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hiv treatment update

in this issue

If there's one thing that remains constant in the world of HIV, it's that everything changes. The contents of this issue highlight this axiom beautifully.

Almost three years after the disappointment – and important learning curve – of the SMART study, the concept of structured treatment interruptions refuses to die. Why? Primarily because people living with HIV are not drug-taking robots but, rather, complex human beings. Many of us find it difficult – for a wide variety of reasons – to remain on a daily treatment for life.

Although it's too early to say whether the two treatment-interruption protocols examined in this issue will ever be officially recommended, they counterpoint another study reported in this issue, that suggests starting treatment at a CD4 cell count of 500 results in a 70% reduction in illness or death compared to starting at 350 (as recommended by the most recent guidelines).

With one camp pushing for increasingly earlier treatment and another trying to make life with HIV a little easier (and more affordable), it's not yet obvious from a patient's point of view which is actually better (and safer).

If those of us who are old and experienced enough to be able to grasp the complexities of treatment adherence are confused, imagine how a young adult – who may have only recently learned they had been infected – feels. Their experiences, explored in the main article this month, remind us of the challenges of living with HIV at any age.

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editor Edwin J Bernard
sub-editing & proofreading Selina Corkey
design Kieran McCann
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contact details
Lincoln House, 1 Brixton Road,
London, SW9 6DE, UK
tel: 020 7840 0050
fax: 020 7735 5351
email: info@nam.org.uk
web: www.aidsmap.com

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upfront

The return of treatment interruptions?

by Edwin J Bernard. Reporting by Gus Cairns

Two and a half years after the SMART study of CD4 count-guided treatment interruption was halted because of a higher risk of death in people who stopped treatment, it seems that the concept of structured treatment breaks refuses to go away. Two new studies on this subject were reported at the Ninth Congress on Drug Therapy in HIV Infection in Glasgow last month.

The LOTTI study[1]

It was with some trepidation that Dr Franco Maggiolo presented four-year results from the LOTTI study, a five-year, Italian, structured-treatment-interruption study that is still ongoing. "My task this morning is not easy: it's a difficult thing to talk about strategic treatment interruptions since the SMART trial," he told the conference, "but I'm here to convince you there are some good options for patients."

In the LOTTI study, 329 individuals were randomised either to receive continuous antiretroviral therapy, or to stop treatment when their CD4 counts reached at least 600 and to resume when they fell below 350. To be eligible for the study, however, patients needed to have a current CD4 cell count above 600, a lowest-ever CD4 count of above 200, and to have been on stable antiretroviral therapy with a viral load below 50 copies/ml.

After four years, the proportion of participants reaching the study's primary endpoint (any AIDS-defining event; death from any cause; or hospitalisation) was similar – 12.1% of those who interrupted treatment and 11.6% of those on continuous treatment. During this time, the participants who interrupted therapy were off treatment for two-thirds of the time compared with less than 2% of the time in the continuous-therapy participants.

Unlike the SMART study, in LOTTI significantly more people on continuous treatment experienced a cardiovascular or metabolic event, at a rate of 3.3% per year compared with 0.2% a year in those who interrupted therapy.

Dr Maggiolo commented that the average follow-up time in SMART had been just over a year, compared with four years in his study. If the LOTTI study had been stopped at the same timepoint as SMART, no difference would have been observed in cardiovascular and metabolic events either. He argues that his study demonstrated that it took a long time for the benefits of therapy-sparing regimes to become evident.

He also said that, in his study, 95% of patients had CD4 counts over 350 – compared with 65% on SMART – and 0.5% below 250, compared with 8.6% on SMART. This might explain the higher mortality and illness rates seen in patients off treatment in the SMART study.

