriptase inhibitor based regimens, had been unsuccessful in the developed world. The reasons for the lack of such a trial were mainly two: virologic failures were rare and patients who failed – usually due to poor adherence – were in general not good candidates for enrolling into clinical trials.

The void of data in this scenario has recently been filled by two important clinical trials: SECOND-LINE [1] and EARNEST [2].

SECOND-LINE
The SECOND-LINE trial enrolled 558 patients – protease inhibitor and integrase inhibitor naïve – who had virologic failure after first-line combination antiretroviral therapy based on non-nucleoside reverse transcriptase inhibitors. The trial was carried out mainly in low and middle-income countries. Patients were randomized to receive lopinavir/ritonavir plus two or three recycled N(t)RTIs or lopinavir/ritonavir plus raltegravir. Of 492 patients with baseline genotypic resistance testing 89% had at least one N(t)RTI resistance mutation and 60% had M184V plus one or more additional N(t)RTI mutations. The most commonly prescribed NtRTIs were tenofovir (81%), emtricitabine or lamivudine (87%), and zidovudine (45%). Therefore SECOND-LINE compared fully active lopinavir/ritonavir plus partially active N(t)RTIs versus fully active lopinavir/ritonavir plus fully active raltegravir.

In sharp contrast with recent clinical trials of new antiretrovirals performed in the developed world, the population recruited in SECOND-LINE included a substantial proportion of females (more than 40%), and a high number of patients with low CD4 cell counts. The median CD4 cell count was approximately 190 cells/µL.

In the primary endpoint raltegravir was non-inferior to the N(t)RTIs arm. Proportion of patients with less than 200/50 HIV-RNA copies/mL were 82.6/71.7% and 80.8/70.5% in the N(t)RTIs and raltegravir arms respectively (Table 1). Incidence of adverse events was overall similar. Neutropenia was more common in the N(t)RTIs arm. Total cholesterol, LDL, and

<table>
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<th>HIV-1 RNA &lt;200 copies/mL</th>
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<th>LPV/r + RAL</th>
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<td>mITT Population</td>
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<td>178 (-4.73, 8.30)</td>
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<td>≤100,000 copies/mL at baseline</td>
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<td>Per protocol population</td>
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<tr>
<td>Non-completer = failure population</td>
<td>180 (66.4)</td>
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HDL cholesterol increased significantly more in the raltegravir group than in the N(t)RTIs group.

EARNEST
The EARNEST clinical trial enrolled 1277 patients who were protease inhibitor and integrase inhibitor naïve and were receiving first-line non-nucleoside reverse transcriptase inhibitors. Patients needed to have virological, immunological or clinical failure (defined according to WHO criteria) and viral loads higher than 400 HIV-RNA copies/mL. The trial was performed in Sub-Saharan Africa using a pragmatic approach since investigators did not have access to resistance testing or real time viral loads.

In EARNEST patients were randomized to three arms (Fig 1): lopinavir/ritonavir plus two or three N(t)RTIs – selected by the physicians – lopinavir/ritonavir plus raltegravir or lopinavir/ritonavir monotherapy after a fixed induction period of 12 weeks during which patients also received raltegravir. The primary endpoint for EARNEST was “good disease control” at week 96 defined as being alive and have had no new WHO stage 4 events and a CD4 cell count higher than 250 cells/µL and a viral load of less than 10,000 HIV-RNA copies/mL or higher than 10,000 HIV-RNA copies/mL without protease inhibitor resistance mutations.

The majority – almost 60% – of patients enrolled in EARNEST was female with very low CD4 cell counts: median was just 71 cells/µL. Approximately 40% had more than 100,000 HIV-RNA copies at baseline.

For the primary endpoint there were non-significant differences among the three arms (Fig 2). The lopinavir/ritonavir plus raltegravir arm failed to show superiority over the N(t)RTIs but met non-inferiority criteria. The lopinavir/ritonavir monotherapy arm did not meet the non-inferiority criteria compared to the N(t)RTIs arm. Looking at proportion of patients with less than 400 HIV-RNA copies/mL the lopinavir/ritonavir monotherapy arm underperformed compared to the other two arms. This lack of virological efficacy translated into...
a higher incidence of protease inhibitor resistance in the monotherapy arm (Fig 2). There were no statistically significant differences between the N(t)RTIs and the raltegravir arm in virologic control or resistance development.

In EARNEST lopinavir/ritonavir plus raltegravir had a trend toward better CD4 cell recovery than the N(t)RTIs arm. There were very few differences among the three arms with regard to adverse events.

The good performance of N(t)RTIs arms in these two trial is surprising. Many clinicians – including me – expected that in the setting in which EARNEST and SECOND-LINE were performed the combination of a fully active protease inhibitor plus a fully active integrase inhibitor would be superior to the combination of a fully active protease inhibitor plus a partially active N(t)RTIs combination. In low-income countries failing regimens are maintained much longer than in the developed world. Consequently one should expect the accumulation of multiple reverse transcriptase mutations that would severely compromise the activity of the recycled nucleosides. The TMC125-C227 trial was a clear example of this phenomenon [3].

It should be noted that in EARNEST and SECOND-LINE investigators followed simple WHO algorithms to select the new N(t)RTIs combination: basically use 3TC or FTC along with tenofovir if prior experience with thymidine analogs or along with AZT if prior experience with tenofovir. In SECOND-LINE tenofovir most likely maintained substantial antiviral activity since only 25% of the patients had at least two thymidine analog mutations [1]. Baseline genotype data in EARNEST are yet to be communicated. Nevertheless, both trials provide solid support for the use of WHO algorithms in the absence of genotypic testing. Interestingly the substantial activity of “recycled nucleosides” was predicted in a pilot trial performed in Thailand [4].

Monotherapy with lopinavir/ritonavir, even after a 12-week induction period of dual therapy with raltegravir, clearly underperformed in EARNEST. This is a less surprising result. Protease inhibitor monotherapy is an option only in patients who have remained virologically suppressed for at least six months and if viral load follow up is available. A prior trial performed in Africa [5] had shown that monotherapy without viral load monitoring entails an increased risk of resistance development. Besides, the Abbott 613 trial [6] demonstrated that short periods of virological suppression are not enough to guarantee the efficacy of protease inhibitor monotherapy.

EARNEST and SECOND-LINE have provided consistent data to equally support two strategies for rescue of first line non-nucleoside reverse transcriptase inhibitor regimens. A fully active protease inhibitor plus either “recycled” N(t)RTIs or an integrase inhibitor are excellent options in patients failing initial non-nucleoside reverse transcriptase inhibitor regimens. Defenders of both strategies have now data to back their arguments. However, since N(t)RTIs were the underdog in both trials, die-hard fans of nucleosides would consider themselves slightly more vindicated.

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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: