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The question of when to start treatment is one wrapped in many clinical and personal issues. Some find the thought of starting treatment difficult and hope to delay the possible risks of taking anti-HIV drugs, others want the benefits as soon as possible.

Just last year a friend explained how he regretted begging his doctor to start him on antiretroviral therapy the same week he was diagnosed. He wanted treatment despite having a high CD4 count, because he felt powerless and wanted to take action. The regret he felt came later as he learned more about resistance and long-term side-effects. Had he put his body at unnecessary risk?

The recent 4th International AIDS Society Conference (IAS) in Sydney gave a bumper crop of news, so much so that we've devoted this entire issue to it, but one theme really stood out from the crowd. With several presentations on the potential benefits of early treatment, this conference could turn one man's regret into hope.

Whether those new to treatment will benefit from an earlier starting block is the subject of much debate but the word from Sydney was that it's time for a rethink.

page 3 Tailor-made medicines are the subject of this month's *Upfront*. With genetic screening for abacavir's hypersensitivity reaction pinpointing those at risk, will the side-effect be eliminated for good?

page 4 In our main feature *How soon is too soon?* we've gathered a wide range of evidence pointing towards better outcomes for those who start treatment early. Should treatment begin above the recommended 200 CD4 threshold and if so, when do we start? We asked UK experts what the implications could be for our clinics and find out if it's time for a change in guidelines

page 12 *News In brief* gives some highlights from IAS providing an update on pipeline drugs, as well as those more established, and finds out if efavirenz has met its match.

page 14 Prevention gets a mention too and our final piece gives an update on new technologies and how they can best be used. While condoms are effective, *Enhancing prevention* ensures we do our best in the fight against HIV.



aids treatment update

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bespoke medicines

bespoke treatments could be closer than you think, by Rob Dawson

The advent of genetic screening is seeing established drugs tailored to the individual. Data presented at the fourth International AIDS Society Conference showed just how it could be used to eliminate side-effects and improve outcomes.

Abacavir – also found in the co-formulations *Kivexa* and *Trizivir* – can cause a hypersensitivity reaction (HSR) in a minority of people. This serious side-effect can cause fever, rash and shortness of breath. In some cases, particularly when the drug is stopped and restarted, it can even be fatal. Various studies have shown that people with an inherited genetic variant (called the HLA-B*5701 allele) are more likely to experience HSR than those who don't have the gene.¹

While many clinics already test for HLA-B*5701, studies have been ongoing to try and get genetic screening routinely used. The main hurdle has been trying to determine how accurate the test is at predicting HSR.

HLA-B*5701 is predominantly a Caucasian allele and in Black Africans it is far less common. The SHAPE study was conducted to examine the link between abacavir hypersensitivity and the prevalence of the HLA-B*5701 allele in white and black populations.

So far it has been difficult to get an exact measure of the correlation because there are many things that

could confuse the diagnosis, such as similar side-effects caused by other drugs. However, where the SHAPE study triumphed was in its use of patch testing. This involves putting abacavir onto the skin and seeing if a reaction develops. This skin reaction tells researchers that there is a genuine (immune-mediated) HSR to abacavir. The SHAPE study found a perfect correlation between true abacavir hypersensitivity (as shown by positive patch tests) and the presence of the HLA-B*5701 allele in both ethnicities.²

The author of the study concluded that genetic screening in patients of all ethnicities will therefore reduce the incidence of misdiagnosed HSR and minimise situations where abacavir is inappropriately withdrawn. She also noted that while patch testing is a very useful research tool, it isn't a routine clinical test because it can underperform for technical or biologic reasons. It is designed to look at reported HSR and determine if it is true (immune-mediated) HSR.

The PREDICT-1 study gave more robust data. Patients were randomised to either begin abacavir treatment without testing, or to be tested for HLA-B*5701 and given abacavir accordingly – those with the gene did not start abacavir, whereas those without the gene started treatment with the drug.




If symptoms of HSR occurred among those on abacavir treatment, they were 'clinically' diagnosed. This was followed up using a patch test to confirm true HSR to abacavir.

The results of the study were that 'clinical' diagnosis of HSR fell from 7.8% (in untested patients) to 3.4% (in those tested). When patch testing was used to confirm true cases of HSR, only 2.7% of individuals in the non-screened arm tested positive and all of those patients that had the HLA-B*5701 allele were true HSR-negative.³ So the 100% sensitivity of HLA-B*5701 to patch test positive HSR held up in both the PREDICT-1 study and the SHAPE study.


The studies seem to show that genetic screening could make it highly unlikely that a true HSR to abacavir will occur.

"What we have found with this study is that we can tailor therapy based on the genetic makeup of the patient," said Simon Mallal, Director of Immunology and Infectious Diseases in Murdoch University, Australia, who presented the study.

