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EDITORIAL

This is an exciting and important time for HIV care.

This issue of HTB includes reports from the IAS 2015 conference in Vancouver where new studies on treatment and prevention will change HIV guidelines and programmes worldwide.

These developments are covered in a range of articles that support a radical change in our approach to managing HIV. One such example is that the option to start treatment promptly becomes the routine next step after someone finds out that they are HIV positive.

This does not mean losing the wealth of experience that led to the current multidisciplinary model of care. It means focusing that experience so that some aspects of this approach do not become a barrier to treatment.

The San Fransicso model presented at IAS 2015, in what might be seen as a hard to treat population, showed that the option for same day ART could be expanded in the UK to more than just the few clinics here that currently focus on treating primary HIV infection.

IAS 2015 did not just have implications for the UK but for global health, for which setting the UNAIDS 2014 targets of 90-90-90 produces not just a way to measure how well a country is responding to HIV, but provides a framework for dramatically reducing new infections, even within five years.

This approach involves not just early treatment, but better treatment, better testing and better prevention that includes PrEP.

The draft 2015 BHIVA guidelines, reported later in this issue of HTB, reflect the most significant changes in HIV care and treatment strategies for at least a decade.

Other reports from IAS include notice that WHO 2015 guidelines will similarly recommend ART for all irrespective of CD4 count.

The 90-90-90 targets mean by 2020, 90% of all HIV positive people will know their status, 90% of all people with diagnosed HIV will receive ART and 90% of all people receiving ART will have viral suppression. Many of the developments reported at IAS 2015 – which we cover in this and the next issue – will contribute towards these ambitious goals.

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CONFERENCE REPORTS

8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015)

19 – 22 July 2015, Vancouver, Canada

Introduction

The 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015) was held from 19 – 22 July 2015.

This large biennial meeting has a greater focus on clinical and scientific research than the broader social-based programme of the International AIDS Conference with which it alternates every two years.

The programme for the conference is now posted to the IAS 2015 website as PDF files and the Programme-at-a-Glance (PAG) is also online.

http://www.ias2015.org

http://www.pag.ias2015.org

Many oral presentations are available as webcasts, including some plenary lectures, special symposia, oral abstract sessions and the opening and closing ceremonies. But coverage seems less than previous years and this is a pity. Many of the PowerPoint slides from talks and PDF files of posters are online.

Although currently access to the this material is predominantly through the online programme-at-a-glace, for those who find navigation takes slightly longer, i-Base have published a short access guide.

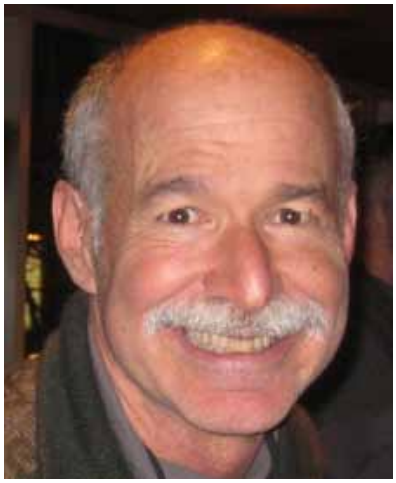
http://i-base.info/htb/28686

Unfortunately, URL hyperlinks to individual abstracts are not available with the current PAG. This is likely to limit practical access to this otherwise important aspect of the conference.

Reports in the issue:

IAS 2015: IN MEMORY

Tribute to Bob Munk: long-time HIV positive US treatment activist and educator



Simon Collins and Polly Clayden, HIV i-Base

It was with great sadness that in the week before IAS we learned of the death of Dr Robert Munk, a long-time US activist, friend and colleague.

We cannot remember a conference over almost twenty years that Bob did not attend, and of course he preceded us in this work by at least a decade. As a small tribute, our reports from IAS 2015 are dedicated to his work.

Bob was one of the first US activists that we met in the late 1990s while working at AIDS Treatment Project before we set up i-Base in April 2000.

Community meetings back then were often lively and Bob was notable for his steady calmness and kindness in interactions that could otherwise be energetic and sometimes volatile. The tributes that have followed his death have all focused on this gentleness and on his generosity to other activists.

Bob also worked internationally and was one of the few long-term US members of the European AIDS Treatment Group (EATG).

Since 1997, Bob started and developed The New Mexico AIDS Infonet resource (www.aidsinfonet.org) of non-technical fact sheets that was unparalleled for both the breadth of the subjects and the insistence on writing for reading age of 12, so that even complex science issues were explained in everyday language. This was driven by the belief that all HIV

positive people had a right to easy-to-understand, accurate and up-to-date information in order to be actively involved in decisions related to their own health care.

Just as importantly, the whole resource was updated in virtual real time as new data and research became available. For years, a monthly email would detail all recent changes, so at a glance this was one of the most comprehensive ways to track developments. Just as importantly, everything was produced in both English and Spanish.

Bob was first active in San Francisco following his diagnosis in 1987 and this experience informed his lifelong activism.

This ranged from responding to individual treatment questions to early Internet support forums such as the Crix-list and PI-treat to long-term involvement on scientific steering groups of international medical conferences, including the annual Lipodystrophy Workshop and the biannual Glasgow Congress. His encyclopaedic knowledge of HIV treatment history and his skill with carefully reporting evidence made his opinion an important voice in any debate.

For many years, Bob showed extraordinary resilience in continuing to attend and report from medical conferences despite increasing mobility difficulties related to a rare and difficult to treat neuromuscluar complications. He continued long after most of us would have settled for tracking everything online on webcasts. He also continued to travel despite many journeys needing three flight changes from his home in New Mexico.

Bob will be greatly missed and our thoughts are with his family and friends at this difficult time, especially with Enoch Ortega, his long-term partner and husband.

Other online tributes

How Would Bob Say It? by Emily Bass, AVAC

http://www.avac.org/blog/how-would-bob-say-it

I will remember you, Bob Munk - by Warren Tong, the body.com

http://www.thebody.com/content/76144/i-will-remember-you-bob-munk.html

IAS 2015: OVERVIEW

Four reasons IAS 2015 will be a milestone HIV conference: a personal view

Simon Collins, HIV i-Base

IAS 2015 will be a milestone conference that changes the way adult HIV is approached globally.

Results from antiretroviral treatment (ART), prevention and programmatic studies naturally dovetailed to provide a new evidence base for rethinking historical approaches to HIV management in order to reduce transmissions, extend life and ultimately produce a cure.

This brief personal review connects new studies in four areas:

- Universal ART should be an option for all HIV positive people irrespective of CD4 count.
- Earlier ART - sufficient to support universal access - provides both clinical and prevention benefits. The prevention benefits - together with PrEP for HIV negative people at risk, made prevention a key focus.
- ART during the primary infection window provides additional exciting options for future chances of HIV remission and cure. This meeting connected earlier ART to cure research with new approaches to HIV latency.
- The option to routinely begin ART on the day of diagnosis as part of a careful management programme is supported by the safety and efficacy of current treatment.

The banner from the IAS meeting in 1996 was an reminder at IAS 2015 of the important part Vancouver played in the history of HIV treatment.

The significance is appropriate given that in 1996, when the IAS conference was last held in Vancouver, it heralded the modern ART era. Within a week of the conference, tens of thousands of HIV positive people started HIV treatment in the US. [1, 2]

Long-term activists, doctors and researchers who had attended that meeting in 1996 often referred to this poignant history. The remarkable changes over the last 20 years have covered both scientific advances and political will to ensure over 15 million people globally take ART.

This year, the new data at IAS 2015 was so important that it has already changed WHO guidelines to recommend universal treatment for all HIV positive people and changed the timeline for the guidelines, with this key recommendation being announced months ahead of schedule. [3]

The WHO changes were largely due to the international START study whose results overturn twenty years of believing that high CD4 counts provide a safety barrier against HIV-related illnesses. While earlier CD4 thresholds were arbitrary - whether at 200, 350 or 500 - the START results showed that ART reduces the risk of serious complications at CD4 count well above 500 cells/mm^3. START showed that it is safer to be on treatment than not being on treatment. It also showed that earlier ART is safe and effective, with a remarkable 97-98% having undetectable viral loads 12 months after starting. [4]

Other important studies at the conference contribute in other ways to a move to routinely treating HIV on diagnosis.

Longer-term follow-up from the HPTN-052 study reported that the dramatic reductions in HIV transmission from the first year of ART were sustained out to five years. [5]

The importance of Treatment as Prevention (TasP) was a major drive behind some treatment guidelines already recommending ART at CD4 counts >500 cells/mm^3. Taken with START results, the overlapping benefits of treatment and prevention support the WHO recommendation that all HIV positive people should have the option to start treatment. [5]

Other prevention studies added to earlier evidence on the potential for oral PrEP to play a more significant role in reducing HIV transmission than from current limited use. Francois Venter made this point very effectively during a refreshingly direct plenary talk. He also stressed how significantly real life PrEP demonstration studies have out-performed the original registrational studies. [6] This talk is one of many webcasts from IAS 2015 that is recommended viewing.

PrEP was elevated to a major theme throughout IAS 2015 - with more than a dozen talks and oral presentations in the main programme, and at least another 20 posters.

Many studies reported that PrEP did not lead people to increase risky behaviour and others showed that those at highest risk were often the most adherent. Most people clearly try hard to remain HIV negative but that they need more options than just condoms to do this.

Other studies compared dosing strategies for PrEP, which has a critical association with access and effectiveness. It is also difficult because traditional approaches to measuring adherence – particularly counting pills taken - have little relevance for PrEP unless: (1) someone actually is a risk of HIV infection, and (2) that protective drug levels are reached when these risks occur. Several presentations from the HPTN 067 ADAPT study showed that, as with treatment, the choice of different ways to use PrEP will be important when individualising care. [7, 8, 9]

Cure research was a fourth main theme at IAS 2015 with consensus that an HIV cure - whether eradication or remission - will require multiple approaches. [10, 11]

Headline news was also made for a new case of post treatment control for a French teenager who had used ART for almost 6 years after birth but has remained off ART for 12 years with sustained undetectable viral load, without ART. [12]

Many studies looked at strategies to overcome HIV latency, principally in resting CD4 cells. This includes: activating these cells (the “shock” in “shock and kill”), gene therapy to manage HIV without ART, and a new approach that instead aims to maintain latency. [13, 14, 15]

In the context of cure research, the smaller this reservoir the easier HIV might be to cure. Using earlier ART to restrict the size of the reservoir was discussed in many sessions as a way to produce the optimal setting for an HIV cure. [16]

In one of the last sessions of the conference, Christopher Pilcher from University of California San Francisco outlined results from a demonstration project in San Francisco that dramatically cuts time to starting ART. This model included rapid referral to an HIV clinic with the option to start ART very shortly after diagnosis including on the same day. This approach had high success rate as part of a public health clinic in San Francisco with a complex patient group (25% homeless and 100% without health insurance). [17]

Same day ART is also the model for the Option B+ programme to reduce mother to child transmission and this WHO recomendation has already been implemented by more than 65% of low- and middle-income countires. [18] However, the context of same day ART and how it is provided is critical . In one Option B+ programme, HIV positive women diagnosed during pregnancy and given same day ART at the testing centre reported greater loss to follow up (LTFU) – 22% vs 8% – compared to women referred to a different treatment clinic. [19]

A more sobering study supporting importance of early ART in order to reduce LTFU was presented in a poster about more than 137,000 people enrolled in 41 Médecins Sans Frontières (MSF) programmes. [20]

Although 64% were eligible for ART at enrolment, 72% of these people started ART, 5% died with 20% LTFU before starting ART. Among those not eligible based on CD4 criteria, almost half (48%) became eligible within a median of 5 months (IQR: 0.2 to 12.0), 1.2% died, 31% were LTFU before starting ART and 20% were still in care.

Of the 13% (17,862) whose eligibility couldn't be determined at enrolment, 39% became eligible in a median time of 6.4 months (IQR 1.8 to 17.6), 2.9% died, 47% were LTFU before ART and 11% were still in pre-ART care.

This suggests that how ART is started in each setting might be more important than timing of same-day ART and was emphasised in the San Francisco study, where current elements of the sequential care pathway were not discarded, but rather the extended systems of delays were removed.

Some UK clinics already have a similar approach to ART, notably those who treat people diagnosed during primary infection. Making these benefits to become more widely available will depend on how doctors, activists and health systems respond to the wealth of new data presented at IAS 2015.

A poster on the views of UK doctors to treatment during primary HIV infection is important for highlighting that this is a key issue for newly diagnosed people living in the UK. [21]

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IAS 2015: ANTIRETROVIRALS

Starting HIV treatment at high CD4 counts protects against both AIDS and non-AIDS events: overall and in subgroup analyses of START study

Simon Collins, HIV i-Base

The international START study produced headline news at IAS 2015 that confirms benefits from starting antiretroviral treatment (ART) at CD4 counts above 500 cells/mm^3. The study also reported no upper CD4 threshold that was protective against AIDS-related events, even though the overall absolute risk of events in START was low.

The START study is notable for reporting results 18 months ahead of schedule, following a recommendation by the studies independent Data and Safety Monitoring Board (DSMB) in May that participants in the arm deferring ART until their CD4 count reached 350 cells/mm^3 should be offered immediate treatment, and that follow-up should continue as planned for both arms.

The results were presented by Professor Jens Lundgren from University of Copenhagen on behalf of the START study team in two sessions at the conference: an opening plenary on the first day and the International AIDS Society members meeting later in the programme. [1, 2] The study was also simultaneously published online in the New England Journal of Medicine. [3]

This HTB report combines results from both IAS 2015 and NEJM paper.

Although preliminary findings were released on 27 May 2015 based on the dataset used for the DSMB decision, the expanded results cover three key areas:

- The additional endpoints in the final dataset modifies the primary endpoint results by finding that the reduction in non-AIDS events now reaches significance in favouring early ART. Back in May, this endpoint fell short of significance.
- New details about the AIDS and non-AIDS events seen in each arm and still finding that AIDS events drove the primary results and occurred at high CD4 counts.
- In subgroup analyses, early ART was consistently protective for all key baseline and demographic subgroups. It is important to stress that benefits from the study were not just for people with the highest risks.

Methods and baseline characteristics

From December 2009 to December 2013, START randomised 4685 HIV positive treatment-naive adults with CD4 counts >500 cells/mm^3 to either an immediate (IMM) or deferred (DEF) ART, with the deferred group waiteing until their CD4 count reached 350 cells/mm^3.

The combined primary endpoint included AIDS related and non-AIDS related complications including grade 4 events and deaths from any cause.

The study included 215 sites in 35 countries, equally divided between high and low/middle income countries. Baseline demographics have already been widely reported and published online [4, 5] and included approximately 27% women, 55% MSM, with a median age 36 years (IQR 29 to 44). Median CD4 and viral load were 651 cells/mm^3 (IQR 584 to 765) and 12,700 copies/mL (IQR 3,000 to 43,000), respectively, with no significant differences between groups. At study entry, median time since HIV diagnosis was 1.0 years (IQR: 0.4 to 3.1).

Primary and key secondary endpoint results

Mean follow-up was 3.0 years (median 2.8; IQR 2.1 to 3.9) with 23% having greater than 4 years follow up. Endpoint results were available for 96% and 95% of the IMM and DEF groups respectively.

By 26 May 2015, 98% vs 48% of the IMM vs DEF participants had started ART (at median CD4 count of 651 vs 408 cells/mm^3 respectively). Although ART in the study was provided free from a central repository, and included the choice of all or nearly all approved drugs, the majority of patients in both arms used tenofovir/FTC as background NRTIs (approximately 90%). Efavirenz was the most widely used third drug, by 73% and 51% of the IMM vs DEF arms respectively, with atazanavir/r, darunavir/r, rilpivirine and raltegravir making up the majority of other combinations. The study reported high rates of viral suppression with 98% vs 97% of those on treatment having <200 copies/mL at month 12.

The final dataset included a total of 140 primary endpoint events: 42 (1.8%) in the IMM arm vs 96 (4.1%) in the DEF arm, equivalent to rates of 0.60 vs 1.38 per 100 patient years, respectively. The hazard ratio (HR) for the composite primary endpoint was 0.43 (95% CI: 0.30 to 0.62), significantly in favour of the IMM group, p<0.001. Hazard ratios for other key secondary endpoints also significantly favoured the IMM group: 0.28 (95%CI: 0.15 to 0.50) for serious AIDS-

related events (p<0.001) and 0.61 (95%CI: 0.38 to 0.97, p=0.04) for serious non–AIDS-related. There was no significant difference between groups for all cause mortality: HR 0.58 (95%CI: 0.28–1.17, p=0.13). See Table 1.

Table 1: Hazard ratio (HR) of primary and key secondary endpoints

	IMM (N = 2326)		DEF (N = 2359)		HR (95% CI)	P value
	no.	rate/100 PY	no.	rate/100 PY		
Composite primary endpoint	42	0.60	96	1.38	0.43 (0.30 to 0.62)	<0.001
Secondary end points						
Serious AIDS events	14	0.20	50	0.72	0.28 (0.15 to 0.50)	<0.001
Serious non-AIDS events	29	0.42	47	0.67	0.61 (0.38 to 0.97)	0.04
Death from any cause	12	0.17	21	0.30	0.58 (0.28 to 1.17)	0.13 NS

Key: IMM=immediate arm. DEF=deferred arm, HR=Hazard Ratio, NS=Non Significant.

Clinical endpoints

An unexpected outcome in START is the degree to which AIDS events were more common at high CD4 counts than non-AIDS events. Throughout the study, the greatest impact of early ART was expected to be reduced inflammation-related events. Also, consistent with the planned study design, only 4% of follow-up time in the deferred arm occurred at a CD4 count <350 cells/mm^3 and accounted for only 5 primary events.

The most common events were cardiovascular disease (29% vs 15%), non-AIDS cancers (21% vs 19%) and tuberculosis (14% vs 20%) in the IMM vs DEF groups respectively.

Endpoints that were significantly reduced in the IMM group included TB (HR 0.29; 95%CI: 0.12 to 0.73), p=0.008) and Kaposi's Sarcoma (HR 0.09; 95%CI: (0.01 to 0.71, p=0.02) but not malignant lymphoma (p=0.07), non-AIDS cancers (p=0.09), cardiovascular disease (p=0.65), Grade 4 events (p=0.97), unscheduled hospitalisation (p=0.28) and combined Grade 4 event, unscheduled hospitalisation, or death from any cause (p=0.25). See Table 2.

Table 2: Other important clinical secondary endpoints

	IMM (N = 2326)		DEF (N = 2359)		HR (95% CI)	P value
	no.	rate/100 PY	no.	rate/100 PY		
Tuberculosis	6	0.09	20	0.28	0.29 (0.12 to 0.73)	0.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01 to 0.71)	0.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08 to 1.10)	0.07
Non-AIDS cancers	9	0.13	18	0.26	0.50 (0.22 to 1.11)	0.09
Cardiovascular disease	12	0.17	14	0.20	0.84 (0.39 to 1.81)	0.65
Grade 4 events	73	1.06	73	1.05	1.01 (0.73 to 1.39)	0.97
Unscheduled hospitalisation §	262	4.02	287	4.40	0.91 (0.77 to 1.08)	0.28
Grade 4 event, unscheduled hospitalisation, or death from any cause	283	4.36	311	4.78	0.91 (0.77 to 1.07)	0.25

§ This category excludes hospitalizations for AIDS-related illnesses.

Clinical events by geographical region

Earlier treatment had better outcomes in both high and low/middle income countries, although there were differences in the type of events by geographical region. Most of the TB cases (16/20) were in Africa and most of the cancers (22/27) and cardiovascular events (19/26) occurred in Australia, Europe, Israel and the US.

Subgroup analysis consistently support earlier treatment

Another unexpected outcome from START was the consistency for the primary endpoint results in sub-group analysis for baseline demographics and other risk factors of serious events, all favouring the early treatment arm.

The expectation that events would only occur in the groups at highest risk and that lowest risk groups would be protected from events was not supported by the results.

This included analyses by age, sex, race, geographic regions, smoking status, cardiovascular risk or baseline CD4 and viral load. Even when 95%CI for the HR crossed 1.0 for several parameters (highest CD4 and CHD risk and lowest VL), none of the p-values for the interaction approached significance. See Table 3.

Table 3: Hazard rates (HR) for primary end point by subgroup

	HR in favour of early ART	p for interaction
Age		0.98
<35 >35	0.47 0.42	
Sex		0.38
Male	0.47	
Female	0.31	
Race		0.65
Black * White Other	0.57 0.40 0.37	
Region		0.55
High income Low/middle income	0.39 0.48	
Baseline CD4		0.71
< 600 600-800 > 800 *	0.28 0.50 0.56	
Baseline viral load		0.25
< 5,000 * 5,000-30,000 >30,000	0.66 0.38 0.37	
Smoker		0.93
Yes No	0.43 0.44	
10 year CHD Framingham risk		0.56
<0.8 * 0.8 to 3.6 > 3.6	0.46 0.39 0.50	

* Although the individual 95% CI crossed 1.0 for these categories the p-value for trend for the subgroup was not statistically significant.

In conclusion, START results support the importance of providing ART for all HIV positive people.

They reinforce the need to further research to understand the pathogenesis of HIV in early infection and the urgency of achieving funding to ensure universal ART becomes a global reality.

Simon Collins is a member of the Community Advisory Board (CAB) for the START study.

C O M M E N T

START has produced a dataset that defines level of risk for not using ART, irrespective of any individual decision to start treatment. The level of confidence for doctors recommending early ART will now increase, even if the scale up issues for universal treatment when global coverage has not yet met this based on CD4 thresholds of 500 or even 350 cells/mm^3.

Earlier treatment was already recommended in guidelines due to the impact that ART has on dramatically reducing the risk of onward transmission. However, START demonstrates the key missing evidence that this approach also produces clinical benefits for the person taking treatment.

These results are expected to change treatment guidelines globally. UK BHIVA guidelines have removed CD4 threshold as a criteria for starting ART in the 2015 draft. [6]

At IAS 2015, WHO announced that the updated 2015 guidelines will also recommend treatment for all HIV positive people. [7, 8]

Follow up for all participants continues until at least the end of 2016 but the unique nature of this group would also support a further extension.

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The option for same day antiretroviral therapy on diagnosis: the future model for HIV care

Simon Collins, HIV i-Base

Impressive results from a demonstration study in San Francisco that dramatically cut time to starting antiretroviral therapy (ART) is likely to become the future model of care for public health settings. [1]

This is especially in the context of results from numerous other studies at IAS 2015 supporting earlier treatment.

Although this study initially involved a relatively small number of patients diagnosed in early infection it was expanded to include people with lower CD4 counts who were diagnosed in chronic infection. It has since become part of the citywide campaign to achieve zero new infections, zero HIV-related deaths and zero stigma. [2]

The model was designed to see whether HIV - as for other communicable diseases - could be treated on the day someone is diagnosed without compromising the effectiveness of long-term treatment. The model recognised that HIV treatment has important differences to other infections but set out to improve clinical outcomes over current standard of care (SoC), and the results were impressive.

From July 2013 to December 2014, the study enrolled 39 men, who had been referred to an HIV outpatient clinic after being diagnosed at a testing centre and who were given the option of starting treatment on the day of their initial visit (rapid visit group). Outcomes were compared to 43 people (92% men) indentified by clinical record review who were diagnosed during the same period and treated using routine SoC.

Both groups received similar counseling, routine laboratory tests, social support including housing and medical insurance, initial medical consultation and prescribing using a multidisciplinary team. For the intervention group, this care was predominantly took place on the same day or shortly after the referral. For the SoC group these were spread over many visits, sometimes taking weeks or months before starting ART.

Baseline demographics for the rapid visit vs SoC groups were similar including median age (range) 32 years (21 to 47) vs 35 (19 to 68), non-white ethnicity 59% vs 71%, and being homeless (28% vs 25%). None of these people had medical insurance. Median (range) CD4 and viral load were 474 (3 to 1391) vs 417 (11 to 1194) cells/mm^3 and 4.9 (2.8 to 6.6) vs 4.5 (1.6 to 6.1) log copies/mL respectively. A higher percentage of people in the rapid visit group were diagnosed during primary HIV infection (21/30 (70%) vs 8/31 (26%).

Because of high levels of transmitted drug resistance (25% vs 42%), predominantly to NNRTIs most people used integrase inhibitor-based (90% vs 83%) or PI-based (10% vs 10%) combinations.

Uptake for ART was high with 90% of the rapid group starting on day 0, 95% by day 1 and 100% by day 30. This compared to 12% in the SoC group starting within the first two days, 28% by a week and 60% by day 30. All participants were given the option to say when they wanted to start ART.

The median overall time from diagnosis to viral suppression was significantly shorter for the rapid vs SoC groups at 1.9 vs 4.2 months ($p<0.001$). Although much of this difference related to reduction referral and waiting time, median time for suppression after starting treatment was also significantly shorter (56 vs 95 days). The rapid group had more treatment changes (26% vs 0) mainly for simplification (ie reduced pill count following HLA-B*5701 results).

Although the researchers expected some reluctance from participants, the opposite occured and the option to start on the same day was universally popular. The high levels of adherence and retention in care were perhaps explained by the "overwhelmingly nurturing and wrap around service that included counselors and social workers all working together on the same day".

These results showed that it is feasible to implement same-day ART for outpatients with newly diagnosed HIV in a well resourced public health setting. This approach has now been rolled out as the model for care in the "Getting to Zero" campaign. [2]

C O M M E N T

Several UK clinics already use a similar intense model of care with the option of same day ART, notably centres that have good experience of starting treatment during primary infection.

A presentation by Sarah Fidler from UCL during the same session highlighted some of the reasons same day ART is especially time-critical during this early window period: more rapid and complete immune recovery, limiting the size of the viral reservoir and reducing the risk of onward transmission. [3]

The rapid service and highly individualised person-centred care also perhaps helps to overcome the shock from an HIV diagnosis that commonly involves weeks and months of anxiety and stress. This highly practical and forward-looking approach has a roll to empower people to take control and move forward.

Calls to the i-Base phoneline from people who are recently diagnosed are increasingly over early access to ART for these reasons. People already know they want to start treatment and if anything the delay for referral appointments and also for time to viral suppression in many ways seems to add to the difficulties of coming to terms with an HIV diagnosis.

The results from START show that routine treatment has benefits that outweigh extremely low risk of serious side effects. This is esepcially true when using combinations that do not include efavirenz.

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Pipeline ARVs at IAS 2015: doravirine, BMS-955176 and BMS-663068

Simon Collins

Several presentations at IAS 2015 included new drugs in development, principally an NNRTI and an attachment inhibitor.

New results for tenofovir alafenamide fumerate (TAF) – which has already been submitted to the US FDA for approval as part of three separate fixed dose combinations – will be covered in a separate HTB report.

A comprehensive review of all pipeline antiretrovirals in advanced development is included in the i-Base/TAG 2015 Pipeline Report. [1]

Doravirine (NNRTI)

Jose Gatell from University of Barcelona presented results from a Phase II study of the NNRTI doravirine being developed by Merck. [2]

This was a randomised, double blind, placebo controlled two part study in treatment naive participants. Part one was a 5-arm 24-week dose-finding study compared to efavirenz with all participants (approximately 40 per arm) using tenofovir/FTC as backbone NRTIs. In part two, the doravirine arms rolled over to the 100 mg selected dose and 132 additional participants were included, randomised to either doravirine 100 mg or efavirenz. [3]

The selected analysis at IAS 2015 combined 24-week results from the 42 people from part one who started at the 100 mg dose together with 24-week results from new participants in part two. Primary endpoints included viral suppression to <40 copies/mL at week 24 and CNS-related side effects at week 8.

Baseline characteristics included approximately 80% white, 92% male, median age 35 (range 20 to >60), with median CD4 and viral load of approximately 400 cells/mm^3 (range 100 to 1100) and 4.6 log copies/mL (range 2.6 to 6.7).

At 24 weeks, viral suppression <40 copies/mL was similar in both groups: 72% vs 73% in the doravirine vs efavirenz groups respectively, difference: -1.2 (95%CI: –13.0 to 10.5), see Table 1. Using the <200 copy cut-off, rates were just under 90% in each group. Median CD4 increases were similar at approximately +150 cells/mm^3.

In the prespecified analysis stratified by baseline viral load above 100,000 copies/mL, suppression to <40 was lower for both groups (~60% vs 56%) compared to 92% vs 95% from those starting < 100,000 copies/mL.

Doravirine had significantly fewer drug-related side effects (28% vs 56%; difference –27.8, 95%CI: –39.9 to –14.8), mostly related to CNS events, see Table 1. Laboratory abnormalities were broadly similar.

Table 1: Selected virological and tolerability results: doravirine vs efaviarine

	doravirine 100 mg	efavirenz 600 mg	Difference (95%CI)
n	108	108	
Discontinued (%)	4.6%	11.9%	
VL <40	72%	73%	–1.2 (9–13.0 to 10.5)
VL <200	89%	87%	+1.9 (–7.0 to 11.0)
Viral failure >40 c/mL, n (%)	17 (15%)	11 (10%)	
Viral failure >200 c/mL, n (%)	4 (4%)	1 (1%)	
Side effects (any grade)	76%	84%	–8.3 (–19.2 to 2.4)
Drug related side effects	28%	56%	–27.8 (–39.9 to –14.8)
CNS-related side effects	27%	46%	–19.4 (–31.7 to –6.6)

BMS-955176 (BMS-176, maturation inhibitor)

Results from a phase 2a study of the second-generation maturation inhibitor BMS-176 were presented as a late-breaker oral abstract by Carey Hwang from BMS. [4]

This was a randomised, placebo controlled, multi-part study. Part one was a 10-day monotherapy dose finding study (20 to 120 mg doses) that selected a 40 mg dose, based on a median maximum viral load decline of 1.6 log copies/mL. [5]

Results from part two, presented at IAS 2015, were from 28 new participants (protease and maturation inhibitor naive), randomised 2:2:2:1 to one of four once-daily groups for 28 days: 40 mg BMS-176 plus either atazanavir/ritonavir 300/100 mg or atazanavir 400 mg, 80 mg BMS-176 plus atazanavir 400 mg or to a control arm of atazanavir/ritonavir plus tenofovir/FTC. All doses of BMS-176 used an oral solution. All participants discontinued all drugs on day 29.

Baseline characteristics included median age 32, male (100%), white (90%) with median CD4 and viral load that ranged from 430 to 580 cells/mm^3 and 4.0 to 4.4 log copies/mL across arms. No IQR or range values were given for each arm or for the overall study population, but CD4 was > 500 cells/mm^3 for the majority of patients and viral load was low. The primary endpoint was viral suppression at day 29.

Median viral load decline at day 29 ranged from 1.6 to 2.2 logs for the BMS-176 arms vs –2.2 for the control arm. Maximum median viral load change at 42 weeks (study discharge) was similar between arms, see Table 2.

Safety and tolerability appeared broadly similar between groups with perhaps the non-ritonavir arms having fewer laboratory abnormalities including lower median bilirubin elevations. There were no serious adverse events or discontinuations.

Further details on the profile of BMS-176 were also presented as a poster, including in vitro activity against Gag polymorphisms associated with lack of activity to the first-generation maturation inhibitor bevirimat. [6]

Table 2: Virological results for dose-ranging Phase 2a study for BMS-955176

	BMS 40 mg + ATZ/r 300/100 mg	BMS 40 mg + ATZ 400 mg	BMS 80 mg + ATZ 400 mg	ATZ/r + TDF/FTC control
Med VL drop day 29 log c/mL (95%CI)	1.99 (-1.04, -3.32)	1.66 (-1.19, -2.04)	2.18 (-1.53, -2.68)	2.22 (-1.83, -2.84)
Max VL drop at day 42 log c/mL (95%CI)	2.20 (-1.24, -3.52)	1.86 (-1.49, -2.37)	2.23 (-1.87, -2.68)	2.39 (-1.83, -3.04)

BMS-663068 (BMS-068, attachment inhibitor)

BMS-068 is an attachment inhibitor in development at BMS, that binds to gp-120 to block entry. As with the BMS maturation inhibitor reported above this compound has great potential to help people with multidrug resistance to currently approved ARVs.

Two posters were included at IAS 2015. The first presented details on the development of drug resistance in a 48 week phase 2 dose-finding study that compared BMS-068 to atazanavir/r (300/100 mg), each in combination with tenofovir DF and raltegravir, and selected 1200 mg QD dose for further development. [7]

A drug interaction poster reported that a BMS-068 600 mg twice-daily (BID) dose can be used with atazanaivr/ritonavir, darunavir/ritaonavir and ritonavir. Even though these combination results in creased drug exposure to BMS-068, no dose adjustments are judged necessary.

With etravirine, even though exposure to BMS-068 was reduced by approximately 50% (for Cmax, AUC and Cmin), no dose adjustment was judged necessary using the 600 mg BID dose of BMS-068.

No significant interactions were reported when used with raltegravir/tenofovir.

