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EDITORIAL

This edition of HTB, might be appropriately tagged *The Conference Issue as it* includes reports from five meetings covering a wide range of treatment issues.

We lead with a report from a workshop held in South Africa in March, that reviews research into nanoformulations of antiretrovirals and whether there is the potential to improve on current formulations.

Reports from the annual BHIVA meeting focus on UK standards of care and new research.

This includes the first report indicating differences in cerebral function shown by MRI scans in HIV-positive children compared to carefully matched HIV-negative controls.

The BHIVA audit of HIV care in immigration removal centres focuses on the shocking treatment of people who have lost thier case to remain in the UK, that is a national shame.

Other reports look at the use of atazanavir during pregnancy, the ageing HIV population in the UK, the transition from paediatric to adult HIV care, and a new way to monitor bone mineral density.

The complexities of current and pipeline drugs are highlighted in reports from this year's pharmacology workshop, which had one of the strongest programmes for several years.

Atazanavir features in several reports including dosing during pregnancy and an intriguing review from leading HIC pharmacologist Courtney Fletcher suggesting that using 50 mg or ritonavir, rather than 100mg, may achieve a similar boosting impact. This has been a focus of community speculation since ritaonavir was initially used universally and produced at 100 mg doses.

We include a rapid report on HCV research from Jules Levin from the principal European liver conference (EASL) with links to NATAP's online reports.The treatment pipeline for hepatitis C is at a similar point today that the HIV pipeline was at in 1996, with the potential to revolutionise management within a few years – even though data on people living with HIV and HCV coinfection is still sparse.

Finally we continue with reports from CROI earlier in the year that as usual has so much to report that we include articles in several issues.

There are also of course additional journal reviews and basic science reports to keep you up-to-date in other news.

Happy summer reading.

CONFERENCE REPORTS

First Workshop on Nanomedicine for Infectious Diseases of Poverty

27–31 March 2011, Magaliesberg, South Africa.

Simon Collins, HIV i-Base

Introduction

An international workshop on nanomedicine for infectious diseases related to poverty was held in Magaliesberg, South Africa from 27–31 March 2011. The meeting was organised by Dr Hulda Swai, chair of the nanotechnology programme at the Council for Scientific and Industrial Research (CISR), a multidisciplinary science and research institute established in 1945 and funded by the South Africa Department of Science and Technology and Economic Commission for Africa (ECA). CSIR is one of two SA government-funded centres with nanomedicine programmes (the other is MINTEC). About 70 delegates from 20 countries attended the workshop.

Nanotechnology is being used in many different aspects of medical care including therapeutics, new drug delivery systems, diagnostics, imaging and surgical procedures. This article principally focuses on new formulations of drugs and drug delivery systems. Nanomedicine - the application of nanotechnology to medicine - has a relevance for HIV and related infections that rarely gets much attention.

Most of the focus on pipeline drugs for HIV and TB is on new compounds or new oral formulations of already approved drugs. However, for the last fifteen years various laboratories have been working with nanoformulations of antriretrovirals, though none have yet resulted in new medicines.

Size and scale

The simplest explanation of nanomedicine is based on a size ranging from 10-100 nm, though the EU definition has an upper range of 1000 nm. One nanometer is one-billionth of a meter (the width of about five atoms). See Table 1.

At this scale particles have different physical properties relating to surface to volume ratio, surface tension, surface charge and quantum dot effect and this can enhance drug bioavailability and solubility. Engineering molecules to target specific cellular and tissue targets has the potential to overcome barriers to sanctuary sites including the blood-brain barrier. Although nanotechnology is generally associated with the concept of the smaller particles, nanomedicine is actually based on drug formulations that are larger that pure drug molecules.

Figure 1: Comparative sizes of nanoformulation particles

Factor of 10	Metric size	Example size	Comment
10 (0)	1 m (1000 mm)	a child	
10 (-1)	100 mm	an orange	
10 (-2)	10 mm	a marble	
10 (-3)	1 mm (1000 um)	a pin head (1mm) grain of salt and an amobea (both ~500 um)	
10 (-4)	100 um	human egg (130 um) hair width (100 um)	
10 (-5)	10 um	Red blood cell (8 um) Chromosome (7 um) baker's yeast (3 x 4 um) mitochondrion (4 x 0.8 um) E. coli bacterium (3 x 0.6 um)	cells
10 (-6)	1 um (1000 nm)	measles virus (220 nm) HIV (130 nm) influenza (130 um) phage (bacteria virus) (70 x 200 um)	viruses, bacteria
10 (-7)	100 nm	hepatitis virus (45 nm) rhinovirus (30 nm) ribosome (30 nm)	viruses, bacteria
10 (-8)	10 nm	antibody (12 nm) tRNA (7 nm) haemoglobin (6.5 nm)	molecules
10 (-9)	1 nm (1000 pm)	adenine (1300 x 760 pm) methionine (1100 x 700 pm) glucose (900 pm) carbon atom (340 pm) water molecule (275 pm)	molecules
10 (-10)	100 pm	hydrogen atom (100 pm)	atoms
10 (-15)		nucleus	

Note: relative size from 10 (0) to 10 (-10) is similar to comparing the size of the world to a golf-ball.

Attaching compounds to larger molecules or encapsulating them inside other molecules can deliver a drug to the target site more accurately. This can overcome one of the main limitations of current oral formulations, where over 90% of medicines are excreted unused.

These improvements include:

- Better bioavailability, as an example this could be achieved by designing formulations that overcome hydrophobic or hydrophilic properties of individual molecules.
- Reducing drug wastage by overcoming protein binding and during oral absorption, where >90% of the active compound of antiretroviral drugs are cleared by blood filtration through the liver or kidneys before it is able to act on HIV.
- More targeted delivery should reduce the quantity of raw materials needed. This, is turn, has the potential to have the biggest impact on drugs used in resource-limited settings. Even though the drugs are much cheaper in poorer countries a much higher percentage of the costs is related to the active pharmaceutical ingredients (API).
- Reducing toxicities related to the metabolism of current oral formulations. For example, if a nanoformulation is designed to increase active drug levels inside cells while keeping blood levels low this has the potential to reduce toxicities related to systemic drug levels.

- Sanctuary site penetration by developing formulations that target immune cells that can cross the blood-brain barrier. In a similar way molecules may be designed to use cells to evade drug transporters such as P-gp that limit penetration of other sites.

However, while the potential benefits are promising, they also bring significant challenges to safety and regulatory approval.

Review of nanomedicine

The conference opened with a plenary lecture from Professor Ruth Duncan from Cardiff University, who has been a leading researcher for over 35 years in community-based research (Cancer UK), industry and academia. This talk emphasised the diversity of expertise needed from different fields including pharmacology, chemistry, medicine, ethics, health policy and politics.

Material science has been reducing the size of everything. Nanotechnology has been a rapidly evolving field that includes a top-down approach (where compounds are reduced) and a bottom-up approach (assembling polymer materials from the bottom up). Advanced drug delivery systems have been the focus of research for over 40 years. Nanomedicines can prolong action using new control/release technology, can target specific organs, cells, or organ space in an organelle, and improve bioavailability, including penetration of the blood-brain barrier.

Systemic distribution of most drugs involves a high level of dilution throughout the body and low concentrations at the active target. Nano-sized particles have different pharmacokinetics, delivering drugs by endocytosis and phagocytosis (cell engulfment) rather than passing directly through a cell wall. In addition to advancing drug delivery some nanoparticles are active in their own right. There are multiple targets through the lifecycle of infection and progression, including latent infection, each using different strategies.

The definition of nanomedicine incorporates engineering tools used outside the patient, biomedical and medical materials, imaging, and drug delivery and formulation. Designing nanomedicine should be easy. Starting with a target disease and product profile it should be possible to choose technologies and benchmark these against current treatment, with a clear stop-go development. Good lead candidates then require five years preclinical trials before getting to human studies. These drugs need a constant awareness of good laboratory practice (GLP), good manufacturing practice (GMP), good clinical practice (GCP) and ethics.

While nanomedicine has an unprecedented opportunity for invention, the lack of current knowledge across the field risks newer researchers repeating mistakes that earlier research has overcome. Against this is a caution that over exaggeration of the benefits will raise unrealistic expectations. Professor Gordon highlighted a limitation from the commercial focus on the target, using genomics and low molecular weight compounds, where 95% of compounds fail, probably because pharmacokinetics is not sufficiently important earlier in the development phase.

The first nanomedicines developed in the1990s based on liposome formulations are at the end of their patent life and are now coming through as generics. However each nanomedicine construct has a different design and route of delivery and every drug must be reviewed separately due to the specific challenges of manufacturing and constructing lipid-based nanoformulations. This field is more complex than generic antiretrovirals for example, where reproducing a compound that has similar pharmocokinetic properties is closely associated to similar safety and activity. From a safety perspective, producing new molecules, each piece (polymer, linker, etc) needs to be designed, requiring preclinical research before human studies. Many polymers for example are rejected for safety. Non-biodegradable polymers can accumulate, especially with long exposure (potentially lifelong) treatment. Pegylation itself covers a wide range of polymers. Currently the EMA opinion on generic formulations of Doxil etc is that bioequivilence does not exist for a liposome, only bio-similar properties and that pegylation on surface of liposome cannot just be duplicated as generic.

This complexity involves molecules travelling in the bloodstream at hundreds of miles an hour and the challenge is how to "stick your arm out to catch them at the right site". Shape and density are essential aspects of design including ionisation of polyelectrolytes and changes in cellular behaviours. Linkers need to be stable and release drug at the right time. Activating compounds can behave differently, including by sex. All of parts of the system will go somewhere and these need to be accounted for to ensure patient safety.

The importance of products used in clinical trials and subsequently approved to have passed good GLP and GMP was introduced as a theme that would be frequently revisited throughout the workshop.

Historical perspective of nanomedicines in cancer treatment

Dr Theresa Allen from the University of Alberta, Canada, and Alberto Gabezon from the Shaare Zedek Medical Center, Jerusalem gave lectures on the historical perspective of nanotechnology drawing on the impact that it has had on cancer therapy.

Although molecules on a nanoscale have been known since 1900 the term is associated with a lecture given by the Nobel physicist Richard Feynman in 1959 setting two challenges based on the theory that "atoms on a small scale behave like nothing on a large scale".

Nanotechnology based products already in common use include sunscreens (nanomolecules of titanium dioxide and zinc oxide are translucent, not white), self cleaning windows, pharmaceutical inks printing on medicines, and fabrics and coatings treated to variously repel dirt, water, bacteria, fungus or creasing.

In medicine, applications include imaging, diagnostics, drug delivery and therapeutic agents able to cross biological barriers. Nanomedicines deliver proteins, plasmid DNA, siRNA and antisense, enhanced permeability and retention (EPR) effect for

solid tumours (where molecules target tissues with increased permeability and are only released in inflamed tissue and tumour damaged sites).

Nanomedicines can improve properties of existing drugs, reducing toxicity and improving bioavailability (poor bioavailability currently wastes an estimated 68 billion dollars annually).

Liposome and other lipid-based systems are the first and most common lipid medicines. They are simple, self-assembling, with proven safety, with flexibility in terms of particle size, release rates and bio distribution. A principal behind nanoformulations is that a drug changes its biological pharmacokinetics and distribution properties, generally being protected from degradation and metabolism, and only behaving as a regular molecule when released as free drug.

Examples of widely used nanomedicines include Doxil (a pegylated liposome encapsulation formulation of doxorubicin used to treat Kaposi's sarcoma [KS] and ovarian cancer), the antifungal AmBisome (a liposomal formulation of amphotericin-B) and pegylated interferon (used with ribavirin to treat hepatitis C), Abraxone (a nanoformulation of paclitaxil used to treat metastatic breast cancer), Rapamune (formulation of sirolimus that is milled down and stabilised to become soluble) and Genoxol PM (a micelle formulation of paclitaxil). See Figure 2.

Figure 2: Examples of currently approved nanomedicines (currently 18 in the EU)

Name	Year	Clinical indication	Comment
Doxil	1995	Kaposi's Sarcoma (KS) Ovarian cancer	Pegylated liposome encapsulation formulation of doxorubicin
AmBisome	1997	Fungal infections, some antiprotazoal activity.	Liposomal formulation of amphotericin-B
PegIntron and Pegasys	2001, 2002	Hepatitis C	Pegylated interferons.
Abraxone	2005	Metastatic breast cancer	Nanoformulation of paclitaxil.
Genoxol PM	1999	As paclitaxil: ovarian, KS, breast cancers.	Micelle formulation of paclitaxil.
Rapamune	2000	Immunosuppressant to prevent organ graft rejection.	Formulation of sirolimus that is milled down and stabilised to become soluble.

The first oncology nanomedicine was Doxil, approved in 1995 as a treatment for AIDS-related KS under fast track orphan drug designation with development time of less than ten years. Subsequent approvals for relapsed ovarian cancer, metastatic breast cancer and as a substitute for doxorubicin resulted in Doxil becoming a commercial 'blockbuster' drug.

Doxil is a 100 nm diameter surface-graft pegylated long-circulating formulation where the active drug stays in a liposome, increases the concentration in sold tumours and slow releases in tumour cells. If ligands are added to particles, the resulting package can enter a cell in larger quantities and where it is then released.

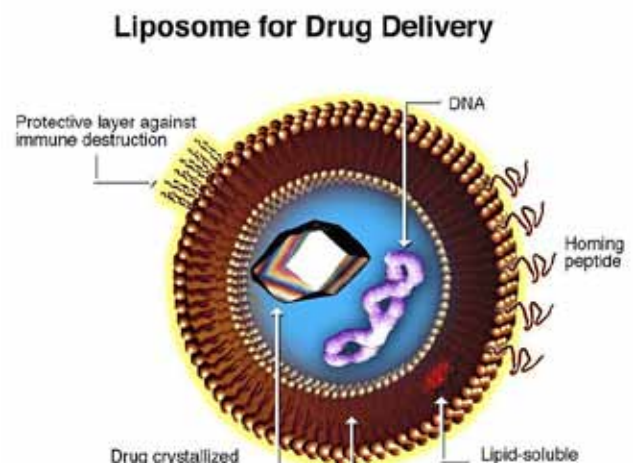
Compared to the original doxorubicin, Doxil dramatically reduced clearance by 1000-fold (extending the half-life to 50-70 hours) and increased drug accumulation in tumour tissue (approximately 80 ug vs 0.5 ug in skin a few millimetres away). This enabled a 4-fold lower dose of Doxil to have a 30% higher cure rate and reduction tumour volume. Unfortunately, in this early example, side effects were not always reduced and a higher rate of palmar-plantar erythema rash occured in some patients.

Nanomedicine can also incorporate combination chemotherapy in single constructs using drugs that use different mechanisms and that have non-overlapping side effects. It is possible to mix two liposomes or to add multiple targets on each (for example to target to nothing, CD20, CD19 or both and produce additive effects). In oncology, combination approaches to target and kill blood vessels in tumour tissue starve the tumour of oxygen and nutrients (though peripheral tumour cells survive). New blood vessels in a tumour are damaged, disorganised and with incomplete endothelial lining, allowing particles up to 400 nm to penetrate. An early paper in 1982 showed the potential of liposomes to carry adriamycin in mice. Conventional liposomes reduced cardiovascular risk but did not target liver tumours and were leaking drug in blood. Changing the lipid concentrations in new formulations changed pharmacokinetics with a 20-fold increase in concentrations in the tumour and 4-fold reduction in spleen, highlighting the importance of liposome design.

Targeted siRNA or antisense molecules can be effective but the high charge restricts transfer across cell membranes. Adding ligands enables a Trojan horse effect so a drug can cross cell membranes. For example, antibody-targeted coated cationic liposomes can be used to inhibit anaplastic lymphoma kinase (ALK) in neuroblastima-bearing mice with anti-GD2-targetted CCLs entrapping ALK-siRNA. Free siRNA cannot cross cells but can in a nanoformulation.

A brief history (and reality check) of the time it has taken to develop nanomedicines starts with the first description of liposomes in the early 1960s, which became the foundation of many formulations. Liposomes are 100 nm nanoparticle spheres (visicles) consisting of a phospholipid shell where one end is hydrophobic (usually the outer surface) and one is hydrophilic, enclosing an internal water phase. Drug molecules can be either encapsulated in the water phase or entrapped in the lipid shell. See Figure 3.

Figure 3: Cross section of liposome used for drug delivery



Source: http://en.wikipedia.org/wiki/Liposome

Further research led to the development of "stealth liposomes" in 1987 that used polyethylene glycol (PEG) studding on the outer coating to evade the mononuclear phagocyte immune system. AmBisome was approved in 1990, SMANCS (styrene maleic acid neocarzinostatin) in 1993 and Doxil in 1995. Nano-based drug delivery systems began entering mainstream medicine after 2005 and by 2011 there are over 38 nano products on market (worth $6.8 billion annually) with generic systems on the horizon.

The challenge for nanoformulations is to get an appropriate drug using appropriate delivery system that is the right size (not damaging other tissue) with low toxicit, for sufficient duration to solve an unmet medical need.

Crucially this needs to be at a sufficiently low cost to make it usable in a way that is safer and more effective than current treatments. Involvement of Indian companies has successfully radically reduced costs in many areas. In addition to reducing antiretroviral treatment from $10,000 to under $100 per year, the cost of hepatitis vaccinations have been reduced from $20 to $1, psoriasis treatment has been reduced from $20,000 to $100 and cataract surgery is carried out at 1% of the UK cost.

While the political aspects of new technology for infectious diseases have a high level of collaboration between countries at end stage distribution, the level is low for the early stages of research and development. The research presented at this workshop is going some way to address this.

A nanoformulation of paediatric efavirenz

Dr Alejandro Sosnik from the University of Buenos Aires discussed the potential applications of nanotechnology for paediatric formulations of HIV medicine. [4]

HIV in rich countries has become a largely manageable adult disease with more than 25 antiretroviral drugs and early diagnosis and access to HAART has reduced mother to child transmission to rates less than 1%. However, in most poorer countries HIV remains an acute disease with an estimated 1000 new paediatric infections globally each day, mostly in sub-Saharan Africa. Only 10% of children with HIV currently have access to treatment, and this drops to 2% in some regions.

Paediatric treatment in all countries is limited, with only 12 approved paediatric formulations. In particular, the lack of appropriate formulations, difficulties of dose adjustment, pill swallowing, and poor taste add to the challenges of enabling children to achieve the similar benefits from the advances seen in adult HIV care.

Dr Sosnik presented an example of a potential nanoformulation for efavirenz from his research group. Although a paediatric liquid formulation of efavirenz is produced by BMS this is not available globally and the indication is for children older than 3 years (and greater than 13 kg). The current oral formulation has lower bioavailability (by 40-45%) than capsule formulations and "tastes like liquid Vaseline" confirmed by associated weight-loss and diarrhoea. Interpatient and intrapatient bioavailability varies by 55-58% and 19-24% respectively.

The research goal and important unmet medical need is to develop a highly concentrated aqueous formulation with higher bioavailability, working with existing polymers like PEO-PPO polymeric micelles (poloxamers andoloamines) that are already commercially available in a broad spectrum of molecular weights and that already have a proven safety record (ie ethylendiamine).

So far, efavirenz-loaded micelles using surface aptamers to target CD4 cells have been produced in an oral solution and animal bioavailability data has been published. [5 - 9]. A micelle is an aggregate of compounds that lower the surface tension of a liquid and that are evenly dispersed.

In male rats the efavirenz-loaded micellar formulation was compared to that of a suspension prepared with the content of efavirenz capsules in 1.5% carboxymethylcellulose PBS solution (pH 5.0), and an EFV solution in a medium-chain triglyceride (Miglyol 812).

This formulation showed that the encapsulation of efavirenz, which is otherwise poorly water soluble, into polymeric micelles of different poly(ethylene oxide)–poly(propylene oxide) block copolymers significantly improves oral bioavailability and reduces the interindividual variability.

The solution has an improved taste, using only excipients approved by the FDA, and requiring less API has the potential to lower production costs.

A protocol has already been approved by an ethics committee in Buenos Aires for first in-human pharmacokinetic studies in HIV-negative volunteers, which if successful will progress to studies in HIV-positive adults and then HIV-positive children.

One of the discussion points after the presentation included the use of the formulation first in HIV-positive adults. This has been by the research group and not being linked to clinical HIV centres in Argentina. Expanding on this, Dr Soznik explained, "funding is difficult, industry studies are dominant. We need to now see if human exposure is similar to rats. Further animal studies might help but these are too expensive".

Other antiretroviral nanoformulations

Two other research groups at the workshop also presented data on formulations of antiretrovirals that are already approved, though none have yet been used in human studies.

Dr Lebogang Katata from CSIR in South Africa presented a poster on spray-dried efavirenz nanoparticles that was previously shown at the IAS conference in Vienna last year. [10, 11]

In this process, efavirenz is encapsulated in a polycaprolactone (PCL) polymer by a double emulsion spray drying technique using two organic solvents. The nanoparticles have an average size of 220.6 ± 0.950 nm when using ethyl acetate and 372.1 ± 19.96 nm using dichloromethane. This formulation also overcomes the hydrophobic nature of efavirenz to improve bioavailability and it has met other manufacturing standards including encapsulation efficiency and a smooth particle surface. It also results in prolonged release compared to formulations of free drug (suggesting weekly dosing might be possible). The group have also produced formulations of other antiretrovirals including AZT and d4T and plan combination formulations. But the timeline for human studies that were due to start this year is likely to be several years away.

A poster from Dr Helanie van der Merwe and colleagues at the North-West University, Potchefstroom, South Africa presented results from a third technology for producing nanoparticles of antiretrovirals. [12]

This research group has encapsulated abacavir and lamivudine (3TC) in visicles using a technology called pheroid, that resulted in higher bioavailability in in vitro studies.

Professor Anne Grobler from North-West University explained pheroid technology in an oral presentation. [13]

This talk started with an example of South African drug development of Exorex. This is a coal tar preparation for psoriasis that was initially developed by an American individual for his personal treatment and was then developed by the University into a global treatment, with the advantage of greater efficacy from using a much lower percentage of coal tar (1% vs 5%). [14]

Pheroids use a form of colloidal transport (usually at 100 nm size but sometimes larger) using long chain fatty acids, modified in different ways, ie with pegylation to have with hydrophilic tails. The technology is apparently easy, and inexpensive but it was originally difficult to predict the type of pheroid because it was not designed working with the active compound. All fatty acids are currently being taken safely by humans and the technology allows packaging of more than one drug in each vesicle.

In addition to abacavir and lamivudine the group have produced Pheroid formulations of antimalarial [15] and antituberculousis drugs [16, 17] that in preclinical development consisted of comparative in vitro and animal efficacy, bioavailability and pharmacokinetic studies and limited toxicology studies.

These studies reported enhanced rates of in vitro efficacy and in vivo bioavailability of first and second-line antimalarial compounds (including chloroquine, mefloquine, artemether and artesunate) and extended in vivo pharmackinetics and efficacy studies with formulation of tuberculosis drugs in mice.

Formulations of anti-TB medications

The CSIR research programme for formulations of TB medications is more advanced than that for HIV. Dr Rose Hayeshi, expanded on this programme. [18]

The group have encapsulated four first line anti-TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) with an encapsulation efficiency varying from 50-65% in particles of 250-400nm, using a multiple emulsion spray-drying technique.

The polymer used is poly(lactide-co- glycolide), (PLGA). The particles are taken up by macrophages in vitro indicating feasibility of intracellular drug delivery. Studies in mice using fluorescently-labelled PLGA nanoparticles indicated distribution to a broad diversity of tissues including macrophages of the peritoneum cell exudates that cross the blood brain barrier. Safety in mice after up to 10 days exposure was supported by histopathology on all major tissues including the spleen, lungs, kidney, liver, spleen, heart and the brain, which found no evidence of lesions.

Pharmocokinetic studies in mice showed that the drugs were released over a period of six days and the minimum inhibitory concentration for rifamicin and izoniazid was maintained over this period. Pharmacokinetic curves are similar to those of free

drug, with an initial increase from drug on the outside of the molecule followed by slow release compared to free drug.

A study in six TB-infected mice dosed daily for four weeks showed a reduction in colony forming units in spleen, liver although there is a need to target actively to lungs. When repeated over nine weeks an improved pathology was observed in the lungs. The nanoformulation is a weekly dose compared to current requirement for strict daily dosing.

The research group are now looking at scale-up plans for all formulations, improved preclinical, dose formulation and design and then first clinical studies. Currently single formulations are used but combinations are planned and the group is working with compounds held by the TB Alliance.

The discussion after this presentation focused on the need to clarify the mechanism and route of administration for TB drugs. This included whether the controlled release is in blood, tissues, or the cells. Oral formulations are difficult to target to cells, and compounds often need IV administration, which is not practical in resource-limited settings.

Aptamers in nanomedicine

Dr Makobetsa Khati, also based at the CSIR explained the utility of nanoaptamer biconjugates against infectious diseases with a focus on HIV. [19]

DNA or RNA aptamers were first developed in 1990 and are usually short strands of artifical oligonucleotides that are selected in vitro using SELEX (systematic evolution of ligands by experimental enrichment).

At a size that is less than 10 nm radius they can increase tissue specificity with minimal impact on the size of the formulation. Current uses include delivery of drugs to treat age related macula degeneration. Aptamers have the molecular recognition properties of monoclonal antibodies in terms of their high affinity and specificity. They are chemically simple, easy to make, have high target specificity, are non-toxic and non-immunogenic. Aptamers are used in many of the formulations already discussed in order to identify target cells for nanoformulations.

As aptamers can block entry this group has worked with oligonucleotides that are active against gp120. [15] The aptamer doesn't affect cell metabolism with toxicity, immune of cardiovascular cells. Over 80% of cells were sensitive with IC50 <1 nm and non-toxic at concentrations over 1000 nm.

In humanised mice Neff and colleagues showed reduction in viral load and a protective effect on CD4 counts with either the anti-gp120 aptamer or an aptamer-siRNA combination (that provided more extensive inhibition, resulting in a significantly longer antiviral effect that extended several weeks beyond the last injected dose). [20]

In the discussion after the presentation it was noted that the loss of the patent for the one aptamer on the market has dramatically reduced the cost (from $100,000 down to $25 per mg. However, as they are highly negatively charged this raised the issue of pharmacokinetics and side effects (clotting, platelets and immune effects).

Other subjects covered by the workshop

The workshop explored a wide range of other potential indications for nanomedicines that are not covered in this report including pulmonary fungal and parasite infections (including paracoccidioides brasiliensis), tuberculosis, malaria and prostate cancer.

It also included sessions on regulatory issues (with reference to the recent first meeting of the EMA on nanotechnology) and practical aspects of intellectual property, patents, technology transfer and international research collaborations.

Meeting summary

Many aspects of these new technologies are still in early development, even though some nanoparticle medicines have been used so extensively used that they are now off-patent. Each molecule has specific efficacy and safety issues dependent on the particular manufacturing process and cellular target.

Antiretroviral compounds show exciting pharmacological properties in in vitro studies. Particularly greater potency and that they require lower quantities of the API. The benefits from suspension formulations in development from researchers on nevirapine in South Africa and efavirenz in Argentina could have global impact as paediatric formulations. However, they still need to show proof of concept for overcoming obstacle associated with lymphocyte target cells.

The potential for TB nanoformulations may be closer than those active against HIV. The CSIR researchers have nanoparticle formulations of the four main first-line TB drugs and are working with the TB Alliance on newer compounds including TMC 207.

Some issues from a regulatory safety perspective are still not resolved . The FDA is more advanced than the EMA. Nearly all research is preclinical, with animal or in vitro data to support advantages of nanformulations. Particles based on molecules with established safety data should be easier to assess than totally new constructs. But one of the discussions on regulation of generic formulations of Doxil indicated that the complexity of the manufacturing process is likely to require in vivo safety and efficacy data from new studies in every molecule rather than just bioequivalence studies that enabled easier widespread use of oral antiretrovirals.

It is also important to balance expectations with likely realities for this research. Nanoformulations look as if they will offer exciting solutions to some specific currently unmet challenges rather than the potential to revolutionise treatment for every disease indication. Specific targeting of malignant tissue and its supportive vascular structures is revolutionising approaches to treatment of some cancers.

The political aspect of the workshop included the importance of technology being developed in countries where the demand for final medicines exists. With broadly 10% of global research focused on the 90% of global medical need. Less than 2% of patents are held in Africa and intellectual property and patent legislation are determined to benefit companies based in the developed world.

Of note, several recent reviews have summarised research over the last 15 years into nanoformualations of antiretrovirals. [21, 22]. See Figure 4.

This research is generally conducted by small independent groups working without sufficient funding to discover whether the potential of this technology can be realised for HIV care.

Given the potential advantage of providing reduced toxicity, more durable formulations with improved pharmacokinetics (ie targeting macrophages to increase concentrations in lymph tissue and dramatically extending half-life and dosing intervals) and at a reduced cost makes it frustrating that so far none of these formulations has yet progressed to human studies.

Figure 4: Examples of antiretroviral formulations with improved pharmacokinetics

ARV	Process	Aim/target	Study model	Effect	References
AZT, 3TC (also d4T, delavirdine, saquinavir)	Multiple polymers and solid lipids.	Aim to cross blood brain barrier by endocytosis and/ or phagocytosis to release drug intracellularly.	In vivo (cell)	i.e. permeability of AZT increased 8-20 fold and 3TC by 10-18-fold with PBCA. 100% increase across BBB.	Kuo et al. Int J Pharm 2005, 2006, 2007, 2008.
lopinavir	Emulsion templated, freeze-dried nanoparticle dispersions	Improve PK, develop PI formulation that doesn't need ritonavir boosting.	In vivo (cell)	Increased cellular uptake vs aqueous fomulation.	Smith D et al. CROI 2011.
d4T, AZT, 3TC, efavirenz	Spray dried PCL nanoparticles.	Improve PK, reduce dosing time and toxicity.	Mouse	Sustained release reducing dosing.	CSIR, South Africa
saquinavir	Nanoparticles with PEG and gene delivery	Increase PK, controlled release in mucosal tissue	In vivo	Large particles (200-500 nm) able to overcome challenge of mucosal PK.	Lai et al. Adv Drug Deliv Rev 2009.
Ritonavir, lopinavir, efavirenz, indinavir	Added to poly-caprolactone polymer in methylene chloride (multiple emulsion solvent)	Improve PK, reduce dosing time and toxicity. Cross blood-brain barrier and macrophage uptake.	In vitro	Drug detected after 28 days in PBMCs vs <2 days with unencapsulated formulation.	Destache et. CROI 2008. BMC Infect Dis, 2009.
CCR5 inhibitor (TAK-779)	Gold nanoparticles as a base scaffold.	Restore activity of an inactive CCR5 inhibitor.	In vitro	Proof of principal for drug delivery.	Bowman et al. CROI 2008.
AZT	PLA and PLA-PEG blend particles	Increased uptake by phagocytes.	In vitro	Improved phagocyte uptake with PLA.	Mainardes et al. J Pharm Sci 2009.
3TC, efavirenz	Tuftsin dendrimers	Target macrophages, prolong half-life	In vitro	Cellular uptake >20-fold higher vs free drug, prolonged release >140 hours, increased ARV potency at lower concentrations.	Dutta et al. Biophys Acta 2007 Eu J Pharma Sci 2008

Adapted from Malipeddi and Rohan (2010), Govender et al (2008) and others.

Further reading

The following links are included for further reading.

US NIH nanotechnology research. Links to an extensive NIH funded research programme established in 2005.

http://www.nibib.nih.gov/Research/NIHNano

http://www.nih.gov/science/nanotechnology/

EMA's First Scientific Workshop on Nanomedicine. September 2010.

Little information is online but a few large video files from some sessions are available to download.

http://vod.ema.europa.eu/100902/

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CONFERENCE REPORTS

17th Annual Conference of the British HIV Association (BHIVA)

6–8 April 2011, Bournemouth

Introduction

This year the annual BHIVA meeting was held in Bournemouth and included important studies reported below.

The abstract book from the conference, published as a supplement to HIV Medicine is available to download free as a PDF file from the BHIVA website.

http://www.bhiva.org/ConferenceAbstracts.aspx

Reports in this issue include:

- Atazanavir in pregnancy: 155 cases in London clinics
- Co-morbidity and late presentation – findings from an over 50s cohort
- Health outcomes for young adults with perinatally acquired HIV infection following transfer to adult services
- The use of calcaneal stiffness index to screen for osteoporosis in HIV-infected individuals
- Frequency and characteristics of long-term non-progressors and HIV controllers in the Chelsea and Westminster cohort
- Cerebral function in perinatally HIV infected young people and HIV uninfected sibling controls
- Treatment in seroconversion maintain HIV specific immune responses similar to long term slow progressors
- An audit of HIV care provision for Immigration Removal Centre patients

Atazanavir in pregnancy: 155 cases in London clinics

Polly Clayden, HIV i-Base

Atazanavir is increasingly used in pregnancy. There are limited data to guide this use.

In an oral presentation at the spring 2011 BHIVA meeting Miriam Samuel presented data from a retrospective case note review of atazanavir-exposed pregnancies at 12 London sites.

The review included 155 pregnancies in 145 women since December 2004.

The majority (118, 71.6%) of women were Black African and a small proportion were IDUs (5, 3.2%). Their median age was 32 years (15–47), 6 were Hepatitis B and 2 Hepatitis C co-infected. Only 15 (9.7%) were diagnosed this pregnancy and 105 (68%) were receiving HAART when they conceived. Their median CD4 was 401 cells/mm3 (range15–1161 cells/mm3).

Over half (93, 60%) conceived while receiving ATV; 20% of the remainder changed from another drug and 20% started with ATV first line in pregnancy. Only 9% of women received AZT and 16% abacavir but 72% received tenofovir as part of their nucleoside backbone.

Overall, atazanavir was well tolerated with 98/155 (63.2%) reporting no side effects. The commonest side effect was nausea, which was reported by 53/155 (34.2%) of women. Only 3/155 (1.9%) of women discontinued ATV due to side effects.

Of 21 women who switched to atazanavir due to GI side effects from a previous regimen (20 PI based), symptoms improved in 19. One woman stopped atazanavir due to persistent nausea.

There was a low overall incidence of hepatotoxicity; 9 (5.8%) women developed G1-4 raised transaminase. Of these, 5 women switched to atazanavir with pre-existing hepatotoxicity,1 from nevirapine and 4 from lopinavir/r. LFTs resolved in 3 women and 2 had persistent hepatotoxicity and ATV was discontinued in both cases.

Of the 130 women with viral load data available, 104 (80%) had <50 copies/mL at delivery. As would be expected, of the subset that started atazanavir in pregnancy (n=25), the proportion with an undetectable viral load increased with time on treatment: 29% and 72% with <12 and >12 weeks of HAART respectively.

Of the 133 deliveries with data available, 64 (48%) were by elective caesarean, and half the remainder by vaginal delivery and the other half emergency caesarean (both 26%). Pre-term delivery <37 weeks occurred in 13/130 infants (10%).

The 94 infants with neonatal bilirubin measured had a median 71umol/L(range 3-258 umol/L). Three neonates had phototherapy; 1 polycythaemic (bilirubin 258 umol/L); 1 infant haemolytic anaemia (bilirubin 109 umol/L) and 1 no other cause (bilirubin 194 umol/L). There was 1 congenital cardiac abnormality.

There was only one transmission, reported to be in utero, to a mother with a history of poor adherence.

The investigators concluded from this case series (the largest to date) that atazanavir is well tolerated in pregnancy with low toxicity and discontinuation rates. This applied to women conceiving on atazanavir, starting in pregnancy or switching. The infant safety data are reassuring.

C O M M E N T

Data on atazanavir PK during pregnancy at the PK Workshop, from the IMPAACT investigators in the US, reported in this issue of HTB, suggest that the dose of ATV/r should be increased to 400/100mg during the third trimester and the same considered during the second. The dose used in this study was 300/100 mg for the majority of the 149/155 women who received ATV boosted.

Currently, in the UK, most caregivers of pregnant women stick to the standard dose and some use TDM. However in this cohort only 17 women had routine third trimester TDM and 11 because of elevated viral load, despite it being available (though some don't think it is evidence based or cost effective). Although the third trimester levels in patients on tenofovir might be of concern, these investigators do not report treatment failure.

In this study women who conceived on HAART did very well and did not loose virological control in the third trimester.

The 80% rate with <50 copies/mL at delivery among women initiating HAART in pregnancy improved with longer duration of treatment, as would be expected.

This case note review goes back to 2004, so a good proportion of women will have been treated prior to last years report emphasising the importance of earlier initiation of HAART in pregnancy at higher viral loads to ensure viral suppression and in turn greater choice over mode of delivery.

Reference

Samuel M et al. Atazanavir in pregnancy: a report of 155 cases. 17th Annual BHIVA Conference, 6–8 April 2011, Bournemouth. Oral abstract O25.

Co-morbidity and late presentation – findings from an over 50s cohort

Charlotte Walker, HIV i-Base

The number of HIV positive patients accessing care in the UK who are aged over 50 years old has more than tripled between 2000-2009 from 2,432 to 12,063. Twenty percent of adults presenting for HIV care are now over 50. Previous cohort data showed an increased incidence of co-morbidities in the this patient group in relation to diabetes, hyperlipidaemia, cardiovascular and bone disease. [1, 2]

This study focused on the 504 patients aged over 50 out of a cohort of 2,700 patients attending Guys and St.Thomas' Hospital as of 1 December 2010. [3]

Median age was 54 years (range: 50-83, IQR: 52-59), 76.4% (n=385) were male, 54.8% (n=276) were white, 38.3% (n=193) were black, 47.4% (n=239) were MSM. Median age at diagnosis was 46 years (range: 22-82, IQR: 40-52) and the median time since diagnosis was 9 years (range: <1-28, IQR: 5-14). Of the group, 35.3% (n=166) were aged 50 or over at diagnosis.