Although this study did not see any, it was noted that the chance of rare immunological reactions to abacavir that are not related to HLA-B*5701 cannot be ruled out and that clinical vigilance should remain a priority.



Finding the optimum time to start antiretroviral therapy (ART) has been a key issue since the first trials of AZT monotherapy in the late 1980s. As we reached the 90s, the strategy of hitting the virus early became commonplace. When concerns over long-term toxicity, adherence, and resistance came to light, expert opinion soon changed and the current recommendation of delaying treatment until absolutely necessary was born.



Now that we're seeing new drugs which are easier to take and less toxic, should we continue to hold back ART initiation or raise the lower CD4 threshold for starting therapy? As our confidence in ART grows, the balance of the risk and benefits of early treatment is changing. Data from several recent studies presented at the fourth IAS Conference suggest that a fresh look at when to start treatment is overdue.

how soon is

potential benefits of early treatment, by Rob Dawson,
with additional reporting by Keith Alcorn and Michael Carter



s too soon?

In a symposium on 'Treatment of Early HIV Disease', Professor Yves Levy of the Henri Mondor Hospital, Paris, argued that our immune system needs earlier assistance to help protect it from the onslaught of HIV. What happens to the immune system during the early phase of HIV infection (immunopathogenesis) could play a key role in our long-term health.

Restoring CD4 cell count to normal levels is something ART rarely achieves. This sustained dip in immune cells could be related to the chronic immune activation that drives HIV disease. Immune activation occurs when our immune system is 'switched on' by a virus, bacteria, or other foreign substances. The level of this immune activation, though it correlates with the amount of virus present in our blood, can be used independently to predict the progression of HIV disease. When immune cells are activated they express markers which researchers can identify to monitor this process. Using these markers, it's clear to see that chronic immune activation starts early on in infection and the damage that accumulates may be going untreated.

The cause of immune activation

This chronic immune activation may be linked to what happens in the gut. Eighty-five per cent of our total lymphoid tissue is located in the gut and this tissue is packed with the cells that HIV needs to replicate.

It's no wonder then that there is a massive and rapid depletion of CD4 T-cells seen in the gut during HIV infection. This is distinct from the reduction in CD4 cells observed in our blood. This depletion can be seen within weeks of infection, it persists throughout the chronic phase of infection and is rarely restored by ART.¹

In 2006, researchers discovered that this damage to our gut enables particles of bacteria and other microbes to leak from the gut into the bloodstream. It was proposed that,

once in the bloodstream, these could trigger our immune cells and result in a widespread and chronic activation of the immune system.²

Researchers measured one particular microbial product that could enter the bloodstream called lipopolysaccharide (LPS). They found that there is a higher level of LPS in the blood of those who are chronically infected with HIV than in those who are uninfected. This could contribute to the growth of the population of activated CD4 cells in our bodies, and since HIV needs these cells to replicate, a higher level of immune activation could lead to faster progression of HIV disease.

While Dr Levy said that LPS does not explain the full story of immune activation, he pointed out that "the dynamic relationship, within weeks of the primary infection, between the patient and the virus is a critical phenomenon that may predict clinical outcomes".

He also noted that the level to which our immune system is restored can be predicted by the status of the immune system when treatment is started or by the nadir (lowest ever) CD4 cell count reached during chronic infection. By minimising damage to the immune system with earlier initiation of treatment, we could see better outcomes.

A CD4 plateau

Levy also highlighted data published earlier this year showing that those taking ART saw a significant increase in CD4 cell count in the first four years of treatment before eventually reaching a plateau for the final two years of analysis.³ This raises the possibility that patients starting ART with low CD4 counts might never experience a level of immune restoration that would return their risk of death to that of comparable people who are uninfected. The analysis showed that a baseline CD4 cell count above 350 cells/mm³ predicted greater CD4 cell gains following six years of HIV therapy.

This is backed up by a more recent study showing a greater chance of normalising CD4 count if treatment is started earlier. A total of 2,435 patients (1,281 from the APROCO COPILOTE cohort and 1,154 from the AQUITAINE cohort) were included in an analysis with a baseline average (median) CD4 count of 270 cells/mm³. They were followed-up for 6.8 years, on average. Overall, mortality was seven times higher in HIV-infected adults than in the general population. However, among patients whose CD4 counts had reached 500 cells/mm³, the mortality rate became similar to that of the general population after the sixth year of follow-up.⁴

Non-AIDS illness

Levy isn't the only one praising early treatment. Dr Jim Neaton, Professor of Biostatistics at the University of Minnesota, feels we're ignoring an array of ill health when we focus treatment on avoiding opportunistic infections.