However, the once-daily 1200 mg dose of BMS-068 is contraindicated with rifampin 600 mg QD due to significant reduced levels of BMS-068 (approximately 80% reductions). [8]

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IAS 2015: GLOBAL HEALTH

New directions in the 2015 WHO ART guidelines

Polly Clayden, HIV i-Base

The 2015 World Health Organization (WHO) Consolidated Antiretroviral Guidelines will recommend antiretroviral therapy (ART) at any CD4 count for HIV positive people of ages. The guidelines will also recommend new alternative first- and second-line regimens. [1]

Meg Doherty from the WHO HIV department presented new directions in the future consolidated guidelines at a WHO satellite preceding IAS 2015. The previous day WHO's Gottfried Hirnschall had provided a "sneak preview" of the in-the-process-of-being-updated guidelines at the UN 90-90-90 Target workshop: lessons from the field. [2]

A summary of what to expect in the 2015 guidelines is presented in Table 1.

Table 1: What to expect in the 2015 WHO ART guidelines

Adults	Start ART at any CD4.
	Prioritise symptomatic and CD4 < 350.
Pregnant and breastfeeding women	Start ART at any CD4 and continue lifelong (Option B+).
Adolescents (new age band: 10 to 19 years)	Start ART at any CD4.
	Prioritise symptomatic and CD4 < 350.
Children	Start ART at any CD4 if <1 year old.
	Start ART at any CD4 if 1 to 10 years old.
	Prioritise starting if <2 years or symptomatic or CD4% < 25% (<5 years) or CD4 < 350 (>5 years old).
New ARV options	Integrase inhibitor (DTG) and optimised (EFV 400 mg, DRV/r) options in 1st and 2nd line therapy.
PrEP	PrEP as an additional prevention choice for all people at substantial risk of HIV infection (> 3% incidence).

Answering the question, "why now?" Dr Doherty explained that since the 2013 guidelines, START and TEMPRANO trials of early versus deferred treatment had begun to report results. Results from trials of key antiretrovirals in specific populations had also been reported. New antiretrovirals and new doses and formulations – including dolutegravir (DTG), efavirenz (EFV) 400mg, and co-formulated darunavir (DRV/r) – will begin to become available for adults. A solid pellet form of lopinavir/ritonavir (LPV/r) has finally been approved for children and more optimised regimens and strategies are in the pipeline.

The new guidelines will also reflect the balance of point of care versus standard CD4, viral load and early infant diagnosis (EID) platforms. WHO recommendations will prepare programmes for greater numbers of people on ART with strategies to improve linkage to care, referral and adherence.

Following this preview of the key recommendations, interim guidelines on when to start and pre-exposure prophylaxis (PrEP) will be launched in September/October and the full updated guidelines on 1 December 2015.

Systematic reviews

The WHO guidelines recommendations development process considers: the assessment of evidence and ranking of its quality (GRADE) using systematic reviews; assessment of feasibility and cost using modelling; and preferences and values from the standpoint of the community and health care workers.

The evidence for when to start in adults used a comparative pair-wise and network meta-analysis to evaluate 76 trials for direct and indirect evidence: 35,270 participants randomised to 171 treatment arms. The systematic review included 18 eligible studies: 17 observational cohorts and one randomised controlled trial (RCT).

The studies reported on eight separate outcomes (mortality, severe HIV disease, HIV disease progression, AIDS events, non-AIDS events, AIDS and non-AIDS malignancy, and tuberculosis) in people with <500 CD4 and ≥500 CD4 cells/mm^3. The review found clinical benefits of ART initiation over 500 CD4 to all HIV positive people compared with <500 CD4 initiation, including the reduction of severe HIV morbidity, HIV disease progression and HIV transmission, and without increased grade 3 to 4 adverse events.

For what to start with, the evidence for comparative efficacy and safety of integrase inhibitors compared to EFV 600 mg was from six RCTs: SINGLE, PROTOCOL 004, GS 102 study, GS 104 study, SPRING-1 and STARTMRK. Combined data from these studies found integrase inhibitors to be more effective than EFV and other regimens for viral suppression at 24, 48 and 96 weeks, and DTG better than raltegravir. The evidence for EFV 400 mg was from ENCORE 1.

For children and adolescents there was a lack of direct evidence to support starting earlier (particularly for horizontally infected adolescents). But indirect evidence suggests a reduction in mortality and improvement in growth (particularly in children 5 to 10 years old with CD4 >500). A growing body of evidence shows the benefit of ART on growth, neurodevelopment, immunological recovery and in preventing pubertal delays. But these gains appear to be limited for vertically infected adolescents.

The rationale for treating all children and adolescents was largely programmatic – Dr Doherty noted that all but 17% would be already eligible under existing criteria. Treating all eliminates the need for CD4 count to start ART and avoids delays in settings without access to CD4 testing; should simplify paediatric treatment and help to facilitate the expansion of ART in this population (through task shifting and decentalisation which has been much more successful in adults); and is likely to improve retention in care compared with that pre-ART.

Community consultation

Various community groups – including the African Community Advisory Board (AFROCAB) and the International Community of Women living with HIV (ICW) – conducted a global consultation across 24 workshops in eight countries. Participants included: adolescents/young people, adults, parents/caregivers, people who use drugs, sex workers, men who have sex with men and transgender people (206 HIV positive people across the sub groups), and 74 health workers. The findings were presented to the guideline group.

The consultation revealed that starting treatment earlier was acceptable among the community. The importance of a collaborative decision driven by the patient's readiness was stressed. As well as feeling ready, early initiation requires good treatment literacy information to ensure an informed decision. The participants noted that starting ART is easy but maintaining adherence is harder. Stigma and discrimination were highlighted as important concerns by all participants, which they saw as a barrier to treatment access and adherence.

Some countries are already treating all (or treating all in specific populations)

Dr Doherty briefly showed data from two national programmes: one that is treating all and the other treating all children and adolescents less than 15 years of age.

Brazil has been treating everyone with HIV since changing its national guidelines at the end of 2013. This has led to an increased median CD4 at initiation of 419 compared with 265 in 2009. The Brazilian national programme reported similar retention in care and viral load suppression at 12 months in people with higher and lower CD4 counts: 81% for CD4 > 500.

Uganda started to treat all children less than 15 years in 2014. This has led to an increase in the overall number of children receiving ART. Retention at 12 months is also similar in this programme and viral load suppression is 84%.

C O M M E N T

Considering that START was one of the main drivers of the WHO decision to change to ART for all, the step from publication to policy was pretty nimble.

Introducing DTG as an alternative to EFV 600 mg first-line (with some restrictions) will spur on research to fill the knowledge gaps that will better inform its use in low- and middle-income countries (particularly information about DTG in pregnant women and with concomitant tuberculosis treatment), and the development and manufacture of generic versions.

ViiV Healthcare (the originator manufacturer of DTG), Aurobindo Pharma, and CHAI recently announced that Aurobindo has submitted an Abbreviated New Drug Application (ANDA) for generic DTG 50 mg, to the FDA for tentative approval. [3] This product is expected to gain tentative approval in the first quarter of 2016.

Several generic manufacturers are working on FDCs of DTG/TDF/3TC. ViiV has also licensed DTG to the Medicines Patent Pool (MPP). [4]

Planned or ongoing studies to inform recommendations of new drugs and formulations are described in the 2015 Pipeline Report. [5]

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Rapid implementation of the 2013 WHO ART guidelines

Polly Clayden, HIV i-Base

World Health Organization (WHO) included over 50 new recommendations for HIV treatment and care in the 2013 Consolidated Antiretroviral Guidelines. WHO also supported countries to adopt the new policies faster than in previous years.

Meg Doherty from the WHO HIV department showed findings from an analysis of country adoption and uptake of the 2013 recommendations at IAS 2015.

Dr Doherty stressed that progress towards the ending the AIDS epidemic by 2030 depends on the adoption and implementation of global guidelines with evidenced based approaches to treating people with HIV. The 2013 guidelines included new recommendations on clinical, operational, programmatic and M&E aspects of HIV treatment and care.

Following the launch of the guidelines in July 2013, between August 2013 and May 2014, WHO with partners conducted nine dissemination meetings in six regions for over 100 countries. Since that time WHO has established a database to monitor countries' progress in adapting and implementing its recommendations.

WHO used baseline surveys from the dissemination meetings, annual e-surveys with national Ministries of Health programme managers, peer reviewed literature, national strategic plans and concept notes to the Global Fund, to analyse the extent to which the 2013 recommendations had been adopted and implemented.

Results were compared to Global AIDS Response Progress Reporting. Any discrepancies were verified at country level with programme managers.

The evaluation looked at barriers to implementation using an esurvey conducted with programme managers, between May and June 2015 before WHO began the 2015 guidelines.

Dr Doherty presented data from 144 low- and middle-income (LMIC) countries and 58 WHO focus LMIC (with the highest burden of HIV) to the end of 2014. She showed data on both the adoption of recommendations as policy and the implementation.

For starting ART in adults and adolescents at a CD4 threshold of $\leq$500 cells/mm^3, the survey showed 53% of 144 LMIC had adopted this recommendation, and 6% treat all (including Brazil, Thailand and Yemen). Of 104 countries that reported on uptake, 52% reported countrywide implementation of this policy recommendation.

PMTCT recommendations have been adopted and implemented fairly rapidly. Across 144 countries, 95% reported the recommendation of Option B+ or B. Implementation varied: 65% of 94 responding countries reported full countrywide implementation of B+.

WHO paediatric policies (treating all infants and children < 5 years of age) were adopted in 40% of 144 countries, and 3% treat all children (including Uganda and Ethiopia). Implementation of paediatric policies also varied: 81% of 99 countries reported full countrywide implementation.

The recommendation to treat positive partners of HIV negative people was adopted in 65% of 144 countries – several countries are not reporting on this policy.

Adoption of the WHO preferred first-line regimen of efavirenz (EFV) plus TDF plus XTC (3TC or FTC) was high: 80% of 144 countries. Dr Doherty highlighted problems in Eastern Europe where multiple regimens are recommended – not always including the WHO preferred first-line.

Routine viral load monitoring was adopted in 63% of 144 countries. WHO are evaluating implementation data for routine viral load monitoring; this is expected to be quite a bit lower than that for adoption of the recommendation.

Option B+ and B have been taken up by nearly 100% of the 58 WHO focus countries as has the preferred first-line regimen. Treating people with CD4 <500 cells/mm^3 was more variable and treating all has "crept into the data" more recently.

WHO also monitors adoption and uptake of service delivery recommendation in the 58 focus countries. Integrating TB treatment into the ART programme has been taken up fairly well for adults and children but other recommendations (ART

provision in TB, mother/child heath, and opiate substitution therapy settings, and engaging community health workers in patient support) have not been taken up widely. The poorest implementation is of ART in opiate substitution therapy settings – this was reported in less than 15% of 58 countries.

Dr Doherty summarised the results for the 58 WHO focus countries 18 months after launching the 2013 guidelines:

- 100% adopted at least one major recommendation.
- 60% adopted a policy of starting treatment at CD4 $\leq$ 500 cells/mm^3.
- 93% adopted EFV/TDF/XTC as preferred first-line.
- 60 to 90% were implementing integration of services (mainly TB).

"Full implementation of these recommendations will lay the foundation to achieving the 90-90-90 target", she said.

C O M M E N T

WHO is working on an evaluation of time to (and barriers to) implementation of the 2013 consolidated guidelines. This will be important to inform the uptake of the new 2015 recommendations.