The FOTO study[2]

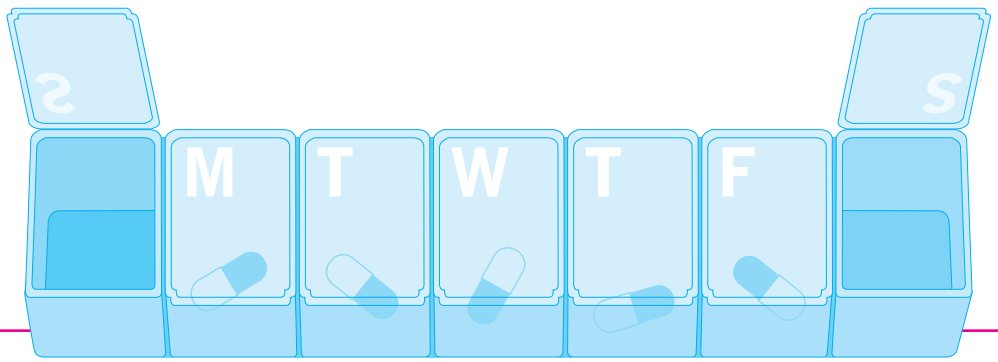
Dr Cal Cohen then presented results from the much smaller FOTO (Five On, Two Off) study, which randomised 60 participants with an average CD4 count of 670, either to continue treatment with efavirenz (*Sustiva*) and tenofovir/FTC (*Truvada*) or to stop taking it at weekends.

After 24 weeks, 80% in the continuous treatment arm and 83% in the weekend-off arm had a viral load under 50 copies/ml, a non-significant difference.

Did participants adhere to the strategy? In the FOTO arm, three patients took over five doses a week at some point and, although eight individuals took three days off, none developed a detectable viral load (viral loads were measured on Mondays). As well as the weekend-off protocol saving 29% on drug costs, Dr Cohen said, his patients strongly preferred to have weekends off treatment. When asked on a scale of 0 to 10 whether they preferred stopping their drugs at weekends, where zero indicated total disapproval and 10 total approval, the average score was 9.5.

Unlike the LOTTI strategy, the FOTO protocol also kept viral loads undetectable, meaning that it did not entail the problem of potentially raising the sexual infectiousness of the participants.

Will either strategy make it into UK HIV clinics? Dr Maggiolo told the conference that doctors might like to see more evidence before recommending structured treatment interruptions, but when asked what further evidence would be required before it is considered to be safe clinical practice, he replied, "It already is mine. It's not for every clinician or every patient, but it's a safe option for some."



Growing pains

Why ageing with HIV isn't just a concern for the over 50s,
by Edwin J Bernard

Earlier this year, in our March 2008 issue (*HTU* 174), when we examined the health issues faced by an increasingly ageing HIV-positive population, we focused on those who are over the age of 50.

However, there is another group of people who are also ageing with HIV – those born with the virus who are reaching young adulthood and those infected (usually via sex) in their teenage years. Together, these young adults (defined as being aged between 16 and 24 years old) make up an ever-increasing number of people living with HIV in the United Kingdom.

Increasing numbers

In 2007 (the year with the latest complete data from the Health Protection Agency[1]), out of 56,556 diagnosed HIV-positive people attending HIV clinics in the UK, 2245 were young adults – more than double the number seen in 2001 when the numbers hit four digits (1005) for the first time.

More remarkable is the number of young people over the age of 16 attending UK HIV clinics who were infected during their mother's pregnancy, during birth or via breastfeeding (known as vertical transmission), which has increased even more substantially – more than sevenfold during the same period, from 28 to 208.

According to data from the CHIPS (Collaborative HIV Paediatric Study) cohort[2], last year there were a further 187 teenagers aged 15 or older receiving paediatric HIV care who would have begun the transition to adult HIV services in 2008. Waiting in the wings are another 418 children aged 11 to 15 who are well on their way to becoming young adults living with HIV.

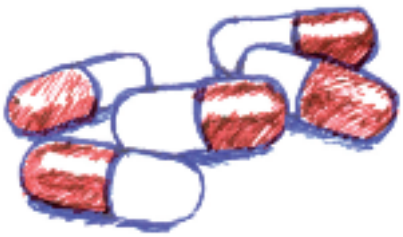
Dr Hermione Lyall, consultant in paediatric infectious diseases at St Mary's Hospital in London – which has the largest paediatric HIV clinic in the country, seeing around 200 of the 1200 HIV-positive children currently living in the UK and Ireland – recalls a very different picture just a decade ago.