The CD4 count at diagnosis was available for 298 patients: 216 cells/mm3 (range: 3-1100, IQR: 79-401), of which 70.8% (n=211) had a CD4 count <350 cells/mm3 (50.2% of whom were <50 at diagnosis), 24.2% (n=72) had a CD4 count of 201-350 cells/mm3 at diagnosis (48.6% of whom were <50 at diagnosis) and 46.6% (n=139) had a CD4 count of <200 cells/mm3 (51.1% of whom were <50 at diagnosis).

Their current treatment included 46% on NNRTI-based regimens, 36% on PI-based regimens and 11% on other regimens, 5% were HAART naïve, 1% not currently on HAART and 1% not documented. The median time on ARVs was 7 years (IQR: 3-11 years) and 55% of the group are still on their first prescribed ARV combination.

The cardiovascular health of these patients showed a median 10 year Framingham cardiovascular risk score of 12.3%. Hyperlipidaemia was present in 44% of patients (with or without a statin or other lipid lowering agent). Currently 15.7% of the group are smokers and 11.3% have diabetes. Cardiovascular events were seen in 7.3% (n=37) of patients including 7 myocardial infarctions, 6 strokes or

transient ischemic attacks, 8 positive coronary angiograms. Of these 37 people, 6 (16%) were current smokers, 29 (78.4%) were on statins and 5 (13.5%) were diabetics.

Bone health is always a concern in anyone over 50. In this study 134/504 patients (26.6%) have had a DEXA scan. Of those 134 people, 70 (52.2%) patients had results showing reduced BMD, 22 (16.4%) had a diagnosis of osteoperosis, 48 (35.8%) had a diagnosis of osteopenia, 8 (11.4%) were current smokers, 6 (8.6%) had concurrent renal disease.

Renal disease was documented in 39 patients (7.7%) and of these, 8 (20.5%) were currently on dialysis, 6 (15.4%) had documented HIVAN and 4 (10.3%) were diabetics.

Mental health problems were documented in 154/504 patients (30.6%), 104 (67.5%) of which had depression cited in their medical notes and 41 (8.1%) had documented memory impairment.

In conclusion, 35.3% of patients at Guy's and St Thomas' were aged 50 or over at diagnosis and 41.9% of patients aged over 50 presented with a CD4 count of <350 cells/mm3. This group have been found to have multiple co-morbidities affecting cardiovascular, renal, bone and mental health. Future work to follow on from this study will include comparisons between HIV positive patients over 50 and HIV negative patients over 50.

C O M M E N T

This report provides important cross-sectional data on the changing demographics at many clinics and the high rates of comorbidities and polypharmacy associated with ageing with HIV.

It is notable that only 16% of serious cardiovascular event and only 11% of reduced bone density events occured in current smokers and that the smoking rate for this cohort was only 16%. This perhaps indicates that patients have already made proactive lifestyle changes but still remain at high risk of residual complications.

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Health outcomes for young adults with perinatally acquired HIV infection following transfer to adult services

Charlotte Walker, HIV i-Base

Globally there are an estimated 2.1 million children under 15 infected with HIV. In the UK, the Collaborative HIV Paediatric Study (CHIPS) estimates the number of HIV-positive children to be 1,645 as of March 2010. Of these, 65% are over 10 years. A total of 262 have now been transferred to adult care.

As HAART has only been available since 1996, this is the first generation born with HIV to have survived to adulthood. As a result the long-term outcomes of HIV infection from birth and HIV treatment in childhood is still relatively uncertain.

This study aimed to examine the health outcomes of a cohort of 58 young people with perinatally acquired HIV infection that were originally part of the 900 clinic at St Mary's Hospital and are now in adult care. The 900 clinic provides services for young people who were diagnosed with HIV when they were children and have been treated atSt Mary's Hospital since their diagnosis.

This was a case note review of all HIV-positive young people seen at the 900 clinic between January 2006-2011.

The median age of transfer from paediatric care in this cohort was 17.2 years (range 16.3 – 18.6) and the current median age was 20.6 (range 16.9 – 26.1) years. Overall outcomes of the 58 young people includes 5 (9%) who were transferred to local adult services, 51 who were still patients at the 900 clinic and 2 (4%) died (one 20 year old female due to MDR end-stage HIV disease and a 21 year old female due to nephropathy and sepsis who had declined ART). There was no loss to follow up and 7 of the patients included in the study had babies.

Of the 51 patients currently at the 900 clinic, their median current CD4 count was 425 cells/mm3 (IQR: 30-1140). More specifically, 22% had a CD4 count of <200 cells/mm3, 8% had a CD4 count of 200-350 cells/mm3 and 69% had a CD4 count of >350 cells/mm3. Of the 51 patients, 5 (10%) were ART naïve, 14 (27%) were on NNRTI-based regimens, 18 (35%) were on PI-based regimens, 2(4%) were on triple NRTI-based regimens and 12 (24%) had stopped ART.

Focusing on the 34 patients currently on ART, the median CD4 count was 480 with 6 patients had a CD4 count of <200 cells/mm3 (of which 3 had detectable viral loads), 2 had a CD4 count of 200-350 (of which 1 had a detectable viral load) and 26 had a CD4 count of >350 (of which 1 had a detectable viral load).

As far as complications of disease and treatment were concerned, 2 patients required gastrostromy tubes to help adherence, 6 (12%) had severe lipodystrophy (5 requiring surgery and 1 injectable fillers), 11 patients had a history of mental health problems (this included 4 patients who had intentional overdoses requiring admission to hospital) and 7 (14%) who had been prescribed antidepressants at some point.

Of the 51 patients currently at the 900 clinic, 13 (25%) had been admitted to adult inpatient services for a median duration of 9 days (range 3-133), 2 for OIs (PCP and MAI), 4 following overdoses and 1 for CVA and osteonecrosis.

The investigators concluded that after 2 decades of living with HIV, 20% of the patients at the 900 clinic have severe immunosuppression (CD4 <200), 25% have required hospital admission an 3% died. There were high rates of co-morbidity, lipodystrophy and depression. There are also a small group of young people who remain off ART with low CD4 counts. Overall 85% of those on ART currently have undetectable viral loads.

C O M M E N T

The high rate of suppression on HAART (>85%) is a significant achievement given complicated treatment histories. Complicated balance for people still of treatment given the focus of long-term uncontrolled viraemia in adult patients, but also balanced with concern for long-term complications including cardiovascular and bone health.

Rate of psychiatric-related morbidity is especially concerning.

Ref: Wan T et al. Health outcomes for young adults with perinatally acquired HIV-1 infection following transfer to adult services. 17th Annual BHIVA Conference, 6–8 April 2011, Bournemouth. Oral abstract O31.

The use of calcaneal stiffness index to screen for osteoporosis in HIV-infected individuals

Charlotte Walker, HIV i-Base

Chelsea and Westminster Hospital reported results on the feasibility of using calcaneal stiffness as an indicator for osteoporosis in HIV-positive patients. [1]

Currently, a DEXA scan remains the gold standard measure of Bone Mineral Density (BMD) with a T-score of -1 and above being normal -1 to -2.5 indicating osteopaenia and <-2.5 indicating osteoperosis. However, DEXA scans are not available in all clinics, require extra patient attendance and radiation safety approval and cost around £60.

Several studies have previously shown a significant difference in BMD and fracture prevalence in both HIV-positive men and women. A population-based study by Triant et al. reported a high level of significance (p=0.0001 in men and p=0.002 in women) in bone fractures between over 2,200,000 HIV-negative patients and 8,525 HIV-positive patients. [2]

Scourfield et al at Chelsea and Westminster Hospital have found that a calcaneal ultrasound test using the GE-Achilles Insight machine is able to calculate the calcaneal stiffness index (CSI) and estimate the t-score. In HIV-negative people, CSI is currently used to predict hip fracture risk and vertebral fracture in post-menopausal women. However, this is not yet used in HIV-positive people.

The test is portable, takes 15 seconds to perform with minimal inter-operator variability. Osteopenia is most readily apparent in parts of the skeleton with high bone turnover as found in highly trabeculated, weight-bearing bones. The calcaneus (heel bone) is ideal as it is easily accessible, comfortable for the patient and weight-bearing.

The study aimed to correlate CSI with DEXA scan results in an HIV-positive population to assess the value and cost-effectiveness of using the GE-Achilles Insight machine as a screen tool for osteoperosis.

CSI measurements using the GE-Achilles Insight were performed on 100 people at random who had undergone a DEXA scan within the last 6 months. Their median age was 51 years (IRQ: 46-58), 85% were male, positive for a median of 15 years (IQR: 11-20) and with a BMI of 24 (IQR 21-26). Ethnicity of participants was 83% white Caucasian, 10% black African, 4% SE Asian, 1% black Caribbean, 1% Middle Eastern and 1% Indian. CSI scores were analysed to determine the optimum sensitivity. A cost-effectiveness analysis was then conducted.

The DEXA scan showed a prevalence of 15% osteoporosis and 55% osteopaenia. The CSI t-score showed 67% positive (estimated t-score =<-1.0) and 43% negative (estimated t-score >-1.0). This meant in the CSI t-score had 100% sensitivity but only 51% specificity compared to the DEXA scan. The positive predictive value of a CSI score of =<-2.5 for osteoporosis was 30%.

The cost-effectiveness analysis concluded that CSI is reliable and cost-effective method. If the 100 study participants involved in this study who had all previously undergone the DEXA scan had been screened first with CSI using a cut-off value of =<-1.0 this would have resulted in all cases of osteoporosis identified and 43 fewer DEXA scans which amounts to a saving of £2,795 (at an average cost of £65 per scan). However, due to the lower level of specificity, this would also have meant that 19 cases of oesteopenia were missed.

C O M M E N T

The cost of the GE-Achilles Insight is only £12,000 and for a minimal investment the considerable ongoing concerns of high levels of currently undiagnosed bone disease could be easily addressed in every large clinic.

EACS guidelines recommend repeat DEXA screening every 3-5 years in patients at higher risk of BMD and include HIV as a risk factor when using the FRAX calculator and age over 50 years as a risk factor if not using FRAX. The financial and health saving appear significant given aging positive population.

CSI t-scores are also quicker, easier and less inconvenient for the patient. Patient volunteers or staff without medical training can also perform these to reduce cost further.

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Frequency and characteristics of long-term non-progressors and HIV controllers in the Chelsea and Westminster cohort

Charlotte Walker, HIV i-Base

There is no internationally agreed definition of a long-term non-progressor (LTNP), in recent years more usefully referred to as a slow progressor, or an HIV controller (HIC). As a result several different interpretations of what parameters can make someone a LTNP or a HIC exist and these change both between and within countries. Either way these atypical patients are an important group to research as they have the potential to increase our understanding of HIV pathogenesis.

Mandalia and colleagues performed a retrospective review of the Chelsea and Westminster patient database to determine the prevalence of LTNPs or HICs and their associated rates of progression.

In this case LTNPs and HIC were defined as being HIV-1 positive for >7 years, with a CD4 T cell count >=450 cells/mm3, CD4 T-cell slope >=0 since entry to cohort, no OIs and naïve to ART. LTNPs were defined as having varying HIV-1 RNA plasma load which is mostly low but detectable whereas HICs maintain undetectable levels of viral load.

The study cohort looked at all patients registered from January 1988 to February 2010. CD4 count slope was derived from a random intercept model. A stable CD4 T-cell count was defined as patients whose CD4 T-cell count slope was >=0. Survival analyses were used to estimate time to HIV progression and data were censored at the most recent visit to the clinic.

Out of a total cohort of 14,227 patients, only 12 people were LTNPs and 1 person was a HIC. These 13 patients account for 0.38% of the total cohort that is in line with the results from a similar cohort in France where 0.4% of patients were LTNPs (although their inclusion criteria was slightly different).

Of the 1,204 patients who had been HIV positive for over 7 years with no history of ART, 965 had a CD4 count <450 cells/mm3 whilst 239 had a CD4 count of >=450 cells/mm3. The median time of disease progression in the cohort with CD4 count <450 was 4.0 years (IQR: 1.0-7.3), while those in the cohort with CD4 count >=450 had a median time to progression of 6.2 years (IQR: 2.0–9.6). The difference in time taken for disease progression was statistically significant (p=<0.001) suggesting that patients whose CD4 counts remain within “normal” range progress less rapidly.

References

Mandalia S et al. Frequency and characteristics of long-term non-progressors and HIV controllers in the Chelsea and Westminster HIV cohort. 17th Annual BHIVA Conference, 6–8 April 2011, Bournemouth. Oral abstract O28.

Cerebral function in perinatally HIV infected young people and HIV uninfected sibling controls

Charlotte Walker, HIV i-Base

A study by Ashby and colleagues aimed to characterise the neurocognitive function of young adults with perinatally acquired HIV (paHIV) infection and compare them to their HIV negative siblings or family members as aged matched controls.

The study had two arms, group 1 was made up of 33 perinally infected HIV-positive young people aged 16-25, group 2 was a control group of 14 HIV-negative young people matched by age who were aware of their family member's HIV status. Both groups completed a series of computerised neurocognitive tests, prospective and retrospective memory questionnaires (PRMQ) and the International HIV Dementia Scale (IHDS) testing. There was an additional sub-study, which involved Magnetic Resonance Spectroscopy (MRS) scanning of which all candidates were eligible. The MRS sub-study used 8 participants from group 1 and 4 from group 2.

The two groups were evenly matched in terms of demographics as shown in Table 1.

Of the 33 young people in group 1 who were HIV-positive, the median CD4 count was 444 cells/mm3 (IQR: 174-725), median CD4% was 21%, 18 (55%) young people had a HIV viral load of <50 copies/mL. The median age at diagnosis was 5 years (IQR: 0-9) with the median number of years since diagnosis of 15 (IQR: 13-20). Currently 26 (79%) of young people were on ARVs with the median age of starting ARVs being 13 years (IQR: 8-13) and the number of years since starting ARVs being 8.5 years (IQR: 4-13).

The results are shown in Tables 2 and 3. Results are mean scores unless otherwise stated. The only significantly different result from neurocognitive panel of tests between the two groups was the Prospective and Retrospective Memory Questionnaire (PRMQ) test where group 2 scored lower than group 1.

However, the MRS sub-study results showed significant differences between the two groups in terms of concentrations of Chol/Cr and MI/Cr. This indicates significant increases in cerebral metabolite inflammatory factors despite the fact that 5/8 people in group 1 had a plasma viral load of <50 cells/mm3.

Table 1: Baseline demographics

Parameter	Group 1	Group 2
Number of subjects	33	14
Number of subjects undergoing MRS	8	4
Age, years (mean, range)	20, 17-23	20, 16-24
Black/Mixed ethnicity (%)	85	86
Male gender, n (%)	11(33)	4 (29)
Recent recreational drug use (%)	2 (6)	1 (7)
Ever used recreational drugs (%)	13 (39)	6 (43)
English is first language (%)	29 (88)	13 (93)
Number of years education (years)	14	15

Table 2: Results of neurocognitive tests in HIV-positive children and age-matched HIV-negative siblings

Domain	Best score	Total score (n=47)	Group 1 (n=34)	Group 2 (n=14)	**p** (for group differences)
Speed	Low	10.64	10.66	10.57	0.27
Executive function	Low	17.83	18.18	17.00	0.68
Accuracy	High	3.02	3.03	2.99	0.78
IHDS	High	-	11.3	11.3	0.861
PRMQ (IQR)	Low	-	42 (36-49)	35 (28-43)	0.023

Table 3: Results of the sub-group MRS study

		Best score	Total score	Group 1 (n=8)	Group 2 (n=4)	p
Right Basal Ganglia	NAA/Cr	High	20.21	2.13	1.77	0.17
	Chol/Cr	Low	0.76	0.83	0.63	0.02
	MI/Cr	Low	3.30	3.43	3.03	0.09

Key: Cr = creatine, Chol = choline, MI = myo-inositol, NAA – N-Acetyl Aspartate

C O M M E N T

This is the first study to looked at neurological function in HIV-positive children using MRS with an appropriate HIV-negative control group.

While the clinical implications are unclear this is clearly an aspect of paediatric care that demands further research, especially given the expanding interest in questions related to HIV and ageing, and the potential role of HIV-mediated inflammation in people with unsuppresed viraemia.

Ref: Ashby J et al. Cerebral function in perinatally HIV infected young people and HIV uninfected sibling controls. 17th Annual BHIVA Conference, 6–8 April 2011, Bournemouth. Oral abstract O30.

An audit of HIV care provision for Immigration Removal Centre patients

Charlotte Walker, HIV i-Base

This year the BHIVA audit focused on the Immigration Removal Centres (IRCs) linked to Hillingdon Hospital in Uxbridge. It included eleven IRCs in the UK that dealt with people at all stages of an asylum application.

The audit was a retrospective review of medical notes from all patients seen between January 2008 and January 2010 and included all routine clinical data. The audit included patient characteristics, comparisons between practice and BHIVA/NAT advice on care for HIV positive detainees and comparisons between practice and recommended clinical guidelines.

The study included 116 patients referred to Hillingdon Hospital and a further 18 (16%) who were not seen because of deportation, release, transfer to another IRC or delays due to IRC regulations. Of the 18, 50% (9) were HIV positive. A total of 60/116 patients referred were HIV positive. Of these, 85% were on ARVs with prior care in 36 different UK centres. Their median age was 33 years (IQR: 28, 41). The median number of visits was 5 (IQR: 2, 6).

Following detention, 24 patients (39%) were deported, 20 (33%) released, 11 (18%) still detained at the time of analysis and 6 (10%) had unknown outcome. Of the 44 people removed from the IRC (24 deported and 20 released), only 8 (18%) were given prior notice (5 were given 1 week notice, 2 were given 2 weeks notice and 1 was dying). Of the 8 who had preparation for removal, none had a 3-month contingency supply of ARVs, 5 (63%) received information about HIV support facilities in onward destination and 4 (50%) had a medical summary letter.

Aspects of health care in detention centres where information was not available due to lack of records included missed ARV doses at time of arrest and detention, treatment interruption after detention, standards of medical care in detention.

The study concluded that the IRCs audited were not able to meet BHIVA/NAT standards for detainees. These included unbroken access for ARVs, availability of past medical information, preparation for removal of HIV positive detainees. It found that 82% of patients were not given prior notice of removal and of the 18% who were given notice the time was inadequate to meet the standard recommendations.

The authors recommended that data collection become standardised in centres for asylum seekers, that there is a national audit of IRC medical services, and greater advocacy to empower patients and medical staff to make BHIVA/NAT advice mandatory.

COMMENT

The Detention Centres Services Operating Standards Manual states that asylum seekers "must have available to them the same range and quality of services as the general public receives from the National Health Service". This is clearly not happening.

A similar report by Medical Justice looking at the clinical care of detainees with HIV released in 2011 concluded: "This report provides evidence to suggest that immigration detainees living with HIV have been subjected to practices which, in other circumstances, would be considered unacceptable. Our records indicate that breaches of the NAT/BHIVA advice are routine; they occur intentionally in some cases, and as a result of inadequacies in others. Taken together, these breaches amount to a system of care, which is frequently detrimental to the health and well-being of those detained for immigration purposes. The UKBA claim that they are neither willing nor able to enforce the provisions of the NAT/BHIVA advice within immigration detention."

How we treat failed asylum seekers awaiting deportation is to our national shame.