To support uptake of the 2013 recommendations, a survey among programme managers indicated the need for: greater preparation of health services, increased domestic investment and donor support and training of more health workers

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Large variation across countries in meeting UNAIDS 90-90-90 targets

Polly Clayden, HIV i-Base

Analysis of national treatment cascades showed huge variation in achieving UNAIDS 90-90-90 targets. The proportion of HIV positive people with undetectable viral load ranged from 68% in Switzerland to 9% in Russia. No country analysed met the UNAIDS final target of 73% achieving undetectable viral load.

UNAIDS 90-90-90 targets, set in 2014, aim to diagnose 90% of all HIV positive people, provide ART for 90% of those diagnosed, and 90% of those receiving ART achieve viral suppression, by 2020. Overall this means at least 73% of all HIV positive people should achieve a suppressed viral load.

The analysis compared published estimates of HIV treatment cascades across 19 individual countries and combined data from the sub-Saharan African region. Jacob Levi from Imperial College presented findings on behalf of researchers from Imperial College, London and Cantonal Hospital of St. Gallen, Switzerland at IAS 2015.

The researchers used the most recent UNAIDS data and a systematic review of viral suppression rates to estimate where we are currently and compare this to 90-90-90 targets. This comparison revealed, of an estimated 36.9 million HIV positive people worldwide, 19.8 million (53%) know their status and 13.4 million are undiagnosed. Approximately 15 million (41%) are on ART, with 14.9 million untreated, and 11.6 million (32%) virally suppressed.

The researchers defined the stages in the cascades where the targets are being missed – where more than 10% of people are lost – as breakpoints. "So can the UNAIDS 90-90-90 target be reached?" they asked.

The study included 11 full treatment cascades (percentage and number of people for all three UNAIDS targets reported and the viral suppression cut off used) and nine partial cascades (percentage and numbers for all three UNAIDS targets not reported and does not report viral suppression cut off used). Definitions and estimation methods varied between cascades, for example linkage and retention were defined differently between countries – ranging from attendance at healthcare facilities to blood tests within a given time frame.

The researchers calculated the results for the first target by dividing the number of people diagnosed with HIV by the estimated number of people living with HIV in each country. The calculation is tricky as both numbers are estimated in different ways with different testing procedures in different countries.

Estonia, Australia, USA and Denmark reported 85% or more people with HIV were diagnosed compared to less than 50% in Russia, Columbia and Ukraine (the lowest at 44%). The proportion in the UK was 76% and across the African region it was 51%. Diagnosis was the greatest breakpoint globally and the greatest point of attrition for: Switzerland, UK, the Netherlands, the region of sub-Saharan Africa, Columbia and Ukraine.

Estimates for ART provision – the second target – were calculated from: pharmacy records, governmental drug purchases, and healthcare dispensary records. The researchers did not differentiate between ART regimens. They noted that the thresholds for starting treatment varied between countries and changed within countries.

Providing ART to those diagnosed was the greatest breakpoint for: Australia, Rwanda, Denmark, Brazil, Cuba, US, Estonia, Vietnam, Georgia, Kyrgyzstan and Russia. In the US only 37% of people with HIV received ART although 86% were diagnosed. In Estonia only 29% of people received ART despite having the highest rate of diagnosis of the cascades in this evaluation. Poor ART coverage was seen across all Eastern European countries including: 26% Georgia, 22% Ukraine, 19% Kyrgyzstan and 11% Russia.

Countries also varied enormously in achieving the third target of 73% of all HIV positive people with viral suppression. Only Switzerland, Australia and UK achieved above 60%. Russia only achieved 9%.

For this target UNAIDS defines viral suppression as viral load <1000 copies/mL but some countries use undetectable viral load with various cut offs (<40 to <500 copies/mL), when they define the final target. The researchers noted that the definitions change the final percentage described as successfully treated. This means that the viral load cut off needs to be accounted for when comparing cascades. Brazil, for example, would achieve 35% with a cut off of <50 copies/mL (undetectable) but 40% with <1000 copies/mL (suppressed).

The researchers identified large disparities between countries. Although no country or region analysed so far met the final UNAIDS target, overall Switzerland, Australia, UK, Belgium and the Netherlands were not too far off achieving this – particularly with improvement in diagnosis.

The analysis showed all Western European countries achieved viral suppression for over 50% of HIV positive people. But all Eastern European countries only achieved viral suppression for 20% or less of HIV positive people.

The researchers recommended a standard reporting method should to be implemented to facilitate comparisons between countries to allow breakpoints to be better identified. “Identifying breakpoints allows us to prioritise resources to fix them”, Levi added.

Reference

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http://pag.ias2015.org/PAGMaterial/Webcast/653_12062/webcast.mp4 (Webcast)

Low dose boosted atazanavir is non-inferior to standard dose in Thai treatment optimisation study: LASA

Polly Clayden, HIV i-Base

Atazanvir/ritonavir (ATV/r) 200/100 mg is non-inferior ATV/r 300/100 mg according to results presented at AIDS 2015 by Torsak Bunupuradah on behalf of the LASA study group.

Dr Bunupuradah explained that the standard dose of ATV/r is associated with high exposure in Thai people in a previous study: median AUC 41 vs 72 h*mmg/L in Caucasian and Thai people respectively receiving ATV/r 300/100 mg; but AUC 42 h*mmg/L in Thais receiving 200/100 mg.

For the LASA study, 559 people receiving boosted protease inhibitors (PIs) with viral load 50 copies/mL for at least 12 months were randomly assigned to receive ATV/r 200/100mg or ATV/r 300/100mg once daily with two NRTIs at 14 sites in Thailand.

Participants were assessed every 12 weeks until week 48. Virological failure was defined as confirmed viral load >200 copies/mL. The primary endpoint was the proportion of participants with viral load <200 copies/mL at 48 weeks. Non-inferiority was defined as the lower limit of the 95% confidence interval for the difference in viral failure above -10% by intention-to-treat (ITT) analysis at 48 weeks.

Of the randomised participants: 279 vs 280 received ATV 200/100 mg and 300 mg respectively. For ITT analysis (non-completer=failure/snapshot) 273 vs 277 participants were included and 259 vs 244 were included in the per protocol (PP) analysis, from the respective treatment arms.

At baseline, 85% of participants were receiving lopinavir/ritonavir. Mean age was 42 years old, weight 59 kg, CD4 539 cells/mm^3, total bilirubin 0.85 mg/dL. They had received PIs for five years previously and approximately half of the participants were women.

At week 48, in ITT analysis, the proportions of participants receiving ATV/r 200/100 mg vs ATV/r 300 mg with viral load <200 copies/mL were: 97.1% vs 96.4% (95% CI: 0.68, -2.29 to 3.65). The respective proportions with <50 copies/mL were: 93.4% vs 91.7% (95% CI: 1.71, -2.67 to 6.09). In PP analysis the proportions with viral load < 200 copies/mL were

98.5% vs 99.2% (95% CI: -0.72, -2.6 to 1.16). In non-completer=failure (snapshot) analysis the proportions with viral load <200 copies/mL were 96% vs 91%, p=0.02, and <50 copies/mL were 92% vs 86%, p=0.03.

A higher proportion of participants receiving ATV/r 300/100mg arm discontinued treatment overall: 2.6% vs 7.6%, p=0.01. The proportion was also higher for discontinuation due to clinical jaundice: 0.4% vs 2.2%, p=0.06. Only one participant receiving ATV/r 200/100 mg developed resistance to ATV: 150L, V82A and L90M. This participant had a self-reported history of non-adherence.

At week 48, mean total bilirubin was 1.9 (SD ±1.1) vs 2.2 (SD ±1.2) mg/dL and proportions of participants with grade 3-4 hyperbilirubinemia (≥3.12 mg/dL) were 17% vs 35%, in the ATV/r 200/100 mg vs ATV/r 300 mg arms respectively (both p<0.001). There was no difference in CD4, ALT, creatinine clearance, total cholesterol and triglycerides between treatment arms.

Based on the December 2014 antiretroviral price list at The Thai Red Cross Research Centre, the investigators calculated up to US$ 58 million savings over five years treating 20,000 people with the lower dose.

C O M M E N T

These results, including the cost analysis, make a compelling argument for lower dose ATV/r in Thailand.

Ref: Bunupuradah T et al. Atazanavir/ritonavir 200/100 mg is non-inferior to atazanavir/ritonavir 300/100 mg in virologic suppressed HIV-infected Thai adults: a multicentre, randomized, open-label trial: LASA. 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention.19-22 July 2015. Vancouver, BC, Canada. Oral abstract TUAB0101. Webcast:

http://pag.ias2015.org/PAGMaterial/Webcast/483_12177/webcast.mp4

IAS 2015: HIV PREVENTION

HPTN 052: no HIV transmissions on effective ART but only limited data on viral failure and drug resistance

Simon Collins, HIV i-Base

Several important presentations from the HPTN 052 study were presented at IAS 2015.

Although the international HPTN 052 study made headline news at the IAS conference in 2011 after reporting benefits of antiretroviral treatment (ART) to reduce the risk of HIV transmission, long-term follow-up meant that final results again produced more headlines at IAS 2015.

HPTN 052 randomised the HIV positive partner in 1763 serodifferent couples at sites in Africa (54%), Asia (34%) and South America (16%) to either immediate ART (at a CD4 count between 350 to 550 cells/mm^3) or deferred ART (at CD4 count 250 cells/mm^3). The primary endpoints were (i) linked HIV transmissions to the negative partners and (ii) clinical outcomes related to ART in the positive partner.

In April 2011, the study DSMB recommended stopping the randomisation to offer all positive participants ART, due to significantly lower rates of linked transmissions in the immediate vs the deferred ART arm (n= 1 vs 27; 96% reduction, p<0.001). The single transmission occurred early after starting ART before viral load was likely to be suppressed. [1]

At IAS 2015, Myron Cohen from University of North Carolina at Chapel Hill presented results from >9800 patient years of follow-up collected until May 2015, together with combined overall results. [3]

Retention was higher for the positive partners with 87% still in the study, compared to <70% of the negative partners, reflecting changes in relationship status.

Although all positive participants were offered ART in April 2011 and 70% had started within 6 months, a small percentage continued to decline ART (16%, 7% and 3% after 1, 2 and 3 years respectively, with only 2% still not on ART when the study finally closed in May 2015.

During the last four years, an additional 9 linked transmissions occurred, 2 vs 7 in the early vs deferred groups respectively (at rates of 0.08 vs 0.29 per 100 years of follow-up; with a rate ratio 0.28 and 72% reduction in the early ART group).

As would be expected from the study design, the numbers of unlinked transmissions was similar between arms, with 14 vs 12 in the combined 2015 analysis.

Only 1/9 transmissions occurred before starting ART, with 4/9 occurring very early after ART was started and 4/9 occurring after the positive partner had virological failure on ART.

The presentation concluded that no HIV transmissions occurred over the whole study period from HIV positive partners who were on ART with undetectable viral load.

Susan Eshelman from Johns Hopkins University presented details on the phylogenetic analysis, which were used to confirm the linkage of within-partner transmission in HPTN 052, as a late breaker oral abstract in the same session. [4]

Other important results from HPTN 052 - about participants who experienced viral failure that therefore also impacted the efficacy of TasP for both partners in the study - was only available in a poster rather an oral presentation. [5]

Of concern, the analysis presented at IAS 2015 is only for the participants in the early treatment arm whose treatment failed by May 2011 during the blinded phase of the study.