Recognising that serious non-AIDS conditions can occur more frequently in untreated people has serious implications for ART initiation and calls for a rethink of antiretroviral treatment at CD4 cells counts higher than current guidelines recommend. While the SMART study had disappointing results in terms of treatment holidays, it helps to prove his point:

In the SMART study of treatment interruption, a 350 cell threshold for interrupting treatment was chosen, partly because it is the trigger for considering treatment initiation in US and European treatment guidelines. This is higher than the current lower limit of 200 in UK recommendations. Participants resumed treatment if their CD4 cell counts fell below 250 cells/mm³. Because of this study design, information from the SMART study about differences between people on and off treatment within the 350-250 CD4 cell range has been extremely influential in the debate about when to start treatment.

The SMART study found that people not taking treatment in the 250-350 CD4 cell range had a significantly higher rate of serious non-AIDS-defining conditions (like cancers, liver disease and heart disease) than those on treatment.⁵

Neaton also noted that an analysis of blood samples from SMART showed an increase in a biological by-product called D-dimer which has been related to cardiovascular disease (particularly coronary disease and stroke). D-dimer levels increased significantly in those who stopped treatment compared to those who continued ART, after one month of the trial.

While a general increase in these non-AIDS-defining illnesses may be partly due to the fact that treatment is now largely effective at preventing AIDS and so "people have to die of something", as Neaton put it, the SMART study helped to show that this view needs further investigation.

ART and HIV prevention

While much of the discussion at IAS centred on improving outcomes for those with HIV, Dr Julio Montaner addressed the topic of early treatment from a totally different perspective; "In an environment where we can optimise prevention by the various measures that we are familiar with, can we squeeze an additional preventive benefit from early ART?"

Evidence suggests that ART plays a significant role in the prevention of HIV transmission, and not just when looking at mother-to-child transmission. For example, in Taiwan there was a decrease in HIV transmission after the introduction of a policy providing free access to ART.⁶ This was despite the fact that no change in sexual behaviour was seen when looking at the incidence of syphilis.

Using evidence from mathematical modelling on populations from British Columbia, Dr Montaner showed that

expanding ART from a starting point of 200 to 350 cells/mm³, with reasonable adherence and a reasonable uptake, would have a dramatic effect on decreasing new infections. Using their model, they showed that whatever they did to increase antiretroviral therapy (such as raising the CD4 threshold or increasing uptake), new HIV infections dropped. Furthermore, if this potential prevention benefit was taken into account, early treatment would be highly cost-effective.

While this untested hypothesis brings with it long-term concerns regarding safety, toxicity and resistance, the first stage of research will result from expanding ART coverage to those in immediate medical need. These data could then be used to determine the need for further study.

Trial will tell

While it's clear that the SMART study provides evidence for potential benefits of earlier treatment, the best way to answer the when-to-start question would be through a randomised clinical trial, and a growing number of clinicians and patients are calling for just that. To date there has been no trial guiding this important decision and guidelines have been based on anecdotal evidence, cohort studies and expert opinion. While these methods have proven useful, none are as reliable as a randomised, prospective clinical trial.

However, while a trial like this would be beneficial, there are financial and logistical limitations. The study would also need to be long-term and would need to involve a large number of people. At the end of the study, the results may no longer be relevant.

While some feel that the strength of observational data alone is strong enough to justify a recommendation for earlier therapy, Dr Fred Gordin, Chief of the Division of Infectious Diseases at the Veterans Administration Hospital in Washington, argues that there is a

good rationale for an early treatment study and believes that evidence from such a trial would have profound global impact.

AIDS redefined

Using data from several studies (including cohorts from the CASCADE Collaboration and data from the DAD study⁷) to demonstrate increased rates of cancer, liver disease, heart disease and other non-AIDS mortality for those with HIV, Dr Gordin questions the level of damage that is occurring during a period of 'clinical latency' when treatment is currently delayed. While the data are not from robust randomised controlled trials, they do hint that those with CD4 cell counts of 200-349 cells/mm³ are doing better on therapy than off therapy. To ensure that patients are making the most of their treatment, Gordin calls for a shift in focus from opportunistic infections to non-AIDS-defining illnesses so that we can reconsider the way we define HIV-related harm.

“ Whether guidelines reflect the new data or not, it is likely that physicians will wish to at least discuss the benefits of starting earlier with patients. ”

“the real question is where in the range above 350 do you start.”

A significant reduction in serious non-AIDS-defining events has been seen in the small group of SMART patients who entered the study off ART treatment and were randomised to start treatment (earlier than the 200 CD4 cell count threshold). This gives an insight into the impact of serious non-AIDS events at higher CD4 counts.

“This becomes a randomised when-to-start trial, albeit a small one,” stated Dr Gordin. “These are probably really the only randomised when-to-start data out there.”

While there is a need to demonstrate any impact of early HIV infection on both AIDS and serious non-AIDS events, cohort studies are not an effective means of doing this at present, due to insufficient data collection in this area. Ongoing randomised trials of early ART also lack focus on non-AIDS events.