References:

1. Sabapathy K et al. An audit of HIV care provision for Immigration Removal Centre patients. 17th Annual BHIVA Conference, 6–8 April 2011, Bournemouth. Oral abstract O14.
   http://www.bhiva.org/documents/Conferences/Bournemouth2011/Presentations/110407/O14KalpanaSabapathy.pdf
2. Jon Burnett, Eden Fessahaye, and Anna Stopes, Detained and Denied: The clinical care of immigration detainees living with HIV. Medical Justice.
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CONFERENCE REPORTS

12th International Workshop on Clinical Pharmacology of HIV Therapy

13–15 April 2011, Miami

The following reports from the pharmacology workshop this year are selected from excellent more extensive coverage from both Liverpool University's HIV drug interaction website and natap.org.

Please visit these index pages for full coverage from the workshop.

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=543

http://www.natap.org/2011/Pharm/Pharm.htm

Abstracts from the workshop, published in Reviews in Antiviral Therapy & Infectious Diseases 2011_3 are available to download from the meeting website.

http://www.virology-education.com/index.cfm/t/Workshop_Materials/vid/34792068-01CF-4196-986A8271C014BBD7

Selected presentations are also available online.

http://regist2.virology-education.com/2011/12HIV_PK/13_April.html

Articles included in this issue of HTB are:

- Quad reduces levels of oral contraceptives
- Elvitegravir/cobicistat and acid reducing agents
- Lopinavir/r reduces levels of rifabutin
- Cobicistat has little impact on CYP2D6 and CYP2B6
- Atazanavir levels indicate need for higher dose during pregnancy
- Once-daily 150-mg maraviroc explored in people taking atazanavir/ritonavir
- Lopinavir troughs lower in children on once-daily dose with efavirenz
- Dose optimisation: 50 mg ritonavir-boosting, 3TC dosing and raltegravir once-daily

Quad reduces levels of oral contraceptives

HIV-druginteractions.org

This open-label fixed-sequence study investigated the pharmacokinetics of a combined oral contraceptive containing 25 ug ethinylestradiol and norgestimate with a fixed dose combination tablet containing elvitegravir, cobicistat, FTC and TDF ("Quad").

Steady-concentrations of ethinylestradiol, norelgestromin (the active metabolite of norgestimate), EVG and cobicistat were determined in 15 HIV-negative women receiving the oral contraceptive alone or with the "quad" tablet. Coadministration decreased the AUC of ethinylestradiol by ~25% and increased the AUC of norelgestromin by ~2-fold. Concentrations of elvitegravir and cobicistat were within the range of values observed in previous studies. Changes in progesterone and FSH were similar in both treatment phases, but changes in LH were greater in the combination phase.

In light of the decrease in ethinylestradiol, it is recommended that when coadministered with the "Quad" tablet, oral contraceptives should contain at least 30 µg ethinylestradiol.

Ref: German P et al. EVG/cobicistat/FTC/TDF and oral contraceptives Pharmacokinetic interaction between norgestimate/ethinyl estradiol and EVG/COBI/FTC/TDF single tablet regimen. Oral abstract: O_17.

Elvitegravir/cobicistat and acid reducing agents

HIV-druginteractions.org

The effects of omeprazole (20 mg once daily) or famotidine (40 mg once daily) on the pharmacokinetics of EVG and cobicistat were studied in HIV−negative subjects (n=11 per group).

When omeprazole was administered 2 hours prior to elvitegravir and cobicistat the AUC and Cmax of elvitegravir increased by 10% and 16%, but those of cobicistat decreased by 8% and 10%. Separating omeprazole and EVG and cobicistat by 12 h had

no effect (<10% change) on the AUC or Cmax of elvitegravir or cobicistat. Administration of famotidine 12 h apart from elvitegravir and cobicistat had no effect (<10% change) on the AUC or Cmax of elvitegravir or cobicistat.

Similar results were observed in a separate study (n=16) of the simultaneous coadministration of famotidine with elvitegravir and cobicistat. No dosing restrictions are necessary on the administration of EVG and cobicistat with proton pump inhibitors.

Based on the available data, elvitegravir and cobicistat should be administered simultaneously with, and/or 12 hours after, dosing of H2 receptor antagonists.

Ref: Mathias A et al. Effect of acid reducing agents on the relative bioavailability and pharmacokinetics of cobicistat boosted elvitegravir. 12th International Workshop on Clinical Pharmacology of HIV Therapy, 13–15 April 2011, Miami. Poster abstract: P_13

Lopinavir/r reduces levels of rifabutin

HIV-druginteractions.org

This preliminary study investigated rifabutin and LM565 (25 O desacetyl rifabutin) exposures in 14 HIV/TB coinfected patients starting LPV/r (400/100 mg twice–daily) and rifabutin (150 mg 3 times weekly). Control values for rifabutin alone (300 mg once–daily) were obtained prior to starting LPV/r. Control values for LPV/r alone were obtained 10 weeks after stopping rifabutin. Pharmacokinetic parameters (median, range) are shown in the Table 1.

Rifabutin AUC was below the target of 4.5 µg.h/ml in 42% of patients at week 2 of therapy and in 28% of patients at week 6 of therapy. The change in LM565 AUC was significantly greater than the change in rifabutin AUC. When given with LPV/r, rifabutin 150 mg three times weekly may result in low rifabutin concentrations.

Table 1: Rifabutin, LM565 and lopinavir levels administered separately and together

	Rifabutin alone	**Rifabutin + LPV/r week 2**	**Rifabutin + LPV/r week 6**	**LPV/r alone**
Median (range) Rifabutin				
AUC 0-24h (g.h/mL)	330 (106-1950)	4.2 (1.9-5.5)	2.4 (1.3-6.4)	
Ctrough (ng/mL)	91 (11-152)	87 (20-104)	42 (8-114)	
Cmax (ng/mL)	330 (106-1950)	309 (106-564)	239 (151-526)	
Median (range) LM565				
AUC 0-24h (g.h/mL)	0.7 (0.18-2.4)	1.6 (0.35-2.6)	1.6 (0.79-2.4)	
Ctrough (ng/mL)	4 (3-10)	33 (10-71)	30 (13-75)	
Cmax (ng/mL)	52 (32-72)	115 (90-190)	122 (40-221)	
Median (range) LPV				
AUC 0-24h (g.h/mL)		143 (86-278)	137 (47-303)	124 (75-139)
Ctrough (ng/mL)		10 (5.6-20)	8.8 (1-17.6)	7.8 (5.1-9)
Cmax (ng/mL)		14.4 (9.2-34)	16.3 (15.4-33)	13.7 (7.8-20.9)

C O M M E N T

This study highlights the importance of the active metabolite when rifabutin is given with LPV/r.

Ref: Cusato M et al. Pharmacokinetic evaluation of rifabutin and its active metabolite LM565 coadministered with lopinavir/r in HIV infected patients. 12th International Workshop on Clinical Pharmacology of HIV Therapy, 13–15 April 2011, Miami. Oral abstract: O_14.

Cobicistat has little impact on CYP2D6 and CYP2B6

Mark Mascolini, NATAP.org

Cobicistat, the boosting agent being developed for combination with the integrase inhibitor elvitegravir and protease inhibitors, had little impact on two key drug-metabolizing enzymes (CYP2D6 and CYP2B6) or on the drug transporter P-glycoprotein, according to results of a three-part study by Gilead Sciences [1].

In a phase 2 trial, a once-daily single pill coformulation of elvitegravir/cobicistat plus tenofovir/emtricitabine controlled viral replication as well as Atripla, the once-a-day one-pill combination of efavirenz, tenofovir, and emtricitabine, through 48 weeks in previously untreated people [2]. Average elvitegravir trough concentration in that study exceeded the protein binding-adjusted 95% inhibitory concentration of elvitegravir by a factor of 10. In a 44-person pharmacokinetic study, cobicistat boosted elvitegravir to levels equivalent to those reached with ritonavir boosting [3]. Unlike ritonavir, cobicistat has no anti-HIV activity.

Cobicistat is a strong inhibitor of CYP3A, but earlier studies showed that it does not inhibit the enzymes CYP1A2, CYP2C8, CYP2C9, or CYP2C19 and that it is a weak inhibitor of CYP2D6 and P-glycoprotein. The new study evaluated the impact of cobicistat on drugs whose metabolism is strongly affected by CYP2D6 (desipramine), CYP2B6 (efavirenz), or P-glycoprotein (digoxin).

Researchers enrolled 10 people in the desipramine group, 25 in the digoxin group, and 18 in the efavirenz group. Study participants took 150 mg of cobicistat or the probe drug (desipramine, efavirenz, or digoxin) in one of two sequences: (1) cobicistat once daily for 9 day, then one dose of cobicistat and one dose of the probe drug, then a washout period with no drugs, than one dose of the probe drug, or (2) one dose of the probe drug, a washout, cobicistat once daily for 9 days, then one dose of cobicistat and one dose of the probe drug.

Nine people originally assigned to desipramine, 22 assigned to digoxin, and 17 assigned to efavirenz completed the study. Ages averaged 35 in the desipramine group, 33 in the digoxin group, and 33 in the efavirenz group. Respective average weights were 76 kg, 71 kg, and 74 kg. About two thirds of volunteers were white.

Most treatment-emergent toxicities were mild (grade 1), except for a single case of treatment-emergent gastroesophageal reflux after 9 days in the digoxin group that required withdrawal from the study.

Coadministration of cobicistat with desipramine led to a 58% to 65% increase in desipramine area under the concentration-time curve (AUC) and to a 24% increase in desipramine maximum concentration (Cmax). Efavirenz Cmax fell about 13% with cobicistat, while digoxin Cmax rose about 41%. Efavirenz and digoxin AUC changed little with cobicistat. When taken with the probe drugs, cobicistat reached levels similar to those recorded in earlier studies of this boosting agent.

The Gilead team concluded that cobicistat may be classified as a weak CYP2D6 inhibitor since desipramine exposure rose less than 2-fold with cobicistat. The lower efavirenz Cmax and higher digoxin Cmax with cobicistat appear not to require dose modifications.

The investigators believe that additional drug-drug interaction studies are not needed to explore the impact of cobicistat on drugs affected by CYP2D6, CYP2B6, or P-glycoprotein.

References

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Atazanavir levels indicate need for higher dose during pregnancy

Mark Mascolini, NATAP.org

An atazanavir/ritonavir dose of 400/100 mg daily during the third trimester of pregnancy yielded concentrations equivalent to concentrations with 300/100 mg daily after delivery in women taking the protease inhibitors (PIs) with or without tenofovir [1]. IMPAACT P1026s investigators recommended 400/100 mg for the third trimester, regardless of tenofovir use, and suggested it should also be considered for the second trimester.

Previous work by the IMPAACT team found that plasma exposure of ritonavir-boosted atazanavir decreased by about 30% during pregnancy and by an additional 30% when tenofovir was part of the regimen [2]. Those findings led the researchers to propose raising the atazanavir/ritonavir dose from 300/100 mg to 400/100 mg during pregnancy. The new study assessed the impact of the higher dose.

This study is part of IMPAACT P1026s, an ongoing nonblinded trial of antiretroviral pharmacokinetics in HIV-positive pregnant women that includes women taking atazanavir/ritonavir. With or without tenofovir as part of their regimen, these women took 300/100 mg of atazanavir/ritonavir once daily during the second trimester, 400/100 mg once daily during the third trimester, and 300/100 mg from delivery through 2 weeks postpartum. The IMPAACT investigators conducted intensive 24-hour sampling at steady state during the second and third trimester and postpartum.

Atazanavir pharmacokinetic targets were the estimated 10th percentile area under the concentration-time curve (AUC) of 29.4 mcg*h/mL in nonpregnant adults and a 24-hour concentration of 0.15 mcg/mL. The researchers also collected maternal and umbilical cord blood samples at delivery and measured infant bilirubin concentrations 24 to 48 hours and 4 to 6 days after birth.

Of the 59 study participants, 31 took atazanavir/ritonavir with tenofovir and 28 without tenofovir. Twenty-three women were Hispanic, 16 black, 16 Asian, 3 white, and 1 with unrecorded race. Median age and weight at delivery were 29.7 years and 71.4 kg. Median gestational age was 38 weeks and median birth weight 3088 grams.

Among women taking atazanavir/ritonavir with or without tenofovir, median AUC and trough concentrations, and numbers of women who met AUC and trough targets in each trimester showed better exposure with the 400/100-mg dose than with 300/100 mg during pregnancy, see Table 1.

Table 1: PK levels of atazanavir with and without tenofovir during pregnancy

	without tenofovir	with tenofovir
Median (range) atazanavir AUC		
Second trimester (300/100 mg)	24.6 (9.2 to 93.8) mcg * h/mL	26.2 (6.8 to 60.9) mcg * h/mL ($P < 0.05$ versus postpartum)
Third trimester (400/100 mg)	46.6 (11.0 to 88.3) mcg * h/mL	37.9 (9.3 to 88.2) mcg * h/mL ($P < 0.05$ versus postpartum)
Postpartum (300/100 mg)	55.1 (9.9 to 99.5) mcg * h/mL	58.2 (7.5 to 134.9) mcg * h/mL
Women who met target atazanavir AUC		
Second trimester (300/100 mg)	3 of 6 (50%)	7 of 17 (41%)
Third trimester (400/100 mg)	22 of 28 (79%)	23 of 31 (74%)
Postpartum (300/100 mg)	17 of 27 (63%)	27 of 29 (93%)
Median (range) atazanavir 24-hour concentration		
Second trimester (300/100 mg)	0.31 (0.09 to 2.82) mcg/mL	0.44 (0.12 to 1.06) mcg/mL ($P < 0.05$ versus postpartum)
Third trimester (400/100 mg)	0.74 (0.14 to 2.09) mcg/mL	0.59 (0.17 to 2.06) mcg/mL ($P < 0.05$ versus postpartum)
Postpartum (300/100 mg)	0.88 (below quantitation to 2.73) mcg/mL	1.24 (0.24 to 3.65) mcg/mL
Women who met target 24-hour atazanavir concentration		
Second trimester (300/100 mg)	5 of 6 (83%)	16 of 17 (94%)
Third trimester (400/100 mg)	27 of 28 (96%)	31 of 31 (100%)
Postpartum (300/100 mg)	17 of 22 (77%)	29 of 29 (100%)

Median atazanavir cord blood concentration measured 0.15 mcg/mL (range below detection to 1.33), and median ratio of cord blood to maternal delivery concentration was 0.18 (range 0.03 to 4.08). Among 48 women with a detectable atazanavir concentration at delivery, median atazanavir concentration stood at 1.38 mcg/mL (range 0.18 to 5.63). Median ratio of cord blood/maternal atazanavir was 0.14 (range 0.02 to 4.08).

The researchers recorded 37 grade 3 or 4 maternal adverse events, including 23 elevated bilirubin values. All bilirubin levels in infants were normal.

The IMPAACT investigators concluded that atazanavir clearance is increased during the second and third trimesters. Atazanavir exposure improved from the second to the third trimester, when the dose rose from 300/100 mg to 400/100 mg once daily. After delivery, atazanavir concentrations with the 300/100-mg dose equaled or exceeded concentrations with the higher dose in the third trimester.

The researchers proposed that 400/100 mg of atazanavir/ritonavir provides adequate atazanavir exposure during the third trimester "and should be considered during the second trimester as well."

C O M M E N T

The authors commented that their data support use of 400/100 atazanavir/ritonavir dosing in both the second and third trimester.

The FDA is expected ask for a change in the SPC but we haven't yet heard what the EMA will do.

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Etravirine lowers levels of maraviroc given at 300 or 600 mg twice daily

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Etravirine may greatly lower concentrations of maraviroc when the drugs are taken without a ritonavir-boosted protease inhibitor (PI), according to results of a retrospective, multicenter French analysis of antiretroviral-experienced people [1]. Maraviroc concentrations were low regardless of whether this CCR5 antagonist was dosed at 300 or 600 mg twice daily.

Etravirine, the most recently licensed nonnucleoside, induces the CYP3A4 enzyme, while maraviroc is a CYP3A4 substrate. As a result, giving the drugs together may result in lower-than-normal maraviroc concentrations. Thus, a maraviroc dose of 600 mg twice daily is recommended with etravirine. Combinations of antiretrovirals with different mechanisms and with activity against virus resistant to the first three antiretroviral classes are favoured constituents of salvage regimens, which often exclude PIs because of resistance or toxicities.

To assess the impact of etravirine on maraviroc in treatment-experienced people, French investigators conducted this retrospective multicenter study of 67 people taking etravirine and maraviroc with or without one or two nucleosides, with or without raltegravir, and without a PI. The researchers excluded people taking other drugs likely to interact with maraviroc, and they excluded people

with undetectable maraviroc levels. They figured trough concentrations (Ctrough, collected 12 hours after dosing) and Cave (any post dose concentration), and they set the target Ctrough at 75 ng/mL.

The 49 men (73%) and 18 women studied had a median age of 50 (IQR 46 to 55) and a median weight of 62 kg (IQR 61 to 70). Thirty people (45%) were taking 300 mg of maraviroc twice daily, 37 (55%) were taking 600 mg twice daily, and 50 (50%) were also taking raltegravir. Everyone took 200 mg of etravirine twice daily. The investigators analysed 106 samples to calculate Cave and 82 to calculate Ctrough.

In people taking maraviroc at 300 mg twice daily, median Cave and Ctrough were 63 ng/mL (IQR 29 to 127) and 53 ng/mL (IQR 27 to 84); for people taking 600 mg twice daily, median Cave and Ctrough were 62 ng/mL (IQR 35 to 90) and 59 ng/mL (IQR 36 to 84).

For the whole study group, 62% of Cave values and 67% of Ctroughs stood below the target of 75 ng/mL. Among people taking 300 mg of maraviroc twice daily, 60% of Cave values and 71% of Ctroughs were under 75 ng/mL. Among people taking 600 mg twice daily, 64% of Cave values and 65% of Ctroughs were under 75 ng/mL. Even when the Ctrough cutoff was 50 ng/mL, 39% of Ctroughs were suboptimal, regardless of maraviroc dose. So in this population, doubling the maraviroc dose did not lower the risk of subtherapeutic troughs.

Median etravirine Ctrough was 696 ng/mL (IQR 474 to 1068), which is about 180-fold higher than the protein binding-adjusted 50% effective concentration for etravirine against wild-type (nonmutant) virus. Median etravirine Ctrough did not differ significantly between people taking 300 mg of maraviroc twice daily and people taking 600 mg twice daily (813 and 679 ng/mL).

“Surprisingly,” the French team concluded, “maraviroc Ctroughs were very similar” with both maraviroc doses and “quite lower” than concentrations seen when the regimen contained a ritonavir-boosted PI. Those findings suggest that increasing the maraviroc dose has “a modest effect” on CYP3A4 induction by etravirine.

Two small cases series of treatment-experienced people starting maraviroc, etravirine, and raltegravir suggest that the combination can promote a good virologic response through 48 weeks [2,3].

C O M M E N T

The method of determining Cavg here is different from that used previously by Pfizer. There was considerable discussion about maraviroc target concentrations.