In this group, viral failure occurred in 93/832 (11%) of participants in the early ART up to May 2011, with an annual incidence 5.6% (95%CI: 4.6 to 6.9%).

Cumulative rates of viral suppression at 1, 3, 6, and 12 months were 46%, 78%, 89%, and 93%, respectively. In multivariate analysis, higher viral load at ART initiation (HR 0.87; 95%CI: 0.84 to 0.91, p<0.0001) and younger age, (<25 vs 25-39; HR=1.31 [95%CI: 1.06-1.62]; p=0.012) were independently associated with longer time to viral suppression.

Lack of viral suppression by 3 months (and 6 months) was significantly associated with time to ART failure (HR 9.34; 95%CI: 6.14 to 14.2) and risk of subsequent treatment failure (HR 8.99; 95%CI: 5.63 to 14.3), both p<0.0001.

Limited data on drug resistance in HPTN 052, again only until April 2011 and in the participants whose treatment failed in the early ART group, were presented in a second poster. Genotypic resistance results were available from 85/93 (89%) of these participants whose treatment failed. [6]

Resistance was found retrospectively in baseline samples of 7/85 patients (8%): NRTI n=1, NNRTI n=3 and dual NRTI+NNRTI n=3). In samples at time of virological failure, 35/85 (35%) had resistance, including 27 (32%) with new resistance to one or more drugs: NRTI n=4; NNRTI n=4; NRTI+NNRTI n=19. No protease mutations were detected. Only higher viral load at baseline (per unit log increase) was associated with new resistance at failure (OR 1.62; 95%CI: 1.16 to 2.25, p=0.005).

C O M M E N T

Finding no linked transmissions with a further four years of follow up is clearly important and impressive.

However, it is unclear why the extremely limited data on viral failure has been held back for so long. It is also unclear why this aspect of the study was not included with the main results given that response to ART is a co-primary endpoint.

The risk of early failure is particularly important for people in countries with limited treatment choices.

This might still be good news for TasP though if people start ART earlier in infection.

The START study reported 97-98% viral suppression at 12 months. The significantly lower baseline viral load in START perhaps explains the lower rate of viral failure compared to HPTN 052. [7]

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IAS 2015: PAEDIATRIC CARE

Dispersible tablet formulation of dolutegravir is bioequivalent to the granule formulation

Polly Clayden, HIV i-Base

A dispersible tablet formulation of dolutegravir (DTG) has been developed as an alternative to the granule formulation for infants and young children. Data from a pharmacokinetic (PK) data presented at IAS 2015, showed the tablet and granule formulations are bioequivalent.

The authors from ViiV Healthcare noted that the oral bioavailability of DTG is affected by metal cation-containing supplements. Besides comparing the two formulations, the study compared DTG PK when tablets are dispersed in either low mineral content (LMC) or high mineral content (HMC) water. The study also evaluated whether or not consuming the dispersed in water tablet immediately or after the suspension had been standing for 30 minutes made a difference.

It was a randomised, open-label, 5-way, single-dose crossover study in HIV negative adults. DTG was administered at 20 mg as:

A. Granules in purified water, consumed immediately.

B. Dispersible tablets (4 x 5mg) dispersed in LMC water, consumed immediately.

C. Dispersible tablets in HMC water, consumed immediately.

D. Dispersible tablets in LMC water, consumed after standing for 30 minutes.

E. Dispersible tablets in HMC water, consumed after standing for 30 minutes.

All treatments were given under fasting conditions with washout periods of at least seven days in between.

The investigators performed safety evaluations and collected serial PK samples during each treatment period. They used non-compartmental methods to compare treatments by analysis of variance (ANOVA). The participants answered a palatability questionnaire after the first period. A total of 15 participants were enrolled and completed all treatment periods: 4 women and 11 men with a mean age of 39 (SD 12.5) years; 11 white-Caucasian, 2 African American, 1Asian and 1 white Arabic. Table 1 shows ANOVA results.

Table 1. Summary ANOVA results from treatment comparisons

Geometric least square mean ratio (90% confidence interval)				
PK parameter	B/A	C/B	D/B	E/C
AUC(0-inf)	1.06 (1.02 to 1.11)	0.94 (0.90 to 0.99)	1.03 (0.98 to 1.07)	1.04 (1.0 to 1.09)
Cmax	1.12 (1.06 to 1.19)	0.92 (0.87 to 0.97)	0.99 (0.93 to 1.05)	1.05 (0.99 to 1.11)
C24	1.03 (0.97 to 1.09)	0.96 (0.90 to 1.02)	1.07 (1.00 to 1.13)	1.01 (0.95 to 1.08)

The study showed equivalent exposure with the two formulations, so found the DTG dispersible tablet to be bioequivalent to the granule formulation. DTG PK was not affected by water mineral content or 30-minute delay in dispersed tablet consumption. The dispersible tablet can be given under these conditions.

Adverse events were mild and did not cause any participants to withdraw from the study. No grade 2 to 4 laboratory toxicities were reported.

In the limited data collected on palatability, the majority of participants described the taste and mouth feel of the dispersible tablet as acceptable. But the granule formulation appeared to be more acceptable than the dispersible tablet.

The dispersible tablet is undergoing further development and the formulation is being adjusted to improve the taste.

C O M M E N T

DTG is being studied at a target dose of 1 mg/kg in infants (from 4 weeks of age), children and adolescents in IMPAACT P1093. [2] Research is currently ongoing in the 6 to 12 years of age cohort and the estimated primary completion date for the whole study is May 2018. The granules are being used in P1063 – these will not be available commercially but the dispersible tablets will. Taste masking work on the dispersible tablets is also ongoing. The tablets will be strawberry cream flavoured.

Expert groups have identified DTG as a priority for children (as well as adults) in low- and middle-income countries. The development of generic formulations of DTG for children should follow as swiftly as the originator company ViiV Healthcare and regulators allow.

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IAS 2015: CURE RESEARCH

New case of remission in a perinatally infected teenager

Richard Jefferys, TAG

A new example of long-term post-treatment control of HIV viral load was reported on the second day of the IAS 2015 conference in Vancouver, attracting widespread media attention. [1]

Presented by Asier Sáez-Cirión from Institut Pasteur in France, the case involves a teenager who acquired HIV infection perinatally and was taken off ART at around the age of six, subsequently maintaining very strict control of viral load for over 12 years and counting. Sáez-Cirión is also the lead investigator for the well publicised VISCONTI cohort, a group of early-treated adults who are exhibiting long-term of HIV viral load after ART interruption (described in some detail in a paper in 2013, at which time the cohort had 14 members [2], and recently reported to now number 20 with an average time off ART of over nine years). [3]

The new case was discovered as a result of an analysis of the French National Agency for AIDS Research (ANRS) paediatric cohort study, which has been following over 10,000 mother-child pairs sine 1986. A total of 100 infants were identified who had begun ART within six months of birth and, of those, 15 had interrupted treatment after an average of 33 months. Only two of the 15 showed evidence of control of viral load: one for around three years before viral load climbed above 500 copies/mL, the other on an ongoing basis, making her the subject of further investigation.

Records showed that the mother had advanced disease at the time of birth, with a viral load of 4.6 million copies and a CD4 count of 81 cells/mm^3. The baby received six weeks of AZT monotherapy in an unsuccessful attempt to prevent infection, after which HIV viral load became detectable and rose to 2.1 million copies/mL leading to the initiation of ART consisting of AZT, ddI, 3TC and ritonavir (the AZT was later dropped from the regimen due to side effects). Viral load was suppressed but briefly rebounded during two periods of nonadherence, to 75,190 and 97,000 copies/mL, respectively.

In an echo of the Mississippi baby case, the child was lost to follow up between 5.8 and 6.8 years of age. On return to care, it was learned that ART had been stopped several months previously, but viral load remained below 50 copies/mL. During continued follow up, viral load has stayed undetectable with the exception of two readings, one a little over 500 copies/mL at age 11 and another of 48 copies/mL at age 14 (close to the borderline of the more sensitive assay used at that time).

Recently, ultrasensitive tests capable of detecting as few as 4 copies/mL blood have been employed, with no positive results recorded. The CD4 percentage is reportedly within the normal range for a comparable HIV negative person. The individual is now 18 years old. The researchers have tested for the presence of ART in plasma samples to formally rule out any possibility of undisclosed usage, and these tests were all negative.

HIV reservoir measurements revealed that HIV DNA is present at around 125 - 316 copies per million CD4 T cells, and low levels of replication-competent virus were detected in samples of purified CD4 T cells after stimulation. HIV-specific CD8 T cells were detectable but at low levels, and no evidence of CD8 T cell-mediated suppression of HIV replication was observed in a laboratory assay. No data on HIV-specific CD4 T cell responses are available as yet – notably, a poster at IAS 2015 reported that VISCONTI cohort members have "robust" HIV-specific CD4 T cell responses [4], challenging the widely held view that anti-HIV immunity in these individuals is unusually weak. An earlier version of the study was presented at CROI 2014. [5]

No immune response genes known to be associated viral load control were present in the individual and they were homozygous for several HLA alleles, a phenomenon that has been associated with a greater risk of rapid progression in HIV in the absence of treatment. [6]

Analyses of inflammatory biomarkers have not been conducted yet (to the best of my knowledge, no data on inflammatory biomarkers in VISCONTI cohort members has been presented either).

As with the published paper on the VISCONTI cohort, Sáez-Cirión and colleagues were careful to use the term "virologic remission" to describe the outcome in their IAS 2015 abstract describing the case. Although the distinction may seem subtle, this is not necessarily synonymous with just "remission" (the term used in most of the news reports), which is generally interpreted as meaning remission from any increased risk of disease.

At the current time, it is not actually known for sure if the low levels of HIV present in these post-treatment controllers are associated with a long-term health prognosis that is similar to, better, or worse than a comparable HIV-positive individual whose virus is suppressed by ART. As covered in a recent blog post, there are some reasons to be concerned that the HIV suppression in at least some of these cases may not have equivalent health benefits to that achieved by ART. [7]

The researchers have also stressed that post-treatment control is an extremely rare phenomenon and that ART should not be interrupted outside of clinical trials at this time. There have been many published studies of ART interruptions in children and adolescents, some including quite large numbers of participants, but examples of even short-term post-treatment control are few and far between. Examples in the scientific literature include a teenager who maintained undetectable viral load for over five years after stopping ART [8]; however there was no documented history of high viral load prior to treatment and they were found to be heterozygous for the CCR5-delta-32 mutation.

Another paper mentions a participant whose viral load stayed below 400 copies/mL for one year after ART interruption, but no further details are provided. The majority of children in these studies experienced viral load rebound and CD4 T cell loss as a result of treatment cessation. [9]

The new case adds to the evidence that early ART is beneficial and may, in rare instances, facilitate long-term control of viral load after treatment interruption. Ongoing and planned trials in both children and adults aim to carefully investigate the extent to which virologic remission might be achieved by this strategy. Researchers are also exploring early ART combined with additional interventions such as latency-reversing agents and immunotherapies with the aim of increasing the likelihood of virologic remission.