However, one study could provide some of the answers. The INSIGHT Network START Trial (Strategic Timing of AntiRetroviral Therapy) is a randomised controlled trial of immediate versus deferred treatment for those with CD4 counts above 500 cells/mm³. The endpoints for this study will be AIDS as well as serious non-AIDS-defining events.

The five-year trial will eventually involve 3,000 patients initiating treatment mainly in developed countries in North America and Europe, as well as Australia, South Africa, Thailand, Brazil and Argentina.

“We have the drugs that are potent, they’re durable, and they’re more readily available. The drugs are clearly less toxic and easier to take than in the past. We’ve got a research infrastructure available in both resource rich and resource-limited settings and we’ve demonstrated the ability in SMART and many other studies to do high quality long-term follow-up in HIV work,” commented Dr Gordin.

When to start?

Waiting for trial results isn’t something everyone’s keen to do, however. Some clinicians already feel that conservative thresholds for treatment should change now. In an audio interview for *The Body* website, Dr Joel Gallant, Professor of Medicine and Epidemiology in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine, Baltimore, commented on the recent buzz surrounding earlier treatment at IAS: “200 is definitely out, although it’s not reflected in the guidelines yet. 350 is certainly a number that makes sense, and the real question is where in the range above 350 do you start, for example 350 to 500, in what part of that range would you start?”

“My own feeling is that the more relevant question is: when would you not treat a patient? I think you could make an argument for treatment of almost everyone. The notable exceptions are patients who are not likely to be adherent, or people who may be long-term non-progressors.”

Above 500

Analysis of data from a large UK HIV cohort may also back the theory that there can be advantages of starting ART at CD4 cell counts over 500 cells/mm³.

The UK Collaborative HIV Cohort (CHIC) was established in 1996 and has now enrolled over 25,000 patients. Their latest analysis has shown that the higher the current CD4 cell count, the

lower the risk of AIDS and death.⁸ The risk of AIDS or death continued to decrease at CD4 counts above 350 cells/mm³. With a CD4 cell count between 500 and 649 cells/mm³, patients were 55% more likely to develop an AIDS-defining illness than patients with a CD4 cell count above 650 cells/mm³. Individuals with a CD4 cell count between 200 and 350 cells/mm³ were five times more likely to experience an AIDS-defining illness or die than individuals with a CD4 count above 650 cells/mm³.

The analysis included 17,609 patients who were antiretroviral-naïve. The rates of AIDS-defining illness and death (from all causes) were analysed according to current CD4 cell counts. A total of 30,313 person years of follow-up were available for analysis.

Patients with a CD4 cell count between 500 and 649 cells/mm³ had either AIDS or death rate of 1.54 per 100 person years compared to 0.96 in patients with a CD4 cell count of 650 cells/mm³, a significant difference. The risk of AIDS or death was even higher



for patients with lower CD4 cell counts. For patients with a CD4 cell count between 350 and 499 cells/mm³ and 200 and 349 cells/mm³ (the current threshold for the initiation of HIV therapy in the UK) the rate of AIDS or death was 2.49 and 4.91 per 100 person years, respectively. Unsurprisingly, patients with a CD4 cell count of 50-199 cells/mm³ had a much higher rate of AIDS or death.

The investigators found that for patients with a CD4 cell count above 350 cells/mm³, each additional 100 cell increase in CD4 cell count significantly reduced the risk of AIDS or death.

When the investigators took into account additional factors associated with an increased risk of AIDS or death (such as a 1 log₁₀ increase in viral load, each additional ten years of age and injecting drug use) they still found that each additional 100 cell increase for patients with a CD4 cell count above 350 cells/mm³ was protective against AIDS and death.

“it’s also clear that we should not only focus on the long-term toxicity of ART, but also the long-term damage from HIV itself.”

While the risk of AIDS or death for patients with a CD4 cell count above 350 cells/mm³ remains relatively low, the investigators stressed that, “the risk at higher counts is not negligible.”

The investigators argue that their finding contributes to the rationale for randomised controlled trials like START, so that the risks and benefits for initiation of ART in patients with higher CD4 cell count can be evaluated.

How soon is too soon?

With the advent of more convenient, durable and less damaging drugs, concerns around increasing the duration of and numbers of people taking ART are diminishing. It has never been more appropriate to focus research on risk at higher CD4 levels. As our understanding of the way HIV attacks our immune systems increases, it’s also clear that we should not only focus on the long-term toxicity of ART, but also the long-term damage from HIV itself.