"At that time, the future for children with HIV was guarded," she wrote last year in *Positively Women* magazine.[3] "Only about half of them survived to the age of ten and, by that time, most of them were expected to have severe symptoms of their infection. There was no known effective treatment and it seemed very unlikely that children would survive to adult life. Back then, I can remember we had long discussions with families about whether it was more cruel to inform the children of their HIV diagnosis than not. The dilemma being whether if the life of a child was going to be short, would knowing the cause of their suffering make things better or worse."

Life seems quite unpredictable: Lillian's story

"Lillian* is 18 years old, and originally from Ethiopia," says Susan McDonald, clinical nurse specialist at the 900 Clinic. "She was diagnosed HIV-positive following the death of her mother when she came to the UK to be cared for by her mother's sister. She has been on and off antiretroviral treatment for much of her life. By May 2007, with advanced HIV disease and suffering from fatigue, she started on *Kaletra/Kivexa* with support from her grandmother. However, several weeks later her grandmother died and her aunt had to return to Ethiopia, leaving her to care for her younger cousins. This was not ideal in view of Lillian's fragile emotional and physical health. She subsequently stopped her treatment and shortly afterwards was admitted to hospital with HIV-associated thrombocytopenia (low platelets) and anaemia. Her social worker had arranged for her to move into her own flat, where she went when discharged from hospital. Although she wanted to restart antiretroviral therapy she found it really difficult to adhere to the medication. We found a regime that she could take once a day and then linked her in with the local clinical nurse specialist. A joint decision was made for her to have morning visits for directly observed therapy (DOT) from the district nurse. However, after a few weeks, Lillian became frustrated about being visited by a nurse every day and stopped treatment. It has been and continues to be really difficult for Lillian to engage with health services and consequently she remains off treatment. She still has quite a long road ahead, and her life seems quite unpredictable."

**not her real name*



Multiple challenges

With increasing numbers of HIV-positive children growing into independent, sexually aware – and sexually active – young adults, it's become clear that they and their healthcare providers face complex challenges not anticipated a decade ago.

According to guidance from the Children's HIV Association of UK and Ireland (CHIVA)[4], a child born with HIV should ideally be told that they are HIV-positive by the age of 13. This does not always happen, and there are some whose HIV status is kept from them (for a variety of reasons, often linked with parental or family stigma and shame), even as they become sexually active teenagers.

As you can imagine, realising that a major health issue has been kept from you until then, and then facing a life with HIV on top of the conventional challenges of adolescence, is likely to be far from easy.

Last year, at a one-day conference organised by the Children & Young People HIV Network, Judith Dorrell of the Open University[5] presented some important new research about the issues facing young adults with HIV. She conducted in-depth interviews with 20 young people, aged 15 to 24, who had been HIV-positive since birth, and asked them how HIV had affected family, friends, relationships, school/work, health and their feelings about the future. She found that, like the rest of us living with HIV, they wanted to get on with their lives, keep healthy and be 'normal'. Most were hopeful for their future and all of them wanted to be in a loving relationship with a partner where they could be open about their HIV status.

Her research also identified issues and concerns that are relatively confined to vertically infected young adults:

- Family: most had already dealt with loss and bereavement in their immediate families and were concerned about their families coping; they wanted to protect them and not be the cause of distress.

- Isolation: many never talked about HIV within the family; most also had nobody to talk to outside of the medical setting about their HIV-related concerns; and many had difficulties in keeping their HIV status a secret from friends.

- Adherence issues: those who were taking medication were often highly treatment-experienced, and had difficulties managing adherence in their (typically teenager) disorganised lives.

- Sexual anxieties: many were sexually active (three were already parents), but most had fears and anxieties around negotiating sex and disclosure.