Addendum (25 July 2015): VISCONTI cohort update

Asier Sáez-Cirión's slide presentation has now been posted on the International AIDS Society's Towards an HIV Cure Symposium website (along with the other materials from the meeting, which took place in Vancouver on 18-19 July, immediately before IAS 2015). [10]

At the end, the slides include an important update on the current status of VISCONTI cohort participants. Of the 14 individuals described in the 2013 PLoS Pathogens paper [2], one has experienced a viral load rebound (reaching close to 100,000 copies) after six years off ART, necessitating reinstitution of treatment. Another has persistently detectable viral load (in the 100 to 1,000 copy range) and a declining CD4 T cell count that is now below 500 cells. A third is reported to have developed "ORL cancer" (head and neck cancer), and resumed treatment. Lastly, a fourth member of the original 14 is lost to follow up, so a total of 10 continue to be followed with undetectable viral load.

The last slide of the presentation notes that six additional post-treatment controllers have been added to the VISCONTI cohort (explaining the reference to a total of 20 individuals in Sáez-Cirión's latest published review from earlier this year), but no details on their viral loads and CD4 T cell counts are provided. [12]

A graph is shown for one of the new additions who, like several of the initial cohort members, possesses the HLA B*35 allele; the viral load in this individual appears to be well-controlled off ART but the CD4 T count is below 400 cells/mm^3. Hopefully these updated findings will be fully disclosed and discussed soon.

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IAS 2015: OTHER NEWS

IAS 2015: accessing online webcasts and abstracts

Simon Collins, HIV i-Base

Selected webcasts from IAS 2015 conference are now posted online. Abstracts are also available, but only via a pop-up window in the euphemistically named Programme at a Glance, and not with a unique URL.

Also, many oral presentations have not been included in the webcast coverage this year, with no indication in the programme of what will be webcast.

Online access has an essential and established educational role, supported by the IAS, and is the only way many people are able to track the advances discussed at the meeting. The webcasts also broaden the wealth of experience that is brought together for the few days of the meeting.

In recent years, the opportunity to present has been linked to permission to webcast, and it is a shame that this helpful precident seems to have been dropped for IAS 2015.

This year, the main way to access individual webcasts and abstracts is though the online Programme at a Glance:

http://pag.ias2015.org

The interfacce to navigate this online programme is a little tricky.

There are two ways to find a webcast.

1. Use the search link to look for a name or topic, and then click on these search results to open the session in which the talk was presented. If a webcast or abstract is available there will be a button in either the column with the session time and number or underneath the presentation title.
2. Click one of the sessions in the progamme calendar. This will open a new window that lists the talks in that session and, as above, look for the buttons.

A URL for a webcast is available from the “download” link but abstracts do not have this option. Links to download poster PDFs are only via a link at the bottom of the pop-up abstract window.

As with previous conferences, all symposia, plenary and oral abstract sessions are expected to go online. However, the programme doesn’t show which sessions will have webcasts so there is not an easy way to see which other sessions are online.

The interface for watching sessions seems good and shows both the slides and the presenter, either in a web browser screen or as a full screen option.

A limited version of the abstract book and the full abstract book are published in PDF format as a supplement to the Journal of the IAS.

http://www.jiasociety.org/index.php/jias/issue/view/1475

http://www.ias2015.org/WebContent/File/IAS_2015__MED2.pdf (18.4 Mb).

Abstract should become available as single html pages with an individual DOI and html web page, although these links were not yet active as we went to press.

Selected webcasts

With so many talks to chose from, the following three webcasts are recommended as direct and easy to understand reviews of key themes to the meeting: cure research, prevention options and changes for global health.

From care to cure. *Nicholas Chomont, Monday plenary (9 am)*

A 30 minute comprehensive overview by one of the key researchers in cure research on key scientific approaches. (IAS 2015, MOPL0103).

http://pag.ias2015.org/PAGMaterial/Webcast/66_13222/webcast.mp4

Treatment as Prevention versus other biomedical prevention. *Francois Venter, Monday plenary (10 am)*

A direct 30 minute talk by a leading activist doctor and researcher from South Africa, who reviews the dynamic options now available to really reduce new infections and to improve care. He challenges health services to be truly centred on the people who are using them. (IAS 2015 MOPL0106).

http://pag.ias2015.org/PAGMaterial/Webcast/68_12486/webcast.mp4

Rapid uptake and adoption of the WHO 2013 Consolidated ARV guideline recommendations

Meg Doherty from WHO maps the impressive uptake of guidelines that pave the way to achieving the 90/90/90 global target. (IAS 2015 MOAD0101).

http://pag.ias2015.org/PAGMaterial/Webcast/1506_11447/webcast.mp4

CONFERENCE REPORTS

IAS Towards an HIV Cure Symposium

18 – 19 July 2015, Vancouver, Canada

Introduction

The fourth annual Towards a Cure symposium, organised by the International AIDS Society (IAS) before the large summer conferences was held this year on 18-19 July 2015 in Vancouver.

The programme for these workshops is abstract-driven based on the most important cure-related research that will be included in the IAS main conference. The following report summarises the plenary talks at the meeting,

The programme and electronic materials from the workshop are now available on the IAS web page for the meeting.

http://www.iasociety.org/What-we-do/Towards-an-HIV-Cure/Events/2015-Symposium

Plenary talks at IAS HIV cure workshop

Simon Collins, HIV i-Base

The following article summarises the plenary talks at this annual cure research workshop.

Recent progress in cure research

An overview by Dan Kuritzkes, currently leading research as head of the adult ACTG trials network set the stage for the workshop with an update of the progress over the seven years since the successful proof of concept case of the Berlin patient. [1]

Kuritzkes noted that attempts to reproduce the results with other autologous stem cell transplants from CCR5-deficient donors have unfortunately not been successful, perhaps either these cases were too advanced when treated, or conversely, the original case was just lucky. The most worrying possibility is that the mutation that renders cells deficient for CCR5 also affects the efficacy of stem cell transplantation, but it is not yet clear if that may be the case.

Although reversing HIV latency is now recognised as a necessary step for cure research, even if this is achieved, we know that on its own this will not be sufficient to produce a cure.

The talk reviewed the limited successes of latency revering strategies including use of HDAC inhibitors and gene therapy and raised important ethical issues of the need for additional interventions when recommending treatment interruptions for people treated during earlier stages after infection. Many researchers see this as the key population in whom cure strategies are most likely to work but yet they risk acute seroconversion and an increase in HIV reservoir size if they stop treatment.

Community involvement in cure research

In the second plenary, long-time HIV positive activist Matt Sharp expanded on cure research from a personal perspective. [2]

This ranged from early involvement in community responses in San Francisco in the 1980s through to achieving five year follow-up after having been an early participant in the first zinc finger nuclease-based gene therapy safety study: while

his CD4 cells have doubled, there is little understanding of the clinical implications and ageing takes him into uncharted waters as a subject for research.

Diagnosed in 1988 and recently having celebrated his 60th birthday, Matt gave a calm, steady and sober evaluation of being part of a community response that included fellow activists Martin Delaney (who much of the US public cure research programme is named after) and Bob Munk (the popular long-time activist whose death in the week before the conference after a long and inspiring fight against progressively debilitating HIV-related complications left many of us saddened).Matt spoke of the difficulties of having to still educate and explain - to media, HIV positive people and even activists - community myths and misunderstandings about cure research and how a new community educational resource (avac.org/CUREiculum) may help others to do this.

For the future, cure research needs to be central to campaigns such as "gettingtozeroSF.org" and this will require increased funding to overcome the challenges of the sustainability of global universal ARV access.

Broadly neutralising monoclonal antibodies (bNAb's) as treatment

John Mascola from the US NIAID/NIH Vaccine Research Centre gave a review of the treatment potential of bNAbs that included the background, opportunities and recent data from the VRC01 trial. [3]

Although monoclonal antibodies have a long history as potential HIV therapeutic interventions, most notably with ibalizumab and PRO140 - both of which have been in development for many years - more recently developed compounds have both a broader neutralising range and have significantly greater potency.

The first property is essential in order to avoid escape mutations that with single mAbs will lead to resistance similar to monotherapy with antiretrovirals - emphasising the importance of using combination therapy with monoclonal antibodies. The second is needed to enable lower doses to be used - also with longer half-lives - in order to bring manufacturing costs within reach of practical use.

Data was presented for VRC01 (see the MOBS03 bridging session at 11 am on Monday in the main IAS 2015 programme), which together with 3BNC117, is also being studied as a potential prevention intervention in people at high risk of HIV.

Although still in early stages of development, future research has the potential to further increase potency by 10-100 fold, extend dosing to perhaps only require injections every 3 - 6 months and to manufacture bNAbs with characteristics that reduce the risk of resistance.

Immune recognition after reversal of latency

With multiple advances in the approach of activating HIV in the reservoir of latently infected CD4 cells, Marcus Altfied from the Heinrich-Pette Institute reviewed the problem of generating an effective immune response to facilitate elimination of these cells. [4]

Not only are current immune responses typically unable to respond to CD4 cells in which latent HIV has been activated – which themselves might persist for much longer than previously expected – but activation itself can be an incomplete process, stalling at several earlier stages before productively producing new virus.

This session reviewed the kinetics of antigen expression and included new data on using NK cell activity.

Engineering CD4 T cells

The plenary talk on approaches to genetically engineering T cells was given by James Riley from the University of Pennsylvania. Dr Riley stressed the potential for gene therapy to improve on HIV-specific CD4 responses which, in the context of cure research, will need to be sustained for decades if ART is to be stopped. [5]

As well as the history of this field from early studies in 1996 that included antisense molecules targeting HIV, this talked focused on the use of zinc finger nuclease (ZFN) and Sangamo compound SB-728 that modifies and reinfuses CD4 cells to carry CCR5 deletions.

A new approach that targets an HIV fusion inhibitor protein, C34, to the CXCR4 co-receptor (to ensure that the inhibitor is present at or near the site of HIV entry into CD4 cells) is building on this technology with the aim of producing a greater percentage of HIV resistant cells with the hope that this will have a greater impact on viral suppression.

Strategies for viral reactivation and predictors of post treatment controllers

The important question of whether biomarkers can be sufficiently predictive to guide selection of appropriate participants for research studies that involve a treatment interruption (TI) was reviewed by Sarah Fidler from Imperial College London, who also outlined important cure-related studies starting in the UK. [6]

This review included results from the UK SPARTAC study (Short Pulse ART at Seroconversion) presented at CROI 2015 that showed that high pre-treatment levels of PD-1, TIM-3 or Lag-3 (but not at time of TI) were predictive of time to viral rebound after the interruption. [7]

Two new studies in the UK include the prospective HEATHER cohort of HIV seroconverters who start ART within 3 months of diagnosis and the RIVER study that is using integrase inhibitor-based ART plus prime-boost vaccine plus multiple doses of the HDAC inhibitor vorinostat with a primary endpoint of reduction in total HIV DNA.

Thanks to Richard Jefferys for editorial comments.

References

Unless stated otherwise, references are plenary talks in the Programme to the IAS Towards and HIV Cure Symposium, 18-19 July 2015, Vancouver.

http://www.iasociety.org/What-we-do/Towards-an-HIV-Cure/Events/2015-Symposium

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ANTIRETROVIRALS

Rilpivirine/FTC/TAF becomes the third TAF-based fixed dose combination submitted for US approval

Simon Collins, HIV i-Base

On 1 July 2015, Gilead submitted a new drug application to the US FDA for a fixed dose combination tablet that contains rilpivirine, FTC and tenofovir alafenamide fumerate (TAF). [1]

As a priority review, the FDA decision is expected within six months of the filing.