While the scientific hurdles of knowledge and understanding may well be overcome to provide concrete proof of when to start, there are still formidable barriers to early ART. While cost-effectiveness could be shown by increased prevention in the long-term, budgets are rarely geared towards future goals. The additional cost of antiretroviral drugs for those with higher CD4 cell counts could push stretched clinics to the limit. Additional cost would also be needed to increase testing. Even in countries where testing programmes are widespread, late diagnosis is still a major issue with many people presenting with advanced HIV disease and CD4 counts well below the recommended time to start treatment.

The switch in focus from traditional AIDS-defining to non-AIDS illnesses is less of a concern for developing countries. When much of the world can only offer HIV drugs when people’s CD4 counts have fallen below 200

cells/mm³, will a study comparing delayed to early treatment really have such a profound impact?

It’s a question clinicians from around the world have difficulty answering. In an interactive IAS session entitled, ‘New Data and International Antiretroviral Treatment Guidelines’ there was an opportunity for audience members to discuss ways of incorporating new data into treatment decisions and broad guidelines. While there is a general desire to use drugs more often, finding a plan to accomplish that proved elusive.

Current when-to-start guidelines aren’t based on randomised controlled trials and with such compelling information from cohort data and from the SMART study, we may well see a shift in the near future towards treating patients at 350 cells/mm³ or above, instead of in the 200 to 350 cell range. Whether the costs of treating at higher CD4 cell counts (of 500 cells/mm³ and above) will outweigh the benefits remains to be seen. ■



late to initiate?

In light of the accumulating data about the potential benefits of earlier treatment from Sydney and the world over, the implications for HIV services in the UK will need careful consideration. For any change in guidelines to be effective, there would need to be a major effort to diagnose more people earlier, something that we are still not doing very well in the UK.

In order to better understand the clinical impact of raising the latest threshold for starting treatment from 200 to 350 cells/mm³, ATU looked to Professor Caroline Sabin for assistance. Using data from the UKCHIC

database, she gave as an approximate estimate of the number of people that would become eligible for treatment. While Professor Sabin pointed out that this kind of analysis is 'quick and dirty' it does give us a clue to the kind of increases we would expect to see. The analysis reviewed the diagnosed population as it is today to find those currently untreated, living with HIV and with a CD4 count between 350 and 200 cells/mm³.

The information was extracted from data on UK CHIC patients who were under follow-up from 2005 onwards and who had either not started treatment and had at least one CD4

cell count available for analysis or who had started treatment and had at least one pre-treatment CD4 cell count available. The minimum CD4 cell count prior to starting treatment (or over follow-up for those that were not on treatment) was then identified.

There were 11,795 patients who met the criteria, and the following table shows the proportion of these who had and had not started treatment.

Overall, 9,109 patients in this group had started treatment and there were 1,002 patients with a CD4 count in the range 200-349 who had not yet started treatment. If the guidelines changed to

| CD4 cells/mm ³ | number (%) | number who started treatment (%) | number not on treatment |
|---------------------------|---------------|----------------------------------|-------------------------|
| less than 50 | 1,563 (13.3%) | 1,514 (96.9%) | 49 |
| 50-199 | 3,980 (33.7%) | 3,775 (94.9%) | 205 |
| 200-349 | 3,743 (31.7%) | 2,741 (73.2%) | 1,002 |
| more than 350 | 2,509 (21.3%) | 1,079 (43.0%) | 1,430 |

recommend that these patients should start treatment, then we would see an 11% increase in numbers receiving HIV treatment.

"It's important to keep in mind that this is a very rough estimate; many factors would influence the true value," said Professor Sabin. "The true number could decrease if the treatment offer was declined, or increase if we take into account the large undiagnosed HIV population which may come forward to test. However, it does give us a general idea of the potential increase in patients on treatment."

So how would HIV clinics cope with this increase in treatment and do the benefits of early treatment make the shift feasible in the UK? *ATU* asked Dr Mark Nelson (MN), Chelsea and Westminster Hospital, and Dr Ed Wilkins (EW), North Manchester General Hospital for their views.

ATU: Do the benefits of starting patients on treatment at a CD4 count of 350 copies/mm³ or above outweigh the risks?

EW: There is compelling evidence of an increase in morbidity and mortality in patients with CD4 cell counts as high as 350 to 499 copies/mm³. Data have also demonstrated that patients with higher CD4 cell counts when starting treatment are more likely to regain normal CD4 levels. Currently most physicians advise patients to consider commencing drugs when the CD4 cell count is in the 250–300 copies/mm³ range. This somewhat guarded strategy represents a balance between starting treatment early enough to prevent most illness and mortality and minimising the potential of virological failure from the difficulty of maintaining near perfect adherence and long-term drug toxicity. Given the potent, durable, low-tablet once-daily combinations that are now available, with so far limited long-term toxicity, it seems timely to review a return to the strategy of 'hitting early'. Studies are urgently needed to definitively answer this question so as to inform clinical practice and treatment guidelines. Nevertheless, while these data are being

accrued, I believe the weight of cohort evidence is moving patients and physicians to considering earlier initiation of therapy and my practice now is to advise treatment when the CD4 approaches 350 copies/mm³.