Teenage kicks

These issues and concerns were echoed and amplified by clinical nurse specialist, Susan McDonald, from St Mary's Hospital in west London, and by Maria Phelan, co-ordinator of the Children and Young People HIV Network at the National Children's Bureau, both of whom gave presentations to a group of HIV advocates at the October UK Community Advisory Board meeting in London.[6]

Susan McDonald spoke movingly about her experiences at the 900 Clinic - one of only three clinics in the UK to specialise in young adults with HIV as they make the transition from paediatric to adult care (for more on transitional care, see *Making the transition* on page 7 and 8). In particular, she focused on some of the challenges faced by young adults who were born with HIV that are different from young adults more recently infected.

"I think they're amazing young people. Some of them have had very difficult lives at times and I think that most of them are managing to get on with their lives as young adults incredibly well", she said, before highlighting the issue of family illness, and that "quite often they're young carers themselves". She also spoke of the difficulties for some young people of coming to terms with realising that they had been managing a lifelong chronic illness when, until recently, they "weren't aware of the health condition that they were treating".

Rebuilding shattered dreams: Ben's story[7]

I am 17 and I learned that I had HIV when I was 10.

I remember that day perfectly – it was honestly the worst day of my life. My heart broke because I also found that my mom was a prostitute and cocaine addict and that I had been adopted. I have no information on my real mother and want to know so badly but don't know how to go about something that huge.

I've had some issues with my meds and had to deal with almost dying. But now I am living with meds that are perfect and are keeping my virus in remission and that is wonderful.

My life is great now and I actually feel normal and not shunned from the whole world. I am in a relationship and it is wonderful and we both are comfortable with it. My friends are there for me every step of the way. My family is wonderful, even though I feel like there is something missing.

Anyway my life is going great and I am glad I have HIV because if not, then I wouldn't be me, and I love who I am. Although that day when I was 10 shattered all of my dreams and hopes, now that I am older and have had more time to think about it all, I have realised that my dreams aren't shattered – having HIV is just one more thing to make me stronger, and that's exactly what it is doing.

Susan McDonald noted that: "90% of young people don't have the opportunity to take first-line once-daily regimens" because many are already highly treatment-experienced. In fact, the most recent data from CHIPS[8] show that 45% of children over the age of ten have already burned through at least five antiretrovirals.

Although an impressive 78% of those on treatment had an undetectable viral load at their latest clinic visit, around one in five of children over ten were not on treatment because they had interrupted their antiretroviral therapy. One of the reasons for this is that some have run out of viable treatment options, particularly since it seems that some are unable to tolerate drugs boosted by ritonavir (*Norvir*).

"The reality is that some of these medications are really difficult to take," Ms McDonald said, "and there will always be some young people that find taking medication exceptionally difficult. Part of the problem is that having experienced [foul-tasting] liquid ritonavir as children they can't face taking ritonavir capsules as young adults because it makes them feel sick. There are a multitude of reasons why young people either don't want to take medication every day or find it difficult to fit into their daily lives. However, in some cases it is not always clear why some young people can't take their medications. I think sometimes they don't know and sometimes they find it really difficult to articulate the reason why."

Maria Phelan, of the Children and Young People HIV Network, noted: "It's difficult for young adults to cope with the constant taking of HIV medication and, as their lifestyles become less and less predictable, as they start to go out with their friends and have a good time, they've got other things going on and so it becomes increasingly more difficult for them to adhere to their regimen."

Secrets and lies

In her presentation, Ms Phelan highlighted that disclosure was a major issue, not just in terms of non-disclosure affecting the ability to adhere to a daily treatment regimen, but also because

(non-)disclosure coloured every aspect of their lives.

"Often when young people are told about their HIV status they're told to keep it a secret, and this is something that really impacts on how they view their HIV status. Guilt, shame, stigma – all of these things are instilled from minute one," she said. "Not all young people like to lie and keep secrets from their friends. They don't want to have to lie all the time about why they're taking medication, why they're taking long chunks of time off school."