This is the third filing that includes the new TAF formulation of tenofovir. The FDA dates for the two previous submissions are 5 November 2015 for elviregravir/cobicistat/FTC/TAF (E/C/F/TAF) and 7 April 2016 for the dual formulation of FTC/TAF (F/TAF).

Applications in the European Union (EU) were validated on 23 December 2014 for E/C/F/TAF and on 28 May 2015 for F/TAF. The EU application for R/F/TAF is due to be filed in the third quarter of 2015.

Reference

Gilead press statement. Gilead submits new drug application to U.S. Food and Drug Administration for single tablet regimen for HIV containing rilpivirine, emtricitabine and tenofovir alafenamide (R/F/TAF). (01 July 2015).

TREATMENT GUIDELINES

Draft BHIVA 2015 treatment guidelines: the most significant changes for a decade

Simon Collins, HIV i-Base

On 22 June 2015, the British HIV Association (BHIVA) posted a draft of the new HIV treatment guidelines.

Although minor revisions were made in 2013, mainly to include recent HIV drug approvals and the management of coinfection with hepatitis, this is the first major update since 2012.

The most significant changes address the question of when to start treatment together with choice of drugs.

- Based on preliminary results from the START study, the draft guidelines recommend removing the use of a CD4 threshold for starting treatment. This recognises that START reported the benefits of treatment outweigh the risks, even at CD4 counts above 500 cells/mm^3.

- Although not explicitly connected in the document (perhaps related to the timing of the news from START) this recommendation for treatment irrespective of CD4 count should strengthen the use of early ART during primary HIV infection (PHI) and for access to treatment as prevention (TasP).
- For the first time since its approval back in 1998, the NNRTI efavirenz - and therefore Atripla as a fixed dose combination (FDC) - is no longer recommended for first-line therapy.
- The NNRTI rilpivirine had been promoted in the proposed draft from "alternative" to "preferred" first-line therapy. Caveats include that this is only when baseline viral load is <100,00 copies/mL, that more data support its use with tenofovir/FTC as the NRTI background, and (hopefully) that this recommendation is only for people who are likely to be adherent and who are happy to take meds with food.
- Older drugs that have not been widely used for many years have now been dropped even as alternative options. These include lopinavir/r, fosamprenavir/r, nevirapine, ddI and d4T.
- Controversial - due to a lack of data supporting equivalence - 3TC and FTC are not seen as interchangeable options, especially in use with tenofovir.
- The importance of pharmacology and drug interactions is highlighted as an increasingly important concern.
- Fixed dose combinations (FDCs) are not prioritised over separate component combinations.
- Approximately one third of the guidelines cover management of 11 special populations. These are TB coinfection; hepatitis coinfection; HIV and cancer, neurological complications, kidney disease, cardiovascular disease, women, mental health, adolescents, bone disease and HIV in older people.
- A new ARV chart is included on food interactions, produced by the pharmacology department at Liverpool University.

C O M M E N T

Many of the changes in the proposed draft guidelines should lead to improved care, better treatment and easier access to treatment.

It is unfortunate that the consultation period closed on the day before IAS 2105 given this would be a likely forum for new data. As the BHIVA guidelines were already six months over schedule, an additional few days would have enabled people to comment based on seeing the most recent data.

Reference

2015 BHIVA Guidelines for the Treatment of HIV-1-Positive Adults with Antiretroviral Therapy.
http://www.bhiva.org/treatment-guidelines-consultation.aspx

BASIC SCIENCE & CURE RESEARCH

Innate immunity and HIV DNA declines in panobinostat recipients

Richard Jefferys, TAG

Results from a phase I trial of the candidate latency reversing agent panobinostat were published last year in The Lancet HIV. [1, 2]

The paper notes that in an exploratory analysis, a subset of four (out of a total of 15) participants experienced a significant decline in cell-associated HIV DNA levels of around 70-80%, although there was no detectable change in the trial cohort overall. Furthermore, the HIV DNA reduction in these four individuals was associated with a slightly longer time to viral load rebound during an analytical ART interruption. At the NIAID-sponsored Strategies for an HIV Cure meeting in October 2014, Matthias Lichterfeld reported that several measures of innate immunity correlated with the observed diminution of HIV DNA, and these analyses have now been published online in the Journal of Virology. [3]

The most prominent finding is an association between natural killer (NK) cells expressing markers of enhanced functionality (including CD57, associated with cytotoxic activity) and reductions in HIV DNA during the trial. The researchers suggest the effect might be due to reversal of HIV latency causing up-regulation of receptors that activate NK cells on infected CD4 T cells and/or causing down-regulation of HLA class I receptors on these cells (both phenomena would promote NK cell-mediated killing of the CD4 T cells). Complementary correlations were seen with additional

markers of innate immunity, including expression of interferon-stimulated genes and plasmacytoid dendritic cell frequencies. The IL28B "CC" genotype, which has been linked to superior innate immune function against hepatitis C, [4] was also associated with a greater reduction of HIV DNA during panobinostat treatment.

HIV-specific CD8 T cell responses, which have been suggested to be important for mediating clearance of the HIV reservoir after latency reversal, did not correlate with HIV DNA levels. The researchers note that this could be due to the HIV-specific CD8 T cell dysfunction [5] that is known to occur in chronic infection and the presence of escape mutations in the latent HIV reservoir [6] that abrogate CD8 T cell recognition. No evidence of an inhibitory effect of panobinostat on HIV-specific CD8 T cells (a possibility raised by a prior laboratory study) [7] was found. Interestingly, a larger HIV-specific CD4 T cell response at baseline (but not at any other timepoint) was associated with a greater HIV DNA decline during the trial; the explanation for this finding is not known but will be probed in future work.

The discussion section of the paper emphasises that the research involves small numbers and exploratory subset analyses, so the results must be interpreted very cautiously. But the idea that promoting innate immunity may aid in the clearance of the HIV reservoir after latency reversal is encouraging, and will be explored further in ongoing and new clinical trials. For example, toll-like receptor (TLR) agonists may have the capacity to stimulate innate immunity, and several are now being tested in HIV positive people on ART to assess any effects on the latent reservoir (see TAG's cure-related clinical trials page [8] under latency-reversing drugs).

Source
TAG BSVC Blog (4 August 2015)
http://tagbasicscienceproject.typepad.com

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HEPATITIS COINFECTION

Comprehensive review of DAA research at EASL

The rapid pace of development of effective and safe oral treatment for HCV was a major focus for the European Liver Conference (EASL) held from 22-26 April in Vienna.

The link to this comprehesive personal overview by Professor Jurgen Rockstroh makes compelling reading for clarifiy not only what what we know about these exciting new drugs, but the important gaps in the research that need to be addressed in order to understand how to best use them in practice.

The full article reports on over 40 studies and include more than 60 slides.

http://natap.org/2015/EASL/EASL_155.htm

All oral HCV DAA therapy on its way to optimisation: still much to learn - by Jurgen Rockstroh, for NATAP.org

Introduction

The introduction of all oral DAA based HCV therapy has dramatically changed HCV treatment paradigms and promises HCV cure in more than 95% of patients. Nevertheless special challenging patient populations remain which until now have only scarcely been addressed such as patients with renal impairment or on hemodialysis.

At this year EASL results from larger treatment trials in exact that patient population were presented for the first time. Other more challenging patient groups addressed included patients with decompensated cirrhosis and patients post-transplant. Considering that not all patients with decompensated cirrhosis benefit from HCV therapy despite becoming HCV-RNA negative, the question arises whether there may be a point of no return for very advanced liver disease stages.

Also for patients on the transplant list the question remains whether decreases in MELD score following HCV cure may impact the position on the organ waiting list, delay transplantation considerably and thereby increase risk for HCC development while on the waiting list. Furthermore, new data on treatment of HCV genotype 3 were eagerly awaited as there are still many questions about what the most effective treatment strategy, particularly in the cirrhotic patients who are treatment-experienced. This goes hand in hand with the quest for developing new HCV pan-genotypic drugs that would also simplify diagnostic work-up prior to starting HCV treatment.

Large interest was generated around all oral DAA treatment in compassionate use programs and real-life cohorts in order to better understand the risk of virological failure in real-life clinical settings. The question remains on the impact that the emergence of DAA resistance associated variants may have after failing all oral DAA therapy and whether there is a need for genotypic resistance testing at least after failure of DAA therapy.

Finally the new set of EASL guidelines for management of hepatitis C was presented at the conference publically for the first time.

Read the full report. http://natap.org/2015/EASL/EASL_155.htm

ON THE WEB

Community publications

RITA online: feature on bone health

The latest issue of *RITA*, is focused on HIV-related bone density and fracture.

This includes an interview with Michael Yin on bone disease risk factors, screening, and care.

Four review articles analyse:

1. Fracture prevalence and incidence with HIV

2. Bone density risk factors in HIV populations

3. When to use and how to interpret FRAX and DXA, and

4. Treatment.

The latter two articles focus largely on the 2015 HIV bone guidelines in *Clinical Infectious Diseases*.

http://centerforaids.org/pdfs/ritafinal0715.pdf.

Involving people in services: a guide to why and how

http://www.hivscotland.com/news-and-events/latest-news/article/involving-people-in-services-practical-guide

HIV Scotland has launched a new guide: ‘Involving people in services: a guide to why and how’ [PDF - 5MB].

The guide sets out why services across Scotland must involve people living with and at risk of in a meaningful way, and gives advice, tips and suggestions on exactly how services can make it happen.

FUTURE MEETINGS

Conference listing 2015/16

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.

19th Annual Resistance and Antiviral Therapy Meeting

16 September 2015, London

http://www.mediscript.co.uk

17th International Workshop on Co-morbidities and Adverse Drug Reactions

Date and venue TBC, but linked to EACS in Barcelona

http://www.intmedpress.com/comorbidities/default.cfm

6th International Workshop on HIV & Ageing

5 – 6 October 2015, Washington DC

15th European AIDS Conference (EACS)

21 – 24 October 2015, Barcelona

http://www.eacs-conference2015.com

BHIVA Autumn Conference including CHIVA Parallel Sessions

12–13 November 2015, London

http://www.bhiva.org

European HIV Hepatitis Coinfection (EHHC) Conference

10–11 December 2015, London

http://www.bhiva.org

7th International Workshop on HIV Persistence During Therapy

8 – 11 December 2015, Miami

http://www.hiv-persistence.com

6th HIV & Women workshop

20 – 21 February 2016, Boston

http://www.virology-education.com

23rd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

22 – 25 February 2016, Boston

http://www.croiconference.org

22nd Annual Conference of the British HIV Association (BHIVA)

19–22 April 2016

http://www.bhiva.org

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i-Base website

All i-Base publications are available online, including editions of the treatment guides.

http://www.i-Base.info

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

i-Base treatment guides

i-Base produce six 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 2014)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013).

Other publications

- HIV Treatment Bulletin (HTB)
- HTB South
- HTB Turkey
- HTB West Balkans

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  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
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- **Guide To HIV and hepatitis C coinfection** *(November 2013)*
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- **Clinical Trials: a community guide to HIV research** *(March 2009)*
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