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Once-daily 150-mg maraviroc explored in people taking atazanavir/ritonavir

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HIV-positive people taking standard-dose atazanavir/ritonavir plus 150 mg of maraviroc once-daily had lower maraviroc maximum concentrations (Cmax) and average concentrations (Cavg) than HIV-negative people taking 300 mg of maraviroc twice daily without atazanavir/ritonavir. But in this pharmacokinetic modeling study, maraviroc minimum concentration (Cmin) and effective constant concentration (ECC) were similar in the two groups.

Clinical researchers are interested in a regimen combining the CCR5 antagonist maraviroc with atazanavir/ritonavir and excluding reverse transcriptase inhibitors. But finding the appropriate maraviroc dose is complicated because atazanavir/ritonavir raises maraviroc concentrations through inhibition of the CYP3A4 enzyme and drug transporters. And modeling maraviroc pharmacokinetics has proved difficult because of interpatient and intrapatient variability in rate and extent of maraviroc absorption.

Pharmacokinetic data from antiretroviral-experienced people suggested lower maraviroc exposure than predicted by a drug interaction study in healthy volunteers taking 300 mg of maraviroc twice daily with atazanavir/ritonavir (study A4001025) [2].

To further assess maraviroc’s interaction with atazanavir/ritonavir, Pfizer researchers used a semiphysiologic maraviroc PK model to analyze maraviroc concentrations in two groups: (1) 12 healthy volunteers who took 300 mg of maraviroc twice daily without atazanavir/ritonavir in study A4001025 [2], and (2) 58 HIV-positive antiretroviral-naive people who took 150 mg of maraviroc plus 300/100 mg of atazanavir/ritonavir, both once daily, in study A4001078.

The Pfizer team used data from the volunteers to estimate the impact of atazanavir/ritonavir on intrinsic maraviroc clearance and extent of absorption. Then they applied these values to a “rich” set of data involving 145 samples from 15 people with HIV and a “sparse” data set involving 138 samples from 57 people with HIV. The Pfizer investigators used a nonlinear mixed model with two absorption compartments and four disposition compartments. The model introduced absorbed maraviroc into a liver compartment in which atazanavir/ritonavir inhibited metabolic clearance and absorption transporters. The model scaled renal clearance at a baseline creatinine clearance of 120 mL/min.

In the 12 HIV-negative volunteers taking 300 mg of maraviroc twice daily, atazanavir/ritonavir reduced population intrinsic clearance of maraviroc from 90 to 14 L/h, while maraviroc absorption rose from 83.3% to 98.5%. These changes led to the following predicted changes: (1) a 2.5-fold increase in maraviroc Cmax, (2) a 4.6-fold increase in 12-hours maraviroc area under the concentration-time curve, and (3) a 10-fold increase in Cmin.

At the same intrinsic clearance, the 150-mg once-daily maraviroc dose in HIV-positive people resulted in 93.5% absorption. Compared with the healthy volunteers taking 300 mg of maraviroc twice daily without atazanavir/ritonavir, the sparse-data 57-person HIV group taking 150 mg once daily with the protease inhibitors had a lower maraviroc Cmax (591 versus 933 ng/mL) and a lower Cavg (170 versus 213 ng/mL). But Cmin was higher in the HIV group than in HIV-negative volunteers (43 versus 38 ng/mL), as was ECC (95 versus 89 ng/mL).

Analysis of maraviroc concentrations in the 15-person rich-data HIV sample yielded similar results: Cmax 614 ng/mL, Cavg 170 ng/mL, Cmin 44 ng/mL, and ECC 96 ng/mL. However, intrinsic maraviroc clearance in the rich-data analysis was 9 L/h and absorption 69%.

Compared with a maraviroc dose of 300 mg twice daily without atazanavir/ritonavir, the Pfizer researchers concluded that in HIV-positive people a dose of 150 mg once daily with atazanavir/ritonavir "produced less peak-trough fluctuation with very similar Cmin and ECC values." The investigators believe this result "implies similar efficacy for the maraviroc component of any such combination."

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Lopinavir troughs lower in children on once-daily dose with efavirenz

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Children who switched from twice- to once-daily lopinavir/ritonavir plus efavirenz had a low lopinavir trough concentration in a small Thai study [1]. Troughs were not as low during twice-daily lopinavir/ritonavir dosing with or without efavirenz or with once-daily lopinavir/ritonavir without efavirenz. All children maintained an undetectable viral load, and those with low troughs had a dose increase.

In the United States once-daily lopinavir/ritonavir is licensed for antiretroviral-naive adults and for adults with fewer than three lopinavir-related resistance mutations. But data are sparse on the once-daily lopinavir/ritonavir tablet for children. To fill that pharmacokinetic gap, researchers in Thailand mounted a pilot study involving children already taking twice-daily lopinavir/ritonavir with or without the nonnucleoside efavirenz.

The 12 study participants had maintained a viral load below 40 copies for at least 3 months with twice-daily lopinavir/ritonavir. When children enrolled in the pilot trial, researchers collected blood samples over 12 hours to measure lopinavir levels. Then all children switched to an equivalent dose of once-daily lopinavir/ritonavir. Two weeks after the switch, the investigators collected blood samples over 24 hours.

Study group ages ranged from 9.3 to 17.7 years (median 13.1), weight from 26.8 to 50.3 kg (median 40.8), CD4 count from 456 to 1239 (median 699), and CD4 percent from 16% to 31% (median 23%). Five of six children taking lopinavir/ritonavir with efavirenz and six taking the protease inhibitors without efavirenz completed both pharmacokinetic evaluations. Among children not taking efavirenz with the PIs, five were taking tenofovir/lamivudine and one zidovudine/didanosine.

Children combining lopinavir/ritonavir with two nucleosides and *without* efavirenz took lopinavir doses ranging from 255 to 283 mg/m(2) (median 271) with twice-daily dosing and from 514 to 570 mg/m(2) (median 544) with once-daily dosing. These children had the following areas under the concentration-time curve (AUC), maximum concentrations (Cmax), and trough concentrations (C12h or C24h) before and after switching to once-daily lopinavir/ritonavir. See Table 1.

Children combining lopinavir/ritonavir with efavirenz took lopinavir doses ranging from 273 to 338 mg/m(2) (median 303) with twice-daily dosing and from 538 to 645 mg/m(2) (median 612) with once-daily dosing. They had the following lopinavir concentrations before and after switching to once-daily lopinavir/ritonavir. See Table 1.

Table 1: Median (range) of lopinavir PK parameters, with and without efavirenz

	LPV/r without efavirenz (n=6)	LPV/r with efavirenz (n=5)
12-hour AUC twice daily (mcg x h/mL)	172 (125 to 201)	168 (124 to 190)
24-hour AUC once daily (mcg.hr/mL)	200 (95 to 228) *	154 (145 to 182) *
Cmax twice daily (mcg/mL)	8.8 (7.4 to 9.8)	10.3 (9.5 to 12.9)
Cmax once daily (mcg/mL)	12.1 (8.5 to 15.0)	13.5 (11.4 to 15.6) *
C12h twice daily (mcg/mL)	4.2 (2.0 to 6.5)	3.1 (1.2 to 3.4)
C12h once daily (mcg/mL)	3.9 (0.2 to 7.3)	**0.17 (0.08 to 0.43) ***

* P <0.05 for once vs twice daily concetrations within group (not between group)

For all 11 children who completed the study, the geometric mean ratio of lopinavir AUC once daily/twice daily was 1.01 (90% confidence interval 0.85 to 1.21). For Cmin, the geometric mean ratio of lopinavir once daily/twice daily was 0.21 (90% confidence interval 0.09 to 0.48). When taking lopinavir/ritonavir twice daily, all children had a lopinavir 12-hour (trough) concentration above 1 mcg/mL. After the switch to once-daily dosing, 5 of 6 children taking lopinavir without efavirenz and 0 of 6 taking lopinavir with efavirenz had a trough above 1.0 mcg/mL. The 7 children with a 24-hour lopinavir concentration below that cutoff after the switch to once-daily dosing had their dose increased by 20% to 30% after 12 weeks. Troughs remained low in 4 of these 7 children after the dose increase.

With once-daily lopinavir/ritonavir, median efavirenz concentrations were 62.6 (range 36.2 to 197.2) mcg x hr/mL for AUC, 4.1 (range 3.1 to 10.8) mcg/mL for Cmax, and 1.7 (range 0.9 to 6.0) mcg/mL) for Cmin.

All children maintained a viral load below 40 copies/mL through 24 weeks of once-daily lopinavir/ritonavir. No lopinavir/ritonavir side effects emerged, as might be expected in a group already tolerating twice-daily lopinavir/ritonavir well.

Several published studies have addressed lopinavir/ritonavir pharmacokinetics with once-daily dosing [2-4] or with twice-daily dosing with efavirenz [5-7]. In Canada a study of 7 children with a median age of 9.8 years found similar pharmacokinetics with once- and twice-daily dosing and no observable difference in tolerability [2]. A Netherlands study of 19 children with a median age of 4.5 found evidence that a lopinavir/ritonavir dose of 460/115 mg/m(2) "leads to mean pharmacokinetic parameters comparable to data of 800/200 mg lopinavir/ritonavir once daily in adults, although the variability observed in the trough levels is much higher in children" [3]. Another Dutch study of 15 children with a median age 11.8 years found that a lopinavir/ritonavir dose of 300/75 mg/m(2) twice daily compensates for the enzyme-inducing effect of efavirenz given at 14 mg/kg once daily.

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Dose optimisation: 50 mg ritonavir-boosting, 3TC dosing and raltegravir once-daily

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The issue of dose optimisation is important for several reasons, ranging from finding the right dose for an individual patient that achieves the highest probability of therapeutic success with the lowest risk of adverse events, to as a strategy to decrease the cost of antiretroviral therapy in order to increase the delivery of therapy to more individuals. A plenary/round table discussion on 'Dose optimisation and simplification' focused on the decrease cost to increase access issue.

Here are some compelling reasons to pursue this research: "over 90% of HIV-infected individual live in very poor countries where the cost of antiretroviral treatment can still be a major barrier to access" (Andrew Hill, Liverpool University); "antiretrovirals consume 50% of the drug budget for South Africa...the need to reduce antiretroviral prices is becoming more pressing as ART scale up continues in low- and middle-income countries" (Gary Maartens, University of Cape Town); and "while 5 million individual are currently accessing ARV for treatment, 10 million more require therapy" (Steve Becker, Bill & Melinda Gates Foundation).

Atazanavir drug levels similar with 50 mg or 100 mg ritonavir boosting

Abstract P-31 is a good example of one dose optimisation strategy. This study investigated ATV concentrations in 12 healthy volunteers when given with either 100 mg or 50 mg of RTV for 10 days. [1]

The AUC of ATV when given with 50 mg of RTV was 47.09 mg*h/L and was 50.62 mg*h/L with 100 mg of RTV; the 90% CI of the ratio was 82.5 to 116.38. The ATV trough concentrations were 0.59 mg/L with 50 mg of RTV and 0.79 mg/L with 100 mg; all trough concentrations were above 0.15 mg/L, which is the suggested threshold concentration.

There was also no difference in ATV Cmax with the 2 RTV doses. In the 10-day treatment periods, total and LDL cholesterol significantly increased with the 100 mg RTV dose, whereas there were no significant changes with the 50 mg RTV dose.

These data in HIV-negative volunteers indicate atazanavir exposure was equivalent when given with either 100 mg or 50 mg of RTV, but there were fewer adverse effects on lipid metabolism with the 50 mg RTV dose. These data provide a basis for further studies in HIV-infected persons as a strategy to minimise RTV-associated adverse effects, and as a strategy to decrease the costs of therapy.

3TC dose reduction to 150 mg once-daily fails to achieve sufficient intracellular levels

While the atazanavir/ritonavir example above provides an example of a dose optimisation lead worth pursuing, two other abstracts are examples of strategies that do not.

The first, abstract O-05 evaluated whether a 3TC dose of 150 mg once daily, compared with the usual 300 mg once daily dose, achieved bioequivalent intracellular concentrations of the active metabolite, 3TC-triphosphate. [2]

24 HIV-negative volunteers participated in this study.

The geometric mean 24-hour AUC of 3TC-triphosphate from the 300 mg dose was 59.5 pmol/10^6 cells; this value for 150 mg was 44.0 pmol/10^6 cells. The geometric mean 24-hour concentrations were 1.49 pmol/10^6 cells and 1.23 pmol/10^6 cells for the 300 mg and 150 mg 3TC doses, respectively.

The geometric mean ratios for AUC and trough concentration were 0.73 and 0.82, respectively, indicating that the 150 mg dose was not bioequivalent to the 300 mg dose.

This was a reasonable study to perform. It was possible the intracellular formation of 3TC-triphosphate might be saturable, and thus lower doses would achieve intracellular concentrations the same as higher doses. This study showed, however, this was not the case. Because bioequivalence was not demonstrated, there is no pharmacologic basis to pursue a lower 3TC dose as a dose optimisation strategy.

Once-daily raltegravir PK

The QDMRK study compared once vs twice daily raltegravir in 770 treatment-naive persons demonstrated once daily therapy was inferior to twice daily, with overall proportions of subjects with HIV-RNA <50cpm at week 48 of 83.2% vs. 88.9%, respectively. PK data were provided at CROI and demonstrated raltegravir trough concentrations with 800 mg once daily were substantially lower than 400 mg twice daily dose.

At the PK Workshop, additional PK data were provided in abstract O-09. [3]

Ctrough values, from the 24-hour intensive PK studies, were lower for once daily RAL: the geometric mean was 40nM for 800mg once daily versus 257nM for 400 mg twice daily. The trough concentration were similarly lower from the spare/population PK data: the geometric mean was 83nM for once daily and was 380nM for twice daily.

Significant relationships were also found between raltegravir concentrations and virologic response. For example, the odds ratio for achieving HIV-RNA below 400 or 50 copies/mL increased with increasing concentrations, and the odds of virologic failure decreased with increasing raltegravir concentrations. From the presentation at the meeting, no clear breakpoint or threshold raltegravir concentrations could clearly be identified.

From the data, it looks that a trough concentration less than approximately 60 nM increases the risk of virologic failure.

These data indicate raltegravir and the investigational integrase inhibitors elvitegravir and dolutegravir all exhibit pharmacodynamic relationships between trough concentrations and virologic response.

This raltegravir study is a clear example of a potential hazard for dose optimisation efforts: for all antiretrovirals, there is some threshold concentration you can't go below without increasing the risk of virologic failure for a patient.

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CONFERENCE REPORTS

46th European Association for the Study of the Liver (EASL)

30 March–3 April 2011, Berlin, Germany

Introduction

The development of compounds that directly target hepatitis C virus (direct acting antivirals or DAA's), used with and without pegylated interferon (PEG-IFN) and ribavirin is moving rapidly and with a burgeoning pipeline.

The following report is an edited summary of a rapid summary from Jules Levin whose natap.org website posted numerous studies from this meeting.

Abstracts from the oral and poster sessions are available online at the following links:

http://www1.easl.eu/easl2011/program/Orals/

http://www1.easl.eu/easl2011/program/Posters/

A limited number of web casts are due to be posted online but were not yet available when HTB went to press.

Rapid report: state of HCV policy, treatment, access

Jules Levin, natap.org

This has been a landmark meeting with the leading developments being the oral late breaker in the last clinical session late yesterday afternoon where BMS reported 4/11 genotype 1 non-responders achieved SVR24 cure using only the two oral BMS HCV drugs (the protease inhibitor BMS-650032 and the NS5A inhibitor BMS-790052). [1]

This was proof of concept that we can cure at least some patients without PEG-IFN and ribavirin.

We know that genotype-1a will not respond as well to therapies coming out in the near future, genotype-1b responds better. In the BMS study and others genotype-1a comprised more of the failures.

Patients with viral failure quickly added PEG-IFN plus ribavirin and all responded with undetectable HCV viral load. This was reported in November 2010 at American Association for the Study of Liver Diseases conference (AASLD) and is equally important. BMS also reported that using the QUAD therapy (BMS-650032, BMS-790052 plus PEG-IFN and ribavirin) 9/10 patients achieved SVR24 cure and the outlying patient had <LLOQ at week 24 post treatment undetectable on retesting 35 days later.

BMS also reported impressive data on their peg-lambda interferon in a study comparing it to Pegasys with it showing safety benefit and also surprisingly activity benefit as well, the programme is moving ahead. [2]

The second major story at EASL was the development of potent nucleotides by the small biotech company Pharmasset that appear to have a high barrier to resistance. So far no resistance has been seen and this is a key to the success of these drugs. Pharmasset reported three studies on PSI-938 and PSI-7977 in combination without PEG-IFN and ribavirin in patients with genotype-1. More than 90% patients essentially achieved undetectable over relatively short-term follow up. [3]

They also reported a nucleotide in combination with PEG-IFN and ribavirin that also displayed essentially 100% undetectability in patients in early follow up, and they reported similar results for people with genotype 2 and 3. [4, 5]

Taking these two developments together, the cure data and the potency of these nucleotides, we can perhaps cure HCV with nucleotide therapy using short-term oral combination regimens.

Recently, BMS & Pharmasset announced a joint study that will combine the BMSNS5A with a Pharmasset nucleotide, 2 potent drugs expected to perform well together. Events are unfolding in an accelerated way now in HCV drug development coming out of this meeting.

BMS also reported the first SVR12 results in a dose-ranging study of its NS5A inhibitor BMS-790052 plus PEG-INF plus ribavirin vs PEG-INF plus ribavirin. SVR12 were 92% (11/12) receiving BMS-790052 vs 42% (5/12) receiving standard of care. [6]

Roche reported SVR data on their ritonavir-boosted HCV protease inhibitor danoprevir (RG7227) and on their nucleoside analogue polymerase inhibitor mericitabine (RG7128), both used in combination with PEG-IFN plus ribavirin**.** [7, 8]

Of particular note, this is the first-time data reported on low-dose ritonavir boosting danoprevir. In with HIV protease inhibitors, ritonavir-boosting provides better efficacy compared to unboosted PIs, and although HCV is different boosted HCV PIs may provide additional benefits.

The danoprevir/r results were under-reported due to many other headline studies but preliminary data after 12 weeks in null-responders reported undetectable viral load in 88% (14/16) of genotype-1b patients and 50% (4/8) of genotype 1a. Roche was the first company to report combination therapy with two oral drugs with the INFORM study but their development programme was

delayed because of an ALT elevation observation seen with their PI. Ritonavir-boosting lowers the Cmax and appears to have resolved that issue development is continuing.

Numerous studies were reported by Vertex on telaprevir and by Merck on boceprevir regarding IL28B and other data on how the drug will be used in support of the phase 3 studies reported at AASLD in November. The FDA hearing is scheduled for April 2011 and both drugs are expected to be approved.