This inability to disclose can lead to feelings of isolation, which can have further impact on their mental health. She highlighted a small study from the United States[9] (which might not be representative of the UK experience, and highlights a need for more UK-based studies) which found that, of 47 young people aged between nine and 16 infected at birth, 55% met the criteria for a psychiatric disorder, most commonly anxiety disorders (40%), attention deficit hyperactivity disorders (21%) and conduct disorders (13%).

Risky business

Last year, in a US study (which, again, might not be representative of the UK experience), Wiener and colleagues[10] interviewed 40 young adults (66% female; 55% white) who had acquired HIV early in life, either at birth (65%) or through a blood transfusion (35%). These interviews were 21 months apart when the participants were around 16 and 18 years old.

They found that 28% were sexually active at the time of the first interview and 41% were sexually active at the time of the second interview, and that knowledge regarding sexual-transmission risk behaviours was relatively low but increased with age. Although reported use of condoms was relatively high, "almost one fifth of the sexually active sample had either become pregnant or gotten someone pregnant in their lifetime," they concluded, "suggest[ing] ... inconsistent condom use".

The UK has the highest teenage conception rate in Western Europe[11] and under-25s also bear the brunt of the majority of sexually transmitted infections.[12] Of 20 young adults attending the St Mary's 900 Clinic in 2007, only five had disclosed to their sexual partner(s).[13] And yet there had been three pregnancies, as well as several diagnoses of chlamydia, suggesting that unprotected sex without disclosure was taking place. For young adults with HIV, concerns around the social and legal implications of disclosure, condom use and risk reduction are pressing, particularly in the context of the criminalisation of HIV transmission.

It's difficult for adults, and it's even more difficult for young people that don't necessarily have the kind of skills to negotiate safer sex. You can provide all the safer sex education, but actually they need to have the confidence to then carry it out.
Susan McDonald, St Mary's Hospital

"The Crown Prosecution Service has said that they would never prosecute a young person," notes Maria Phelan, but they haven't specified an age. So how young is 'young'?" She noted the 2005 case of a young Welsh woman infected with HIV at the age of 15, arrested at 17 and prosecuted at 18 for 'recklessly' infecting her former boyfriend, who was the same age.[14] "Can a 15 year old still be prosecuted for infecting a fellow 15 year old?" she wondered.

She also wondered how an effective duty to disclose before sex that risked HIV transmission (in order to avoid criminal liability) would affect young adults. "Can their equally young partners keep their HIV status confidential?" she asked. "There isn't a confidentiality pact in the bedroom. You can't guarantee that that's not going to go out all over the school or all over the college. What impact will that have on a young person's life?"

Susan McDonald also spoke about the "fear of onward transmission for these young people. It's difficult for adults, and it's even more difficult for young people that don't necessarily have the kind of skills to negotiate safer sex. You can provide all the safer sex education, but actually they need to have the confidence to then carry it out."

Making the transition

A 2004 UK study exploring the experiences of the first group of HIV-positive young adults moving between paediatric services at Great Ormond Street and adult HIV care services at the Royal Free found that "on transition, some of the participants were not prepared for the predominately gay male population and were disappointed in not seeing other adolescents. The benefits of transition included the sense of independence, the shift in responsibility to the individual and general satisfaction in being treated as an adult. For those with

strong paediatric staff rapport, a sense of loss in these relationships was expressed."[15]

Data presented at last year's CHIVA conference showed that of 114 young people who were eligible to be transferred from paediatric to adult care, only 40% could be followed up in an adult HIV-cohort database (UK CHIC), leaving 60% unaccounted for. Although this does not necessarily mean that they no longer accessed HIV services, it highlights that young people are a highly mobile population, moving around the country to study or work or travelling abroad for extended periods of time.

It is precisely because of all of these issues that transitional services – providing a clear and defined pathway from paediatric to adult care – have been developed for HIV-positive young adults. To date, three HIV clinics (St Mary's in west London, Great Ormond Street/ Mortimer Market in central London and St George's Hospital in south London) – have set up transitional services. But London is only home to 59% of HIV-positive children and, argues Maria Phelan, these services need to be expanded to serve young adults around the UK.