MN: The majority of doctors in the UK have always been relatively late initiators of treatment with guidelines suggesting that physicians in the UK treat people with CD cell counts above 200 copies/mm³, whilst European and American guidelines have suggested initiation of treatment at a CD4 cell count below 350 copies/mm³. These are not mutually exclusive, but many physicians and patients have chosen to wait until the CD4 cell count is close, or even below, 200 copies/mm³ before commencing therapy. It is a question of weighing up the benefits of early treatment against the risks, i.e. the number of patients we would need to treat with earlier therapy to prevent a single adverse event occurring. Equally, will we be doing harm to someone by starting treatment earlier due to toxicities associated with the medications prescribed? It is a question of understanding the risks, both potential and actual, of early treatment against the risk of the individual developing a disease.

ATU: Do you think early treatment would be feasible, particularly due to the high numbers of individuals diagnosed at lower CD4 counts?

EW: Certainly, until more widespread testing becomes routine, a significant proportion of patients are going to present with late stage HIV infection and therefore not derive the benefits of earlier ARV use and improved long-term immune recovery.

MN: A large proportion of individuals diagnosed present with opportunistic infections and tumours. As we begin to appreciate the probable benefits of earlier initiation of therapy, it is essential that we target individuals prior to them developing such diseases and ensure that individuals live to benefit from the advances in their

medication. This is not only a problem for the United Kingdom, but throughout the world, where greater than 50% of patients who commence therapy do so with a CD4 cell count below 200 copies/mm³.

ATU: What are the implications for clinical practice?

EW: Initiating treatment at higher CD4 counts will inevitably have a knock-on effect from the clinic down to all support services. However, the largest impact will be the increase in ARV costs, although data exist suggesting that such a strategy would not increase overall HIV care expenditure.

MN: The major issue of cost will need to be discussed. It is important that when looking at the cost of therapies we examine not the expense of therapy but the cost effectiveness of earlier diagnosis and initiation of therapy. Certainly data from the United States would suggest that the cost of care of individuals who are diagnosed with a CD4 count below 200 copies/mm³ for the oncoming year was almost double that for those diagnosed above this level.

ATU: So are we going to see a change in guidelines?

EW: Guidelines are informed by data and definitive randomised clinical trials are needed to address the question of starting treatment earlier.

MN: Clinical trials are the best way to answer this, or any question concerning the treatment of HIV. Such trials are now overdue. The high number of individuals recruited to the START [Strategic Timing of AntiRetroviral Therapy] study shows that individuals living with HIV are willing to look at new strategies. One would hope that a large clinical trial would answer once and for all, after almost ten years of HAART, when is the most efficacious time to commence therapy both for the individual and to prevent disease progression. Whether guidelines reflect, or not, the new data available to us, it is likely that physicians will wish to at least discuss the benefits of earlier initiation of therapy with their patients.

Experimental drugs at IAS

Several studies focused on experimental treatments at the recent International AIDS Society Conference in Sydney. Comparisons with efavirenz, the recommended non-nucleoside reverse transcriptase inhibitor (NNRTI) for those starting HIV therapy for the first time, were more than abundant as trials aimed to determine whether benefits would be seen in those new to treatment or reserved for those with more experience.

new drugs

Benefits of a new NNRTI

An analysis of side-effect data from a clinical trial of TMC-278, Tibotec's experimental NNRTI, indicates that it causes fewer changes to lipid (fat) and glucose (sugar) levels than efavirenz. The new data suggest that the drug may have a potential safety advantage over efavirenz.

Study C204 is a 96-week trial comparing TMC-278 to efavirenz, in combination with *Truvada* (tenofovir plus emtricitabine) or *Combivir* (zidovudine plus lamivudine). Data

from the trial, reported at the 14th Conference on Retroviruses and Opportunistic Infections earlier this year, have already demonstrated that TMC-278 has comparable efficacy to efavirenz.

All those enrolled in the study were treatment-naïve (they had not taken any other HIV medications in the past). Total cholesterol increased by 31 mg/dL in the efavirenz group, compared to 5 mg/dL in the TMC-278 group.

new drugs

Maraviroc reserved for treatment-experienced?

While Pfizer's CCR5-blocking entry inhibitor, maraviroc (*Celsentri*), has proven safe and effective in clinical trials involving treatment-experienced patients, new data have found it inferior to the standard-of-care, efavirenz (*Sustiva*), when used by people starting HIV treatment for the first time.

Maraviroc blocks the use of CCR5, one of two coreceptors HIV can use to enter the CD4 cell. Upon entering the study, participants were required to have CCR5-tropic virus (HIV using the CCR5 coreceptor to gain entry to the CD4 cells as opposed to the CXCR4

coreceptor) to ensure benefit from maraviroc.