Pharmasset announced the start of a cutting edge study called Atomic which will look at various treatment schedules. [9]

Novartis presented SVR rates in a phase 2b study of a non-immunosuppressive cyclosporine-A derivative called alisporivir (DEBO25) used with PEG-IFN plus ribavirin in genotype-1 treatment-naïve patients of 76% rate compared to 55% for the PEG-IFN plus ribavirin. [10]

Alisporivir is the first in a new class of drugs called cyclophilin inhibitors. Unlike other compounds in development that target the hepatitis C virus directly, alispirovir, targets host proteins that the hepatitis C virus uses for replication. This therapy has particular appeal because not only does resistance appear hard to develop but cross-resistance to other classes of HCV drugs is unlikely. This increases options for non-responders who could use other experimental compounds. A phase 3 study in gentotype 1 naives is underway and study in non-responders is also planned. A Phase 2b trial looking at the potential of the agent in HCV patients with genotypes 2 and 3 is also underway. The host proteins are needed for replication in all types of HCV infection so there is potential for the agent to have broad activity in all six variations of HCV.

Tibotec had a few presentations on their once daily TMC435 protease inhibitor but as they have already entered Phase 3 having shown an impressive 84% SVRs in treatment-naïve patients in phase 2 and are on a fast track to get to the market. These included IL28B data and a couple of other posters including the ASPIRE Study with preliminary data in nonresponders and a poster of five patients treated with TMC435 monotherapy & retreated with TMC435 plus PEG-IFN and ribavirin showing they were at least in short-term followup able to reach undetectable. [11, 12, 13, 14]

Boerhinger Ingelheim reported phase 2 data on their protease inhibitor BI201335 plus PEG-IRN plus ribavirin in naives & treatment-experienced and announced publicly they are starting phase 3. [15]

Presidio had a poster on their NS5A development programme and issued an announcement about the clinical efficacy of their lead candidate PPI-461 in patients in an ongoing study. [16]

Conclusion

Drug development for hepatitis C is moving up to the next level.

At the meeting many companies reported important new study results. Second generation protease inhibitors are progressing but are still in earlier development stages. They will hopefully provide a higher barrier to resistance and have perhaps activity against some of the mutations the early generation PIs are associated with.

New NS5A inhibitors are in development by several companies in the wake of the potent first in class by BMS. Abbott reported clinical data in patients on their potent looking second-generation protease inhibitor (ABT-450) that will be boosted by low-dose ritonavir. Abbott also has NNRTIs and has reported on them previously but reported here on preclinical data on their own NS5A. So Abbott now has three classes of oral HCV drugs.

Intermune reported on a second-generation protease in development with Roche that appears to be active against the key protease mutation 155, and Intermune also reported for the first time on their own NS5A inhibitor.

Gilead reported 24 presentations at the meeting. This was their coming out party, as they reported follow-up clinical data on their four-drug combination of protease, NNRTI, PEG-IFN plus ribavirin, with all patients becoming undetectable in the follow up. Gilead also revealed the many new drugs they are developing in multiple classes including additional protease inhibitor, their own nucleotide and NS5A inhibitor. So Gilead now has several drugs in several different drug classes. And Gilead also reported on a TLR7 inhibitor that appears to be active against both hepatitis B and C, so this immune-based type of therapy may bring a new dimension to HBV therapy.

GSK has also entered the field. They reported here on two new drugs, a NS5B polymerase inhibitor GSK248585 and GSK2336805, a NS5A inhibitor.

Patients with genotype 1a and IL28 CT and TT do not do as well. So a patient can test to see if they are CC, CT or TT and also if they are genotype-1a or 1b. Genotype 1a is an indication that response to therapy may not be as good, with lower SVR rates observed in several studies. Also CT & TT patients don't do as well as CC patients in terms of SVR rates, so these appear to be important considerations in treatment decision-making.

The expectation is that we will be able in theory to cure HCV in all patients except for those who may be too sick. We are now moving to the next level of drug development where one oral HCV drug plus PEG-IFN and ribavirin is not enough. We need multiple oral HCV drugs in a regimen with or without PEG-IFN and ribavirin. The range of studies is currently looking at a broad range of approaches.

Drug resistance has also evolved to another level. The majority opinion emerging at EASL amongst leading academic and industry researchers, publicly and privately, is that resistance will not be a problem. Resistance is hoped to disappear after 1.5 to 2 years, as

evidenced in the study reported here by Vertex on telaprevir. This would enable people to re-treat with the same protease inhibitor in combination with other classes of oral drugs, after having failed it with resistance mutations. To support this hope Tibotec reported retreating five patients who had received TMC435 monotherapy with TMC435 plus PEG-IFN and ribavirin and in the short-term they achieved undetectable viral load.

There is however a significant minority opinion who feel strongly that we do not yet know yet if this is true. Here it is important to stress that the majority view is only an opinion we do not know what will happen in the future. The worst case scenario is virologically failing patients remain on failing therapy and accumulate mutations and compensatory mutations that do not disappear or they disappear by a insensitive test and reappear after re-using a protease, as in HIV.

The telaprevir-Vertex resistance study above used resistance testing that had a population sensitivity cut-off of 20%, so resistance of less than 20% could not be seen. The Tibotec example also can be undercut because the PEG-IFN plus ribavirin could have been doing all the work. This can only be demonstrated in clinical studies of recycling compounds in people with treatment failure. This type of study is not easy to design and implement.

Another issue being discussed in the wake on much data reported here on how IL28B affects treatment outcomes. Surprisingly, there was a lot of talk about using a lead-in of PEG-IFN and ribavirin to block use of boceprevir or telaprevir in Europe, in the sense that if a patient had a good PEG-IFN and ribavirin response at week 4, they could continue on this and not add boceprevir or telaprevir. This scenario is not in the best interest of patient outcomes as treatment would still be 48 rather than 24 weeks.

At panel discussion on global HCV included Jake Liang from the US NIH and John Ward from the US CDC who did not provide any information suggesting US federal government money will be provided. The HHS HCV Strategy plan is expected to be publicly unveiled in May. There are no federal, state or city large-scale HCV testing & screening programmes. There are no discussions that address large-scale care in HCV, similar to the Ryan White Care Act for HIV.

C O M M E N T

This year EASL as significant in terms of a change in direction for the management of HCV as the World AIDS Conference in Vancouver 1996 was for the management of HIV. 2011 is the year that heralds triple combination therapy for 'difficult to manage' genotype 1 HCV infection. At a preliminary FDA hearing at the end of April 2011, both first-generation NS3/4 protease inhibitors that have completed phase 3 studies (boceprevir from Merck and telaprevir from Vertex/Jannsen-Cilag) received unanimous support from the FDA expert panel and will shortly receive formal FDA approval for treatment in combination with PEG-IFN and ribavirin for genotype 1 HCV infection.

There are, however, a number of unanswered questions for these two drugs. These included whether it will be possible to use a shorter duration of treatment for all patients or will some groups need to use response-guided lengths of therapy? How will clinicians manage the complexities of response-guided therapy? Will virology laboratories manage to turn around HCV viral load results in time? How will we mange potential side effects in clinical practice (anaemia for boceprevir, rash for telaprevir)?

In addition to these, the questions surrounding the emergence of resistance mutations and their significance for future treatment options remain unanswered. Although data from both boceprevir and telaprevir studies suggest that the majority of mutations disappear by 2-3 years post therapy, the potential re-emergence and cross-resistance with the use of second- and third-generation PIs thereby reducing the efficacy of future PI-containing treatment options remains a concern for some.

Whilst we grapple with these issues and learn how to use the first-generation NS3/4 inhibitors, a plethora of other DAAs–PIs, NS5b polymerase inhibitors (both nucleosides and non-nucleosides) and a few NS5a inhibitors–are getting ready to go into phase 3 studies. The next question that whether PEG-IFN and ribavirin can still be considered as standard-of-care therapy for genotype 1 HCV infection?

For HIV doctors treating co-infected patients, although there is some preliminary data with telaprevir in triple combination (CROI 2011), data with boceprevir is yet to be presented. Over the next months, whilst we wait further data and formal approval of the first two anti-HCV protease inhibitors, the key issue to consider is who should we treat now with PEG-IFN and ribavirin and who should wait for triple therapy?

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CONFERENCE REPORTS

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

Introduction

This annual conference remains the most important large scientific HIV meeting and is notable for making web casts of oral presentations and lectures rapidly available. Abstracts are online in a searchable database, many of which also include the option to download the PDF poster.

http://www.retroconference.org

In this issue we continue the coverage started in the last issue of HTB.

Reports in this issue include:

- When to start ART in patients co-infected with TB: results from two trials presented at CROI
- Inflammation and Intervention: how does HIV cause AIDS and how does it cause disease despite ART

Unless mentioned otherwise, all references are to the Programme and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections, 28 February–2 March 2011, Boston.

http://www.retroconference.org/AbstractSearch/

Webcasts are available at the following link:
http://www.retroconference.org/2011/data/files/webcast_2011.htm

When to start ART in patients co-infected with TB: results from two trials presented at CROI

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The complex question of the optimal time to start antiretroviral therapy (ART) in HIV-positive patients co-infected with TB was the subject of two important presentations at a plenary session of the 18th Conference on Retroviruses and Opportunistic Infections. Diane Havlir presented the findings of ACTG's Stride trial and Salim Abdool Karim presented the results of the SAPIT trial. [1, 2]

Stride

Havlir and colleagues conducted an open label international trial to confirm their hypothesis that in patients starting TB treatment, ART initiated within 2 weeks (immediate initiation) could reduce mortality and morbidity compared to patients starting ART within 8-12 weeks (early initiation).

Patients were randomised to immediate (405 patients) and early (401 patients) ART treatment arms. Patients had confirmed or presumed TB and a CD4 cell count <250 cells/mm3. The ART regimen for 97% of patients was efavirenz and tenofovir/emtracitabine. The TB treatment was country approved. Nearly half of the patients had confirmed TB with a median CD4 count of 77 cells/mm3 (IQR: 36-145).

The primary endpoints of the study were all cause--mortality and new AIDS-defining illnesses by 48 weeks. No data is available for after 48 weeks as patients were not followed beyond this endpoint. Secondary endpoints were safety, CD4, HIV RNA changes, TB IRIS and TB outcomes.

The proportion of AIDS or death between the immediate (12.9%) and the early (16.1%) arms were not statistically significant (p=0.45). However, a pre-specified analysis that considered patients with a CD4 cell count <50 cells/mm3 found that the proportion of patients with AIDS or death was 26.6% in the early arm compared to 15.5% in the immediate arm and this was significant (p=0.02). The majority of AIDS or death events occurred within the first 24 weeks after randomisation, with the highest proportion amongst the early arm with a CD4 count <50 cells/mm3. There was barely any difference in endpoints in the higher CD4 strata (11.5% versus 10.3% for the immediate versus early arms respectively; p=0.67).

Thirteen cases of cryptococcal disease made it the most common AIDS primary endpoint (n=63) The next two most common AIDS illness included oesophageal candidiasis (n=12) and Kaposi's Sarcoma (n=11).

There were 31 deaths in the immediate arm versus 37 deaths in the early arm. TB was the largest contributor to deaths (21 out of 68 patients). During question time, Havlir was asked if the 14 TB-related deaths on the immediate arm versus seven in the early arm were indicative of fatal TB IRIS. She pointed out that these cases were reviewed and that they were a consequence of TB progressing in contrast to patients with IRIS who get better and then become ill again.

Twenty-one cases of AIDS-related deaths were reported and 16 non-AIDS related deaths (respiratory, renal and hepatic disease being most common). The frequency of TB IRIS in the immediate arm was 11% and 5% in the early arm (p=0.002).

In summary the investigators found that immediate ART did not overall reduce AIDS-defining disease overall and death compared to early ART, but for patients with CD4 counts < 50 cells/mm3 immediate ART reduced AIDS and mortality. Grade 3 or 4 toxicities, HIV RNA suppression rates or CD4 increase did not differ between the arms. TB IRIS was higher in the Immediate arm although it did not increase mortality. They concluded that in patients with CD4 counts <50 cells/mm3 ART should be started within two weeks.

SAPIT

Salim Abdool Karim and colleagues conducted a 3-armed open label trial called SAPiT. The sequential arm, in which patients first completed their TB treatment course and then initiated ART was stopped by the DSMB due to the significantly higher mortality in that arm. We have previously reported on this aspect of the trial. [3] This report is confined to the results of the remaining two arms.

HIV-positive patients with smear-positive TB and CD4 counts <500 cells/mm3 were randomised into an early integrated therapy arm (214 enrolled and ART initiated within four weeks of starting TB treatment) and a late integrated therapy one (215 enrolled and ART initiated within four weeks of completing the intensive phase of TB treatment). Baseline characteristics for age, gender and CD4 count were similar in both arms.

All participants attended the TB-DOTS programme at eThekwini Clinic in Durban and the study's primary endpoints were death and AIDS defining illness.

Both arms had similar rates of AIDS defining illness or death with 18 deaths in the early arm and 19 in the late arm. The Incidence Rate Ratio (IRR) was 0.89 (95% CI: 0.44 to 1.79; p=0.73).

When the results were stratified for CD4 count of <50 cells/mm3, a 68% reduction of AIDS or death was found in the early and this approached significance (IRR: 0.32 [0.07-1.13], p=0.06). For participants with CD4 counts >50 cells/mm3 no discernable differences in AIDS/Death were noted (IRR: 1.51 [0.61-3.95], p=0.34).

In patients with CD4 counts <50 cells/mm3, the reduction in AIDS/death in the early arm overshadowed the 5-fold higher risk of IRIS (95% CI; IRR 4.7 [1.5-19.6]; p=0.01) and the increasing trend in drug switches.

HIV suppression was greater than 90% after 18 months irrespective of CD4 status. Similarly TB treatment was successfully completed in about 80% of patients with no significant differences across groups.

On the other hand in patients with CD4 counts > 50 cells/mm3 there was an IRIS rate of 15.8 person years and 7.2 in the late arm; CI: 95%; IRR: 2.2 [1.1-4.5]; p=0.02) and this was significant. Rates of drug switches were 7/100 patient years in the early arm and 1 in the late arm (CI: 95%; IRR: 6.8 [0.8-551.1]; p=0.04). The lower rates of IRIS and drug switches in the late therapy arm indicated a slight benefit to starting ART during the continuation phase of TB treatment in patients with CD4 counts >50 cells/mm3.

C O M M E N T

The main results of both studies were similar. Immediate ART is warranted in patients with CD4 counts <50 cells/mm3 while ART for patients with CD4 counts >=50 cells/mm3 can be postponed until the continuous phase of TB treatment, but not beyond.

These studies have implications for some guidelines in high incidence countries. For example, he South African Guidelines for Antiretroviral Therapy in Adults state with respect to patients co-infected with TB state:

"[For patients with] CD4 count <200 cells/mm3: commence ART after it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated. The suggested time period to commence ART is between 2 and 8 weeks after starting TB therapy.

CD4 count 200 - 350 cells/mm3: delay ART until after the intensive phase of TB therapy (2 months) unless the patient has other serious HIV-related illness. The longer delay before commencing ART in this group is recommended to reduce the risk of shared toxicity (as the patient will then only be on fewer TB drugs) and to reduce the risk of the immune reconstitution inflammatory syndrome (see below).

CD4 count >350 cells/mm3: defer ART."

When the guidelines are updated, the drafters will have to consider:

- **Whether the recommendations be modified to explicitly state that patients with CD4 counts <50 cells/mm3 must be started immediately on ART, or does the current framing sufficiently cover that?**
- **Whether the recommendations be modified to initiate ART to patients with CD4 counts of 50-350 cells/mm3 only after the intensive phase?**

The answers to these questions are not clear.

While the SAPIT trial included patients with CD4 counts <500 cells/mm3, there is not yet enough data on patients with CD4 counts of 350 to 500 cells/mm3 to justify a change in guidelines. Hopefully the START and TEMPRANO trials, scheduled to complete in 2015 and 2013 respectively, will help answer this question. [5, 6]

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Inflammation and intervention: how does HIV cause AIDS and how does it cause disease despite ART

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"the consequences of HIV replication clearly persist long after ART has suppressed viraemia ... Interventions in the best of worlds could actually become therapies to be used to improve or normalise immune function and health outcomes, but least interventional clinical experiments might enlighten as to the drivers of HIV pathogenesis despite ART ... Hydroxychloroquine (chloroquine) dampens the inflammatory response ... in ART-suppressed patients without immunological response to ART ... An array of immunological changes were seen ... the potential toxicity of hydroxychloroquine would need to be weighed and tested"

HIV infection was first thought to lead to AIDS by the uncontrolled replication of the highly cytopathic virus, killing CD4 cells and laying waste to the immune system. Some studies, however, suggest that the direct killing of lymphocytes by HIV is insufficient to account for immunodeficiency. A state of chronic, generalised immune activation has been suggested, in combination with viral replication, to be required to ignite progression to AIDS.

A recent paper in Cell by Warner Greene's group has revived the claim that HIV replication is central to CD4 depletion and immune collapse via the triggering of pyroptosis, a form of programmed cell death that engulfs surrounding, uninfected cells in the doom triggered by the viral death of the few. [1] However, this view was not represented at CROI.

The current majority view, reinforced by many related presentations at CROI, emphasised the role in HIV immunopathogenesis played by the mucosal immune dysfunction and its partner in guilt-by-association, bacterial translocation. It has been long observed that antiretroviral therapy (ART) suppression of viraemia usually does not fully resolve immune activation, although for most patients the proportion of cells bearing markers of activation are far below that of untreated patients. Two general types of studies at CROI focused on the issue of immune activation in HIV infection: 1) those outlining phenomena that were associated with immune inflammation, and that perhaps drive the process, and 2) those that used therapeutic interventions in an attempt to perturb the system and perhaps ameliorate pathology.

Observations on inflammation

Various soluble markers such as LPS and bacterial rDNA have been reported to be the result of microbial translocation, and associated with immune activation. Abdurahman and colleagues introduced bacterial flagellin-specific antibodies and an assay of soluble flagellin protein as new surrogate markers for immune activation. [2]

Flagellin is a potent inducer of the toll-like receptor, a human receptor designed to sense foreign proteins and respond by the induction of inflammation. The group showed higher levels of flagellin and flagellin antibodies in untreated patients than in treated patients, both groups being higher than uninfected controls. As with other such markers, flagellin markers were reduced but not completely by the use of ART. The investigators also noted that levels were higher in patients from Ethiopia and Vietnam than from Sweden, but given the diversity of these populations and the small sample size, it is difficult to make much of this difference. It remains to be seen if this biomarker is cheaper, more reproducible, or simpler to use in research setting than others that have been described.

Kamat and colleagues discussed a small but interesting study of the application of serological markers used to diagnose inflammatory bowel disease (IBD) to HIV-infected patients. [3] Antibodies to ASCA, pANCA, anti-OmpC, and anti-CBir1 were measured by ELISA in plasma from AIDS patients (n = 26) with low CD4 counts (<300 cells/mm3) and high plasma LPS (>80 pg/mL), and results correlated with clinical data. A weakness of this study was the fact that only 6 of the 26 patients were virologically suppressed, and in this report suppression was considered to be < 400 copies HIV RNA/ml. Further this was an advanced cohort with a mean CD4 count of 80 cells/µl. However antibodies linked to IBD was detected in 46%, and of these 75% had a Crohn's-like pattern. Analysis showed a positive correlation between the flagellin antibody anti-CBir1 and IL-6 levels ($r = 0.447$, $p = 0.048$). The authors suggested that, like in IBD, these biomarkers might serve to monitor HIV-related gut inflammation. Should specific therapies to downmodulate inflammation be developed, such monitoring strategies might be useful, either in trials or in practice.