"You can't just expect young people to handle the leap all on their own," she says. "There needs to be something in place, good communication. Young people might need more time than other adults to break the ties of the professionals with whom they've established a really close relationship. When you experience loss or bereavement, one shouldn't underestimate the importance of these healthcare professionals in their lives and how difficult it might be for them to move on."

She highlighted four key areas where young adults infected at birth or early in their lives need particular support:

- Communications: good communication between paediatric and adult services.
- Life skills: self-esteem, negotiation, confidence skills are all useful when they will be managing their own healthcare.
- Care management: co-ordinating mental, psychological and behavioural aspects in a young person's care.
- Peer support: both young person to young person, and also making sure that the family support network starts to 'let go'.

Teenage lipodystrophy: Elena's story

"Elena* is a Ugandan orphan, adopted by an English couple, who was diagnosed HIV-positive at the age of seven months after being admitted to hospital with pneumonia," says Susan McDonald, clinical nurse specialist at the 900 Clinic. "She was also infected with the hepatitis B virus, but she actually managed to clear it. Now 19, she's had an extensive treatment history and has also experienced some long-term side-effects associated with antiretroviral therapy, notably some mild renal impairment and quite marked lipodystrophy. Lipodystrophy is difficult for anybody to have to cope with, but for a young person who is dealing with hormone and body changes, bombarded with images of skinny models and trying to fit in, it's even more of a challenge. Due to resistance to her last regime, she opted for a treatment break as she was having difficulty taking the medication. She related this to not coming to terms with her HIV diagnosis and needing to escape from the medication for a while. However, she's also getting on with her life, and has just started living independently at university. She was very open to try some cognitive behavioural therapy and recently opted to restart antiretroviral therapy."

**not her real name*

The 900 Clinic [16]

The 900 Clinic, at St Mary's, was the first clinic in the UK specifically set up to help manage the process of transitioning 16 year olds into adult care.

"There is widespread recognition that the transfer from paediatric to adult services for many chronic diseases of childhood has been very poorly managed in the past," notes Dr Caroline Foster, who runs the clinic with clinical nurse specialist, Susan McDonald. "Now there is increasing evidence that shows a proper transition process with shared paediatric and adult appointments can really help."[17]

The clinic addresses all aspects of a young person's health, including the medical, psychosocial and educational/vocational needs of young adults as they move over into adult services. "There's no chronological age for transferring over to adult services," notes Susan McDonald. "The important thing is that it's individually discussed and assessed with each person. We consider ourselves to be a 16 to 25-year-old young person's clinic."

As of September 2008, four of the young women attending the 900 Clinic have now had children, all of whom are HIV-negative. "This is great news," says Dr Foster, "because teenagers need to adhere to their treatment to make this happen. I think now we can say that there is a wave of young people born with HIV who are surviving on treatment, transitioning, moving into adult services, getting through school to university and who are fully engaged in getting on with their lives."

The Rite Clinic [18]

The Chelsea & Westminster's Kobler Clinic, in west London, is the largest HIV clinic in the country. Although excellent services have been set up to aid the transition of care from paediatric to adult services for vertically infected teenagers, until recently, there were no clinic options for young people who were infected with HIV as teenagers.

CHIVA guidance: Basic principles of transitional care [19]

- Addressing and updating young people's knowledge both about their HIV status and sexual health issues are key for successful transition.
- Whilst there is no absolute 'right' chronological age for starting transition or transferring care, and flexibility of approach is essential, it is suggested that transfer to adolescent or adult services will generally occur between the ages of 16 and 18.
- Transitional services have to recognise individual needs, abilities, experiences, beliefs and expectations and the racial and cultural diversity of the population as well as plan general principles of care.
- Appropriate preparation and support for transition are essential components for both the young person and their carer(s).
- Supporting steps towards an individual gaining greater independence and responsibility, particularly around self-management of health care, will enhance the process of transition and lead to more successful transfer.
- A multidisciplinary approach is essential and should include young people's views about service needs as well as increasing opportunities for participation and choices in their own care.
- These principles of transitional care should apply whatever resources or clinic structures are present.