During the study, 11.9% of those taking maraviroc stopped due to treatment failure, compared to 4.2% in the efavirenz group.

However, moderate side-effect benefits were found to be associated with maraviroc. More people discontinued treatment due to side-effects in the efavirenz group compared to the maraviroc group (13.6 vs. 4.2%, respectively). There was also an advantage when looking at CD4 count increase. After 48 weeks, CD4 cells increased by 144 in the efavirenz group and 170 in the maraviroc group.

new drugs

Update on Merck's integrase inhibitor



Results from an ongoing clinical trial of raltegravir, Merck's experimental integrase inhibitor, have suggested comparable efficacy to efavirenz after 48 weeks of treatment. Encouraging 24-week data have already been seen in treatment-experienced patients at the 14th Conference on Retroviruses and Opportunistic Infections (CROI) in February.

The study enrolled 198 HIV-positive people new to treatment who received either raltegravir (at varying doses) or efavirenz, along with a backbone of tenofovir and lamivudine.

After 48 weeks of therapy, 83-88% of those in the varying raltegravir dosing groups saw their viral loads reduced to less than 50 copies/ml. In the efavirenz group, approximately 87% experienced viral load reductions to less than 50 copies/ml. The differences were not statistically significant, meaning that the variations could have been due to chance. Raltegravir and efavirenz also did equally well at raising CD4 cell counts. In addition, 3% of patients experienced treatment failure (failed to achieve an adequate viral load response) in both groups.

changing treatment



Switching to Kivexa or Truvada?

According to a late-breaker presentation at IAS, switching from an antiretroviral regimen that is currently controlling your viral load to *Kivexa* is more likely to result in toxicity-related treatment failure than switching to *Truvada*. Switching from a successfully suppressive antiretroviral regimen may be necessary for several reasons, including the possibility of long-term side-effects.

Truvada and *Kivexa* are fixed-dose combination pills, each of which combines two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) into a single-tablet formulation. *Kivexa* contains 3TC (lamivudine) and abacavir; *Truvada* is a combination of FTC (emtricitabine) and tenofovir.

The Spanish "Bicombo" trial compared the safety and efficacy of *Truvada* and *Kivexa* after 48 weeks.

Virological failure was uncommon in all participants, occurring in 2.4% of patients taking *Kivexa* and none of those taking *Truvada*. CD4 cell counts increased by 44 cells/mm³ in the *Kivexa* group, while falling by 3 cells/mm³ in those taking *Truvada*.

However, more people in the *Kivexa* arm discontinued therapy prematurely. Whilst nine (5.4%) of those taking *Truvada* stopped due to adverse events, 17 (10.2%) did so in the *Kivexa* group.

The majority of adverse events in the *Kivexa* group were attributed to abacavir hypersensitivity reaction. Participants were not pre-screened for genetic susceptibility to abacavir hypersensitivity (see this issue upfront on page 3). If clinicians were to use genetic screening test to exclude patients who are prone to abacavir hypersensitivity, *Kivexa* and *Truvada* might have shown comparable effectiveness.

Some participants changed from individual drugs to the combination pill that contained the same agents (for example, from separate FTC and tenofovir to *Truvada*), so strictly speaking these patients did not switch therapy.

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enhancing prevention

an update on prevention technologies from the ias conference,
by Rob Dawson

Condom promotion and distribution is a key focus in HIV prevention, and where they are accessible and acceptable there is no doubt about their effectiveness. However, just as HIV treatment evolves and improves to take into account an individual's needs, so too must prevention strategies. Condoms alone are not the answer for everyone, and with such a diverse range of populations affected by HIV, increasing our arsenal of prevention tools could provide a more effective approach.

Several presentations at the recent International AIDS Society (IAS) conference in Sydney helped to advance our understanding of how combining new prevention technologies could enhance condom use, rather than replace it.

Cutting infections

One prevention tool that has received much recent publicity is male circumcision. While studies have found that male circumcision could reduce female-to-male transmission of HIV by around 60%¹, there was debate in Sydney as to whether roll-out of mass circumcision programmes would be effective and feasible.

Circumcision researcher Bertran Auvert and colleagues in France, South Africa and the United States developed a costing model to address some of the issues. They used demographic data from 14 African countries where the prevalence of circumcision was less than 80% and adult HIV prevalence was more than 5%, and modelled the cost for individuals and the public sector of a rapid roll-out of circumcision for adult males. They found that circumcision as an HIV prevention measure would need to have high uptake and substantial funding in the first few years if it is eventually to be cost-effective.² Dr Auvert calculated that you would need to circumcise between four and nine men to prevent each new HIV infection but he believes that, while this would be expensive, it would ultimately be worthwhile given the long-term savings in treatment and care.