Nagy and colleagues showed that antigen-presenting cells, capable of phagocytising foreign antigens and microbes, differed in their behavior in uninfected, HIV-infected, and HIV-infected but ART-suppressed patients. [4] Antigen-presenting cells from untreated HIV-positive patients on average produced more of the pro-inflammatory cytokines TNF, IL-6, and IL-12 when exposed to several microbes, or when stimulated through Toll-like receptors, the innate receptors that detect the presence of such pathogens. In most cases, the dysregulation or hyper-reponsiveness of antigen-presenting cells was ameliorated by suppressive ART. Assays of global cellular gene expression in APCs, illustrated that this dysregulation was correlated with global alterations in cellular gene expression. This observation added to the catalog of cellular immune dysfunction that has been observed in viraemic patients, partially ameliorated by effective ART. It remains to be seen if the duration of ART or the timing of it initiation after infection allows fuller normalisation of this immune response.

In thematic agreement with this observation, Funderburg and the ACTG 5248 investigators examined immune parameters in patients initiating a raltegravir/Truvada regimen. [5] The 37 patients included in this immunological substudy had moderately advanced disease, with a median CD4 count of 259 cells/mm3. In patients in whom viraemia was successfully suppressed, over the 72-week study markers of T cell activation such as the presence of the activation markers CD38 or HLA-DR, the marker of cell turnover Ki67, the levels of TNF receptor and the soluble receptor for lipopolysaccharide (sCD14) all fell precipitously in the first few days of therapy. However, in general, most markers were still measurably elevated after 8 weeks of therapy, and in most

patients did not return completely after 2 years of therapy (week 72) to levels typically seen in uninfected patients. Similarly, bacterial lipopolysaccharide declined but did not normalise. The authors speculated that the association observed between continuing microbial translocation (higher LPS levels) and increased turnover (Ki67+) of central memory CD4 cells might mean that microbial translocation was the cause of CD4 cell depletion.

Similarly, Shive and colleagues from Case Western Reserve University studied a cohort of 61 patients who failed to enjoy immune reconstitution despite durable, successful ART (CD4 <350/µL after at least 2 years of HIV RNA below the limit of detection), and compared these immune failure (IF) patients to 21 HIV-negative controls, and 20 HIV-positive treated patients with immune reconstitution (immune success, IS). [6]

A panoply of soluble markers and mediators of inflammation were measured: the pro-inflammatory cytokine IL-6, the D-dimer coagulation marker, and markers of microbial translocation -- the soluble CD14 LPS receptor and LPS itself. Overall, the mean levels of these markers were statistically different in ways that would be largely expected, given the prior work of this group and others. IL-6 and sCD14 levels were higher in IF than IS, and both higher than in uninfected patients. D-dimer levels were similar in IF and IS, but higher than healthy controls. LPS tended to be higher in IF and IS than in controls, but not significantly. In IF patients, but not IS patients, statistical correlations were seen between duration of untreated HIV infection and IL-6 and to D-dimer levels. What is unsatisfying is that there is considerable overlap in the individual data points, despite the statistically significant difference that can be demonstrated in mean or median values. If these parameters are critical drivers of immunopathogenesis, it is dissonant that these parameters are well within the normal range in a large number of patients with profound immune abnormalities.

A study of 9 patients from UCSF, who initiated therapy with advanced disease (mean nadir CD4 count 87 cells/mm3) and had maintained ART suppression for a median of 40 months, visually quantitated the density of collagen seen on staining of rectal biopsies. [7] Hunt and colleagues speculated that fibrosis in the lymphoid tissue of the GALT might impair functional T cell responses. In particular, it was hypothesised that the maintenance of CD8 cell responses might be impaired by fibrosis. As is generally the case in many such studies, a hyperactivated CD4 cell population was observed. Why abnormalities of lymphoid architecture would specifically lead to a dichotomised phenotype of CD38+ CD4+ cells but not CD38+ CD8+ cells was not addressed. Why the maintenance of an HIV-specific CD8+ T cell response would be expected in patients in whom viraemia had been suppressed for a median of almost 3.5 years was also unclear.

Interventions for inflammation

HIV pathogenesis appears to be extremely complex and multifactorial. Of course, it really is ultimately “all about the virus, stupid,” as without HIV replication there is no pathogenesis. However, the consequences of HIV replication clearly persist long after ART has suppressed viraemia. So the challenge that the field faces is to determine which the myriad effects of the virus on the immune system are the central and significant drivers of pathology, and are there any interventions that can improve health or outcomes beyond those benefits conferred by ART. A radical might even say what interventions can confer benefit in place of ART, but that seems a bit heretical in the so-called “post-SMART” era.

As described above, CROI presented many observations of immune-related phenomenology and associations of these with immune pathology. But to go beyond associative work, the relationship of phenomena to pathology must ultimately be tested with interventions. Interventions in the best of worlds could actually become therapies to be used to improve or normalise immune function and health outcomes, but least interventional clinical experiments might enlighten as to the drivers of HIV pathogenesis despite ART. Happily, several such studies were shared at CROI.

Raltegravir

Several studies have demonstrated that low-level viraemia is unaffected by the intensification of suppressive ART with raltegravir. Lichtenstein and colleagues measured the immunological effects of raltegravir intensification. [8] This was an uncontrolled, single-arm study of 30 patients, with results from 26 being reported. At baseline, patients had CD4 counts <350 cells/mm3 or declining CD4 counts (average CD4 count 273 cells/mm3). ART suppression was in place for > 1 year, but an average of 7.2 years. This was therefore a somewhat unique cohort of patients with discordant immune responses despite very long-term suppression. After 1 year of raltegravir intensification, there was no change in absolute CD4 number, but modest increases in CD4% and CD4/CD8 ratio. So it seemed that therefore CD8 count declined. Also observed was a substantial reduction in activated CD4 cell percent, but it was not clear if this was a 30% decline from a high baseline or from a small number of residually activated cells.

In a larger, controlled crossover study of RAL intensification Ghandi led the ACTG 5244 team to examine the effect of RAL intensification. [9] This work had previously shown no change in low-level viraemia after addition of RAL, but here focused on other potential effects of intensification. In this study they could measure no change in the detection of 2-LTR circles, dead-end products of HIV reverse transcription that can be increased by RAL in vitro. Some patients had detected 2-LTR circles at baseline (2-LTRpos) and others not (2-LTRneg). Like the Lichtenstein group, Ghandi et al. examined CD4 counts and percentages, as well as CD4 and CD8 activation, again measured using the surface markers CD38 and HLA-DR. Neither the 2-LTR-positive nor 2-LTR-negative group had a significant decline in CD4% or CD8 cells that were CD38+HLA-DR+. This group had earlier reported a slight trend towards increase in CD4 cell counts over the 12 week period of raltegravir intensification [10] differing from the modest increase in CD4% but no change in CD4 cell count seen in the Lichtenstein study. Obviously, some of the differences in results might be related to the patient groups: stable patients in the Ghandi study and patients with persistently lower CD4 counts in the Lichtenstein study. But neither study really revealed profound immunological benefits of raltegravir intensification, suggesting that as a clinical maneuver intensification may not be a practical answer to poor immune reconstitution, and leaving doubt that ART intensification could further normalise immune function in a clinically meaningful way.

Massanella also reported on immunological findings in follow-up of their prior raltegravir intensification study. [11] In this study, the investigators had originally seen an increase in 2-LTR circles after RAL addition, but this was measured at two weeks after intensification, and did not persist. Ghandi et al. saw no increase in circles, but did not have samples to examine the two week timepoint, and could only measure later. In the Massanella study, patients in whom an increase in 2-LTR circles was seen also had a greater level of CD8 T cell activation (of HLA-DR+CD38+, HLA-DR+CD45RO+, and CD45RO+CD38+) prior to raltegravir, and a reduction after 24 weeks of raltegravir. Levels of CD8 activation returned to their prior elevated levels after raltegravir discontinuation. However, this deactivation/reactivation effect was not seen in most of the patients (22 of 34) in the study who did not have an increase of 2-LTR circles. Also unlike the Lichtenstein study but like the Ghandi study, no changes were observed in activation markers in CD4 T cells.

What does this all mean? Massanella concluded that the reduction of immune activation in CD8 T cells after 48 weeks of intensification, and the subsequent reversion to pre-intensification levels after RAL discontinuation, suggested that CD8 T cell activation may reflect incomplete suppression of viral replication during apparently suppressive HAART. To this author, this conclusion seems difficult to reconcile, unless one accepts that plasma viraemia – unaffected by raltegravir intensification – is not proportional in some way to viral expression, new cell infection, new viral integration, and new viral production in another (tissue?) compartment.

This is because in patients with measurable 2-LTR circles and stable low-level viraemia (measurable but less than 50 copies/ml), Massanella showed that 2-LTR circles transiently increased after raltegravir – presumably as cells that are newly infected form circles rather than viral integrants. But then concurrent with this, CD8 cell activation declines, presumably as fewer cells experience new viral integrants, and production of virions or viral proteins declines. However, plasma viral load does not change during RAL intensification, and ART resistance does not develop prior to raltegravir intensification, despite these putative ongoing rounds of reverse transcription, integration, and virion production. In my view, the results of these three studies are not concordant, and there is not one model that accounts for all the observations. It is possible some of the observed effects are marginal ones seen in small studies of uniquely selected patient populations.

Maraviroc

Two other studies used the CCR5 entry inhibitor maraviroc as a probe in a manner similar to the RAL intensification studies. During other maraviroc studies, a rise in CD4 cells has been reported. The mechanisms that lead to this rise, and its clinical relevance, have been unclear. Wilkins and colleagues reported follow-up at 48 weeks from an ACTG maraviroc intensification study in patients with CD4 count <250 cells/mm3 after ART. [12] The initial 24-week intensification study had reported declines in CD4+ and CD8+ activation after maraviroc intensification; these changes were seen to partially reverse 24 weeks after maraviroc discontinuation. Absolute CD4 counts did not increase in this trial, as had been reported in some earlier MVC studies. That some measures of immune activation improved after maraviroc intensification, and then partially reversed after maraviroc discontinuation, support the idea that maraviroc was the direct cause of these effects.

An opposite result was found by Hunt and colleagues, who performed a randomised, placebo-controlled trial of 24 weeks of maraviroc intensification in patients with CD4 counts <350 cells/mm3 and plasma HIV RNA levels <48 copies/mL on ART for ≥1 year. [13] Most had been on suppressive ART for about 30 months. The primary outcome measurement examined was an immunological one: the change in percentage of activated (CD38+HLA-DR+) CD8+ T cells in peripheral blood. Maraviroc or placebo was added for 24 weeks, with virologic and immunologic evaluations at entry, week 4, week 24, and twelve weeks after maraviroc was stopped at week 36. Serial rectal tissue sampling was also performed in some patients.

HIV RNA by a single-copy assay declined for week 0 to week 4 in both arms and in both groups CD4 cell counts rose 37 cells/mm3, highlighting the danger of imputing biological effects to small changes in assays near the limit of detection, and the benefit of a placebo control. The overall primary results of the study were even more perplexing.

Starkly opposite of what was expected and hypothesised, through week 24 the percentage activated CD8+ T cells declined in the placebo arm but increased in the maraviroc arm. Again, surprisingly in the rectal tissue, biopsies showed a nearly two-fold increase in rectal CD4+ or CD8+ T cell activation in the maraviroc arm, and small decrease in the placebo arm. To complete the confounding observations, plasma lipopolysaccharide, a marker of bacterial translocation declined through week 24 in the maraviroc arm despite increasing markers of activation, while sCD14 (another marker associated with bacterial translocation) increased.

Again, what are we to make of these discordant results? As maraviroc binds human CCR5 cell receptors, these changes may reflect an immunomodulatory effect of maraviroc, and might not be related to any antiviral effect of the drug in these suppressed patients. But given the different findings in studies, one can only conclude that these discrepancies are related to subtly differing clinical populations, or that some of the changes must be ascribed to chance or biological variation. These results remain to be further confirmed, as does the demonstration that this modest immunomodulatory effect results in improved immune function, or even a clinically relevant outcome.

Hydroxychlorquine

Piconi and colleagues presented a creative study attempting to measure the effect of a direct immunodulatory drug in ART-suppressed patients without immunological response to ART. [14]

Hydroxychloroquine alters lysosomal pH and has been used to treat malaria. It immunological effects have led it its use in

autoimmune diseases, and recently it has been shown to act by blocking the signaling of toll-like receptors on dendritic cells. In this way, chloroquine dampens the inflammatory response.

Twenty patients with nadir CD4 counts of about 50 cells/mm3 and CD4 counts on ART suppression persistently <200 cells/mm3 (median 184 cells/mm3) received 400 mg/day of hydroxychloroquine for six months. An array of immunological changes were seen, some of which reverted to or towards baseline two months after hydroxychloroquine was stopped. These included an increased CD4+ T cell percent, a reduction of activated CD4+T cells, memory and activated CD8+ cells and activated monocytes. Plasma LPS levels were rescued, and this reduction persisted after hydroxychloroquine was stopped. Although the potential toxicity of hydroxychloroquine would need to be weighed and tested, and the potential clinical benefits of these changes demonstrated more clearly, the use of a well-known and inexpensive drug probably deserves more study.

Inflammation and Intervention in the CNS

Echoing this work in the peripheral blood, there were some studies of inflammation and therapy in the CNS presented at CROI. Carsenti-Dellamonica and colleagues measured neurocognitive impairment by psychometric testing, and in 179 patients in whom a plasma sample to measure LPS was available, found that higher LPS levels were associated with neurocognitive impairment. Again, as discussed above, this association may not be causal. The other independent association in multivariate analysis found with neurocognitive impairment was cellular proviral DNA, a measure associated with long-term exposure to viraemia and advanced disease. [15]

In a similar way, Lyons and colleagues found that soluble CD14 was associated with impaired performance on neurocognitive testing. In 97 patients with nadir CD4 counts <300, they found plasma sCD14 levels were higher in subjects with neurocognitive test scores indicating global impairment. However, their cohort was challenging, 38% HCV-positive, 59% using illicit drugs, only 72 of the 97 on ART, and of 57/72 patients had HIV RNA >1000 copies/mL. While the authors suggested the potential utility of plasma sCD14 as a peripheral biomarker to monitor progression of neurocognitive dysfunction related to HIV, this observation may be complicated due to the population's coinfection, drug use, and incomplete ART suppression rates. [16]

Letendre studied the phosphorylated form of the CSF protein Tau, and found that Tau levels were higher in older patients on ART with greater immune recovery, and that this in turn was associated with poorer memory function. Again, the utility and specificity of this biomarker for predicting and following HIV-related neurological disease will have to be expanded and broadened in other patient cohorts. [17]

Dahl and colleagues performed an antiviral intensification study focusing on the CSF. HIV-1-infected patients on therapy for >2 years with plasma suppression <50 copies/mL for >1 year and CSF suppression <50 copies/mL at screening were enrolled in a randomised, open-label study of a 12-week course of raltegravir intensification. HIV RNA in the CSF was detected, but was generally lower than in plasma: HIV-1 was detected in the CSF in 8/36 samples (median 0.3 copies/mL) and in the plasma of 26/40 plasma samples (median 1.4 copies/mL) with a low inter-patient variability. As in the plasma, there was no effect of raltegravir intensification on CSF HIV RNA. [18]

Similarly, Price and colleagues added raltegravir to suppressive regimens should test if this resulted in a further decrease in brain viral replication and its stimulation of intrathecal immune activation. They found no evidence that RAL intensification reduced intrathecal immunoactivation in virally suppressed subjects. [19]

Sacktor and colleagues reported the results of a minocycline trial aiming to treat HIV-associated neurocognitive disorders (HAND). HIV-1-infected individuals with progressive neurocognitive decline were enrolled in a prospective, randomised, double-blind, placebo-controlled study of minocycline, across 16 sites. Participants were randomised to receive either minocycline 100 mg orally or matching placebo orally every 12 hours. 107 HIV-infected individuals, of whom 51% had mild cognitive impairment, and 38% had HIV dementia (mild-MSK Stage 1). Minocycline was safe and well tolerated in individuals with HIV-associated cognitive impairment, but cognitive improvement was not observed in this study. As with the periphery, there are not yet good tools to intervene in the mild inflammation that persists in many patients on ART, and not a clear understanding of the risks and benefits of potential interventions. [20]

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DRUG INTERRACTIONS

Recent updates to the Liverpool University drug interaction website.

Meeting report from 12th Pharmacology Workshop, Miami.

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=543

PDF download:

http://www.hiv-druginteractions.org/data/NewsItem/89_12 PKW Miami.pdf

Meeting report from 18th CROI, Boston

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=535

PDF download:

http://www.hiv-druginteractions.org/data/NewsItem/88_CROI_2011.pdf

Atazanavir/ritonavir and combined oral contraceptives

HIV-druginteractions.org

This was an open-label, three-period, single-sequence student assessing the effect of atazanavir/ritonavir on the pharmacokinetics of oral contraceptive containing either 35 microgram ethinyl estradiol plus norgestimate (OC given alone for days 1-28) or 25 microgram ethinyl estradiol plus norgestimate (OC given with atazanavir/r on days 29-42).

Reductions of approximately 20% in ethinyl estradiol levels were seen, whereas the concentrations of 17-deacetyl norgestimate (active metabolite) were increased (AUC by 85%, Cmin by 102%).

The authors concluded that increasing the ethinyl estradiol component to 30-35 microgram when co-administered with atazanavir/ritonavir might be desirable to minimise breakthrough bleeding.

Ref: Zhang J et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. Antivir Ther, 2011, 16(2): 157-164.

http://www.ncbi.nlm.nih.gov/pubmed/21447864

BHIVA NEWS

BASHH/BHIVA PEPSE guidelines for comment

Draft UK national guideline on HIV PEPSE 2011 are available for consultation until 5th June 2011.

UK GUIDELINE FOR THE USE OF POST-EXPOSURE PROPHYLAXIS FOR HIV FOLLOWING SEXUAL EXPOSURE

The main objective is to ensure the appropriate use of post-exposure prophylaxis (PEP) following potential sexual exposure (PEPSE) to HIV as a potential method of preventing HIV infection.

This guideline offers recommendations on the potential use of PEPSE, the circumstances in which it may be recommended, the treatment regimens which may be recommended and the appropriate use of subsequent diagnostic tests to measure individual outcome. These guidelines are intended to be complementary to the existing DH/EAGA guidance on PEP.

It is aimed primarily at clinicians and policy-makers in sexual health, primary and emergency care within the United Kingdom who should consider the development of appropriate local pathways. It is likely that this guideline will be used by voluntary sector agencies in providing information for individuals who may potentially be exposed to HIV during sexual activity.

Comments should be sent to the CEG guideline lead Dr Keith Radcliffe, marked 'PEPSE':

keith.w.radcliffe@hobtpct.nhs.uk

http://www.bashh.org/guidelines

UK national guideline on safer sex advice

New UK National Guideline on Safer Sex Advice are online until 31 May 2011 for comments.

http://www.bhiva.org/SaferSexAdviceConsultation.aspx.