Separate modelling data were also used to show that targeting only 20 to 30 year-old men - or men with a greater number of sexual partners - may produce the most cost-effective reduction in HIV prevalence.³

While there has been concern that circumcision programmes may encourage men that have had the surgery to take more sexual risks, there are data to suggest that this may not

be the case. Professor Robert Bailey of University of Illinois, Chicago, School of Public Health, speaking during a plenary session at the conference, pointed out that in his study, risk behaviours by circumcised men fell during the twelve months that followed the surgery.¹

Circumcision may be beneficial for some, but there are cultural and social barriers which mean that there is no guarantee that it can be applied. Finding appropriate high-risk groups is key. Bailey noted that general circumcision programmes outside of Africa may not be appropriate or effective but that targeted programmes for high-risk heterosexual men should be explored.

While one study at the IAS conference showed that gay men are willing to be circumcised, another showed that it is unlikely to be an effective form of HIV prevention in this setting.

Dr Juan Guanira, of the Asociación Civil Impacta Salud y Educación, Peru, reported that South American men who had sex with men (MSM) would be willing to participate in a circumcision trial.⁴ However, there were concerns; men worried about undergoing surgery (62%), side-effects of surgery (72%), and encountering partners who would insist on having sex without a condom (75%).

While Dr Guanira argued that his data lay the foundations for a circumcision trial in MSM in the Andean Region, a different study had less promising results for men in Sydney. David Templeton of the National Centre in HIV Epidemiology and Clinical



Research, University of New South Wales, found that circumcised and uncircumcised gay men had the same risk of becoming infected with HIV.⁵

He explained that most HIV infections in homosexual men occur after receptive anal sex, and so circumcision is unlikely to be an effective HIV prevention intervention for Australian gay men. However, he felt that further research is warranted into populations where gay men are more likely to be exclusively receptive or insertive in their sexual roles.

Pre-prepared

The idea that antiretroviral drugs could play a preventative role if taken prior to any risk of HIV infection is not a new one, but developments in this area take time. Pre-exposure prophylaxis (or PrEP as it's known) may have great potential in reducing HIV transmission but determining how they could be best used, if proven effective, needs careful consideration.

With results from the first PrEP clinical trials expected early next year, an IAS Industry Liaison Forum addressed some of the challenges that could be faced. The key areas needing focus in the coming months were defining priorities for PrEP's use and using modelling techniques to help determine what impact it might have on different populations.

Dr Dawn Smith, a medical epidemiologist at the US Centers for Disease Control and Prevention, highlighted the importance of acting now, before the trial data are ready, by surveying stakeholders and potential participants so that they can truly understand how to implement PrEP effectively.

On novel use of PrEP, presented by Pietro Vernazza of St Gallen Cantonal Hospital, Switzerland, was as a safeguard for serodiscordant couples who wanted to try natural conception. This small Swiss study suggested that HIV-negative women may be able to conceive safely by having timed unprotected intercourse with their HIV-positive male partner – as long as the partner's seminal viral load is undetectable.

A combination of couples counselling, STI screening, timed intercourse and a "psychological safeguard" of two doses of tenofovir (*Viread*) as PrEP had resulted in a pregnancy rate of over 70%, and no HIV transmission.⁶

Dr Vernazza told the conference that with a suppressed viral load in semen the risk of HIV transmission "is getting towards zero." He considered PrEP to

be an additional risk-lowering intervention but felt that it was primarily used as a "psychological safeguard" to ease concerns.

Microbicides

New products in microbicide research and development pipeline were discussed by Zeda Rosenberg, Chief Executive Officer of the International Partnership for Microbicides. She made the important distinction between first generation products, which block HIV's interaction with host cells, act over shorter time spans and require application just before sex, and second generation products, which use current antiretroviral agents, may act over a longer time span and allow for different dosing regimens. Her opinion was that long-acting, sustained-release delivery types, such as vaginal rings, are likely to be most useful. These would deliver locally high drug levels at the site of transmission, while levels in the rest of the body remain low. Their success depends on delivery of the right drug (to ensure potency and safety) at the right time and on studies to determine the levels of drug present.

She concluded that combinations of products are under development, with potential blocking multiple transmission pathways, but that increased toxicity and the difficulties of co-formulation must be considered.

Ian McGowan, Co-Director of the Center for HIV & Digestive Diseases, David Geffen School of Medicine at UCLA, showed that the need for rectal microbicides is demonstrated not only by the established risk of unprotected anal intercourse among MSM but by epidemiological evidence showing high levels of anal intercourse among heterosexual populations in some countries. He recommended that rectal safety should be incorporated into the development of new vaginal products, given the likelihood of anal use, as well as expressing the need for specific rectal formulations.

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