The objective of this document is to provide guidance for practitioners in Level 3 Genitourinary medicine (GUM) services (Level 5 in Scotland) on safer sex advice provided in sexually transmitted infection (STI) and HIV management consultations. The guideline consists of:

- Recommendations on the format and delivery of brief behaviour change interventions deliverable in GUM clinics
- Recommendations on the content of safer sex advice given to individuals at continued risk of STI
- Additional advice to be provided for those living with HIV, or from groups with higher rates of HIV incidence.

The Clinical Effectiveness Group of BASHH and BHIVA is grateful for all comments, which will be reviewed before publication.

PREVENTION

FEM-PrEP prevention study using daily Truvada halted during enrollment: interim analysis shows similar infection rates in active and placebo arms

On 18 April a press statement from Family Health International announced that the FEM-PrEP study had been stopped by the trials Independent Data Monitoring Committee (IDMC) due to an interim analysis that showed no difference between rates of new HIV infections in the active tenofovir/FTC (Truvada) group compared to the people using placebo. [1]

In this study Truvada or placebo was being taken daily as a pre-exposure prophylaxis prevention (PrEP) treatment against HIV. When the decision to stop the study was taken, almost 2000 women from Kenya, Tanzania and South Africa were enrolled, just over half the planned number of particiapants.

These results are both extremely disappointing and surprising given that a similar study in gay men at high risk of infection (young, multiple partners and exposures, high alcohol use etc) showed a strongly protective effect. [2]

FEM-PrEP was also being run in a high-risk group: 20% of 3752 women who came forward to participant were already HIV positive when screened.

The approximate rate of new HIV infections among trial participants was 5% per year. The 56 new HIV infections were equally distributed between the active and placebo arm. Although adherence was reported at 95% similar to self-reported adherence in the iPrEX study, a pharmacokinetic sub-study in iPrEX indicated that actual adherence was far lower.

Further analyses from the study are needed to explain the starkly different results compared to iPrEX. The level of protection was expected to be similar based on systemic exposure to the same prophylactic drugs, but this would also be dependent on drug levels achieved in the genital tract.

As with all prevention studies, all participants were given support to reduce their risk of HIV, including advice to always use condoms.

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SIDE EFFECTS

Tenofovir associated with fewer side-effect related switches compared to AZT or d4T in first-line treatment

Nathan Geffen, Community Media Trust

Medecins Sans Frontieres (MSF) have published the results of an analysis of a Lesotho cohort, comparing toxicity and regimen substitutions due to tenofovir versus AZT and d4T (stavudine). [1]

The findings of this nurse-managed community cohort study support the latest WHO guidelines that recommend the replacement of d4T with either tenofovir or AZT. This study confirmed available evidence because it showed that tenofovir has lower side effect rates. This coupled with easier dosing makes it a better option than either d4T or AZT.

Between January 2008 and December 2008, 1,185 adult patients (785 women) were enrolled into care and the records of 1,124 were analysed. All patients were prescribed 3TC and either nevirapine or efavirenz. Their third drug was tenofovir, AZT or d4T (at 40 mg BID dose). This period was chosen because there was overlapping use of the three drugs during this period, as d4T was phased out and tenofovir was phased in.

Nearly all patients initiated on tenofovir were given baseline renal function tests. Patients with low creatinine clearance were not initiated on tenofovir. Therefore 13 patients with severe renal insufficiency (CrCl <30 mL/min) were excluded from the analysis to avoid bias. From HAART initiation the endpoints were death, loss to follow-up or first toxicity-driven switch. Median age was 39 years. The authors noted that proportionately fewer women were initiated on tenofovir than AZT or d4T (53.5% v 89% v 78% respectively) due to misconceptions among health workers that tenofovir should not be initiated in pregnant women.

The study included 587 patients started on tenofovir, 255 on AZT and 282 on d4T with a similar median time on treatment of 483 days (IQR: 392-585), 493 days (IQR: 349–580) and 480 days (IQR: 277–610) respectively.

The overall mortality rate for the cohort was 6.5 per 100 person-years [95%CI: 5.3 to 7.9 per 100 person-years]. For patients on tenofovir, the mortality rate was 5.1 per 100 person-years [95%CI: 3.8 to 7.0), for those on AZT, 7.5 per 100 person-years [95%CI: 5.0 to 11.1] and for those on d4T, 8.3 per 100 person-years [95%CI: 5.8 to11.7]. None of these differences were significant.

The overall rate of switches due to toxicity was 8.0 switches per 100 person-years [95%CI: 6.7 to 9.6]. Based on the regimen that patients were on, this rate of switch differed significantly; for tenofovir the switch-rate was 3.0 switches per 100 patient-years [95CI%: 2.0 to 4.5]; for AZT it was 8.1 switches per 100 patient-years [95CI%: 5.4 to 12.1] and for d4T it was 18.8 switches per 100 patient-years [95CI%: 14.8 to 24.1].

The most common reason for switching regimens amongst patients on tenofovir (n=19) was renal toxicity (18 patients). For AZT (n=15) it was severe anaemia (11 patients) and for d4T (n=42) it was severe neuropathy (29 patients). Also in the d4T group 11 patients switched because of lipodystrophy and two because of severe lactic acidosis.

Tenofovir-associated renal toxicity was low and generally well managed. Of the 5% who developed toxicity, the majority had a creatinine drop of less than 10 mL/min, and all but 3 returned to normal on a subsequent measurement."

The authors conclude that their study indicates that in resource poor settings where the detection of lactic acidosis and the monitoring of neuropathy and lipodystrophy are difficult, the use of tenofovir as the first-line option is advised.

C O M M E N T

This study confirms expectations and adds further evidence to support the changes in WHO guidelines as well as by South Africa and other African countries in recent years.

But this study also allays a concern that renal toxicity rates from tenofovir might be unmanageably high in an African setting. In the US kidney disease is four times higher amongst African Americans than Caucasians. [2] Tenofovir's good side-effect profile was based in large part on its use in non-African settings, though there is no evidence that tenofovir is associated with lower GFR amongst people of African descent in the US and Europe. The Lesotho study is reassuring because it confirms that the drug's association with few side-effects can be expected in African populations as well.

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BASIC SCIENCE

Basic science and vaccine research news from Richard Jefferys excellent web blog.

Reduced HIV replication in CD4 T cells from elite controllers

Richard Jefferys, TAG

A number of studies have investigated whether control of HIV replication in the absence of treatment (referred to as elite control if viral load is <50 copies/mL and viraemic control if <2,000) is associated with having CD4 T cells that are intrinsically resistant to infection. Results to date have shown that elite and viraemic controllers have CD4 T cells that support viral replication just as well as those sampled from individuals with progressive disease. However, Mathias Lichterfeld's laboratory at the Ragon Institute of Massachussetts General Hospital wondered if perhaps the typical conditions for measuring HIV replication in CD4 T cells in the lab—which involve the use of strong activation stimuli such as PHA—were masking subtler differences. They now report on their exploration of this possibility in the Journal of Clinical Investigation. [1]

The study finds that CD4 T cells from elite controllers resist HIV infection and viral replication significantly better than those from individuals with progressing disease and HIV-negative controls. The same is true for viraemic controllers, but in their case the differences are smaller. The pattern remains consistent using a variety of different approaches for measuring HIV infection and replication in vitro, and holds for both R5- and X4-tropic HIV isolates. The researchers, led jointly by Huabiao Chen, Chun Li, Jinghe Huang, and Thai Cung from the lab, go on to uncover that increased expression of a host cell protein called p21 in CD4 T cells from controllers correlates with reduced susceptibility to HIV. This is further confirmed by experiments showing that inhibition of p21 expression using a short interfering RNA substantially abrogates the apparent protective effect. In terms of the causative pathway, the researchers offer evidence that p21 blocks another host cell protein, cyclin-dependent kinase 9 (CDK9), which according to prior studies plays an important role in HIV transcription.

The discussion section of the paper points out that p21 expression has previously been connected to inhibition of HIV in macrophages and hematopoietic stem cells. The authors speculate that the reduced susceptibility of controller CD4 T cells synergises with other

reported mechanisms of immunological control, noting specifically that "a highly functional CD8+ T cell response against HIV-1 may only develop in the setting of a CD4+ T cell compartment that is less capable of supporting highly replicative HIV-1 infection." Broadly similar findings were also reported at the recent CROI conference in a poster by an independent group at the Institut Pasteur in France.

The discovery of p21's role in controllers may open new avenues for inhibiting HIV by targeting its interactions with host cell proteins. It also provides encouragement for strategies aiming to induce CD4 T cell resistance to the virus (such as the CCR5-deletion approach being developed by Sangamo Biosciences), because it implies that these cells would then be better able to support the function of CD8 T cells and possibly other components of the immune response against HIV.

Source: TAB Basic Science Blog. (22 Mar 2011).

http://tagbasicscienceproject.typepad.com

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More studies on the loss of naïve T cells

Richard Jefferys, TAG

An earlier post reviewed work by Beth Jamieson and Tammy Rickabaugh describing the parallel effects of HIV infection and aging on the pool of naïve T cells in humans. Three recent papers address different aspects of naïve T cell loss, including the first study to document a decrease in this population in people with chronic hepatitis C infection. [1]

In PLoS One, Beth Jamieson's group reports on a study of naïve CD4 T cell levels in younger (20-32 years) and older (39-58 years) individuals with untreated HIV infection, compared to age-matched HIV-negative controls. [2]

The researchers use a cell surface marker named CD31 to discriminate between naïve CD4 T cells that have recently been produced by the thymus (CD31+) and those that have proliferated in the circulation (CD31-). Consistent with previous studies, HIV infection had a strong effect on naïve CD4 T cell levels that was additive to that seen in aging; the absolute number of CD31+ naïve CD4 T cells in the younger individuals mirrored those measured in HIV-negative controls who were 17-28 years older. While both HIV infection and ageing were associated with declines in CD31+ naïve CD4 T cell numbers, loss of CD31- naïve CD4 T cells was only observed HIV infection; in this case the effect was independent of ageing as the absolute loss was similar in both the younger and older HIV-positive participants. In a separate longitudinal analysis of the effects of antiretroviral therapy, CD31+ naïve CD4 T cells achieved levels comparable to age-matched controls after two years of treatment. However, CD31- naïve CD4 T cell levels remained significantly reduced.

The researchers also evaluate telomere lengths in both naïve CD4 T cell subsets, finding them to be reduced both as a result of HIV infection and aging; as was seen for CD31+ naïve CD4 T cell numbers, the effects were additive. Jamieson and colleagues conclude by suggesting that their results likely explain why disease progression occurs more rapidly among HIV-positive individuals over the age of 50, because this older population already has reduced numbers of naïve CD4 T cells, making the impact of HIV infection more severe. They also note that incomplete recovery of naïve CD4 T cells may play a role in increasing the risk of aging-associated diseases in people with HIV.

One commonly cited causative mechanism of naïve T cell depletion in HIV is the persistent activation of these cells, which leads to their differentiation into memory cells. Another contributing factor is lymphoid tissue fibrosis (a type of scarring damage associated with immune activation & inflammation). Naïve T cells continually recirculate through lymphoid tissue and depend on signals received in that environment for their survival. A recent study by Ming Zeng and colleagues delves into this link between lymphoid tissue fibrosis and naïve T cell loss in both SIV and HIV infection. [3]

The researchers find that fibroblastic reticular cells (FRC)--which form the pathways along which T cells travel in lymph nodes--are the major source of IL-7, a cytokine essential for naïve T cell survival. Fibrotic damage (measured by the accumulation of collagen) is shown to disrupt the FRC network and therefore impede the ability of T cells to access IL-7, causing an increase in T cell apoptosis. Both naïve CD4 and CD8 T cells are affected. Additional studies reveal that the loss of T cells in turn exacerbates the damage to FRCs by reducing the production of a cytokine called lymphotoxin-β, which is vital for maintaining FRC networks. The results suggest that there is a vicious cycle in which fibrosis damages FRCs, which causes T cell loss, which then further exacerbates FRC loss.

Continuing their investigative work, Zeng et al look for a source of collagen and find that production of the cytokine TGF-beta by regulatory T cells is increased in HIV, and TGF-beta induces collagen production by fibroblasts. In lab experiments, the antifibrotic drug pirfenidone blocks TGF-beta signaling and reduces collagen production, leading the researchers to conclude that this drug may deserve consideration as an adjunctive therapy for promoting immune reconstitution in HIV.

Lastly, a study published in the March 1st issue of the Journal of Infectious Diseases demonstrates that another persistent chronic infection, hepatitis C, can accelerate naïve CD4 T cell loss. The authors conclude that their findings provide an explanation for the reduced response to vaccinations observed in people with chronic HCV.

Source: TAG Basic Science Blog. (17 Mar 2011).

http://tagbasicscienceproject.typepad.com

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The immunological effects of old age and anti-CMV immunity in HIV infection

Richard Jefferys, TAG

Following on the heels of yesterday's post, a study has just been published by the journal AIDS that echoes the same themes. [1]

The researchers, led by Victor Appay, find that depletion of naïve CD4 and CD8 T cells represents the major parallel between HIV infection and aging and, like Beth Jamieson's group, they note that the effects are additive. The researchers also report that immune responses to another chronic infection – CMV – are associated with reduced naïve T cell reconstitution in people with HIV on antiretroviral therapy, consistent with the idea that chronic infections can place a drain on naïve T cell resources (CMV infection has also been associated with reduced naïve T cell levels in individuals not infected with HIV). Additionally, Appay and colleagues look at markers of T cell senescence in HIV and aging, but find that the parallels are not as clear as those documented for naïve T cells.

Source: TAG Basic Science Blog. (18 Mar 2011).

http://tagbasicscienceproject.typepad.com

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JOB VACANCY

Treatment activist post at i-Base

i-Base have a vacancy for a treatment activist.

As we are a small organisation, this involves contributing to all aspects of the project, with an emphasis on the treatment information services (phoneline, email and web-based) and publications (HTB and treatment guides).

The successful candidate is expected to be familiar with the work we do (both nationally and internationally), keep up to date with scientific developments in HIV treatment and prevention and to be able to communicate these to others in many different formats.

We are looking for someone who is dynamic, treatment literate and self motivated. We are looking for someone who is happy to work independently and also as part of a team. There will be opportunities to develop new projects within our organisation.

The goal of our organisation is for excellent quality of care and equality of access for people with HIV.

We have an equal opportunities policy and we are particularly interested to hear from HIV-positive candidates.

This post can be part-time or full-time.

For more information:

http://i-base.info/about-us/volunteering-and-staff-vacancies/

ON THE WEB

Community resources and publications:

TAG hepatitis C pipeline report

FDA approval of two hepatitis C-specific protease inhibitors, the first of the coming wave of oral antiviral drugs, is anticipated later this year. Dozens of drugs are in development to fight hepatitis C virus (HCV).

The Treatment Action Group 2011 Hepatitis C Treatment Pipeline Report is a comprehensive overview of drugs in clinical trials. The Pipeline covers a range of issues, including diagnostics, drug resistance, access to, and delivery of treatment, and population-specific focus on the new HCV drugs, as well as research recommendations.

Download

http://cts.vresp.com/c/?TreatmentActionGroup/b5f575334e/9e21c20d7a/9ae5755cb4/id=4416

FUTURE MEETINGS

2011 conference listing

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

6th International Workshop on HIV Transmission - Principles of Intervention

14–15 July, Rome, Italy

http://www.virology-education.com

13th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV

14–16 July 2011, Rome, Italy

http://www.intmedpress.com

3rd International Workshop on HIV Paediatrics

15–16 July, Rome, Italy

http://www.virology-education.com

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

17–20 July 2011, Rome

http://www.ias2011.org/

51st ICAAC,

17–20 September 2011, Chicago

http://www.icaac.org/

13th European AIDS Conference (EACS)

12–15 October 2011, Serbia

http://www.europeanaidsclinicalsociety.org

2nd International Workshop on HIV & Ageing

October 2011, Baltimore, USA

http://www.virology-education.com

4th Annual BHIVA Conference for the Management of HIV / Hepatitis Co-infection

16 November 2011, London (venue tbc)

http://www.bhiva,org

BHIVA Autumn Conference including CHIVA Parallel Sessions

17-18 November 2011, London

http://www.bhiva,org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website is designed with portals for healthcare professionals, HIV-positive people and community advocates.

It is fast and easy to access, use and navigate.

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

http://www.i-base.info/qa

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

The advocacy resources include an online training manual with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 100,000 pages individual ISP accounts contact the website each month, with over 6000 hits a day.

Non-technical treatment guides

i-Base treatment guides

i-Base produce five booklets that comprehensively cover five important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

http://www.i-base.info/guides

- Introduction to combination therapy (July 2010)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment and drug resistance (February 2011)
- Guide to HIV, pregnancy & women's health (January 2009)
- HIV and quality of life: side effects & complications (December 2010)

Publications and reports

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

http://i-base.info/htb

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

http://i-base.info/htb-south

HTB Turkey

HIV Tedavi Bülteni Türkiye *(HTB Turkey)* is a Turkish-language publication based on HTB and produced three times a years by an independent group of Turkish doctors, activists and health care workers.

http://i-base.info/home/hiv-tedavi-bulteni-htb-turkey/

ARV4IDUs

An electronic publication, Antiretroviral Treatment for Injecting Drug Users (ARV4IDUs) is produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

http://i-base.info/idu

Treatment information needs of African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://i-base.info/home/africans-and-treatment-infomation

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over ten years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A meeting, held in Cape Town focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

Text is provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans.

Translations of i-Base publications

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

http://i-base.info/category/translations

Languages currently include:

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

Advocacy resources

Online advocacy training manual

http://www.i-base.info/education

Entry-level curriculum relating to HIV and treatment. Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

http://www.i-base.info/manual/en/index.html

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 380 members from over 120 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from all meetings are posted. Membership is free.

http://www.ukcab.net

World CAB - reports on international drug pricing

Reports from meetings between community advocates and pharmaceutical companies focused on pricing and global access to treatment. Available as PDF files.

Treatment information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

We can provide information by phone, email and online based on the latest research.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

An online question and answer service that now has over 1500 questions online. Questions can be answered privately, or with permission, can be answered online.

http://www.i-base.info/qa

Recent questions include:

- Is HIV causing my low platelet count?
- What can I do about my high levels of bilirubin now I am on atazanavir?
- If I adhere 100% will resistance happen over time anyway?
- Could my HIV positive test result be caused by EBV infection?
- Can I take antibiotics with my ARVs?
- How can someone with a low CD4 prevent opportunistic infections?
- How can I prevent muscle wasting?
- Is my premature ejaculation related to HIV?
- What does a CD4 count of 11 mean?

- My CD4 count is good but I am ill - is this normal?
- What is happening to my CD4 count and why is it changing?
- What are the side effects of atazanavir, abacavir and Atripla?
- Are my cholesterol levels ok?

Other resources

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

Generic clinic forms

A set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

http://i-base.info/category/publications/clinic-forms

i-Base can add your hospital or Trust logo to these forms.

Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK. Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

http://i-base.info/order

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:
http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources.

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HIV i-Base

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However, any donation that your organisation can make towards our costs is greatly appreciated.

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Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

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From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

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