HIV clinicians Dr Fiona Boag and Dr Amelia Hughes, together with HIV nurse specialist Breda Ward, have now set up the Rite Clinic, aimed at young people aged 16 to 25 who may feel out of place amongst older people at the mainstream HIV clinic. As well as an HIV physician (who doubles up as GUM and contraception physician) and an HIV specialist nurse, other services such as health advisers, pharmacy and a psychologist are available as needed.

"We aim to provide holistic care with every clinic visit," says Dr Amelia Hughes, the clinic's specialist registrar, "highlighting and addressing specific problems for each individual in a supportive environment."

The consultations not only focus on HIV care and treatment, but also specifically focus on:

- support networks and relationships with friends and family
- current psychological wellbeing, and previous psychiatric illness
- sexual relationships and sexual and reproductive healthcare
- difficulties with disclosure and stigma associated with HIV
- social situation including work, education, visa and asylum difficulties and financial difficulties, current and previous support from social services
- current and previous use of recreational drugs and alcohol.

"We expect our patients will also benefit from meeting other young people, which may reduce social isolation and improve social networks and psychological wellbeing," adds Dr Hughes. "We also hope that clinic non-attendance – which we had previously identified as an issue with some of our younger patients – will fall and, in turn, onward HIV transmission may be reduced."

Teen Spirit [20]

Teen Spirit, from HIV charity Body & Soul, was the first project in the UK to recognise that teenagers living with HIV needed support in order to cope. Aimed at everyone aged between 13 and 19 years who knows that they are living with, or closely affected by HIV, the project provides a regular space for HIV-positive teens to discuss issues specific to living with HIV.

The core aim of the group is to equip young people with the skills, information and confidence to respond positively to the challenges they face and to ensure teenagers don't slip through the net.

"When I was 15," writes one participant on the Body & Soul website, "my HIV status was disclosed to me. My life flashed before my eyes and straight away I thought I was going to die. Through Teen Spirit my fear of being misunderstood was exchanged for knowledge and understanding; my fear of rejection was swapped for acknowledgement and acceptance; my fear of loneliness was replaced by companionship, support and love; my fear of helplessness by inspiration, courage, faith and hope; and my fear of death was no longer in me because I felt alive."

The project provides structured support sessions, including a programme of facilitated workshops on HIV and other issues relating to adolescence such as sexual health, drugs awareness, conflict resolution, and self-esteem. There is also one-to-one support and information and advocacy on a range of issues such as careers, relationships, housing and health. ■

ICAAC News

HIV treatment news from the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Washington, DC, in October 2008

by **Edwin J Bernard.** Reporting by **Derek Thaczuk**

Starting treatment above 350 results in 70% improved survival

Current guidelines suggest that antiretroviral therapy should be started when a patient's CD4 cell count falls below 350 cells/mm^3. However, an analysis of ten years' worth of data from a very large North American cohort collaboration presented at ICAAC has found that starting antiretroviral therapy at a CD4 cell count between 351-500 cells/mm^3 results in a better likelihood of survival.

The study contained data from the medical records of 8374 individuals in 22 US and Canadian cohorts, none of whom had taken antiretrovirals before. The investigators compared the risk of death (from any cause) for the 2473 patients (30% of the cohort) who started antiretroviral therapy when their CD4 cell count was between 351 and 500 cells/mm^3 with the 5901 patients who deferred treatment until their CD4 cell count was 350 cells/mm^3 or lower.

They found that the patients who deferred therapy had a 71% increased risk of death compared to those individuals who started treatment at higher CD4 cell counts. The study's lead author, Mari Kitahata, told the conference that "...these data strongly support the use of antiretroviral treatment for patients at a CD4 count of 500 and below, regardless of the presence of symptoms."

Dr Kitahata pointed out, however, that treatment guidelines are unlikely to change until other studies confirm these findings and that, since many people are not diagnosed until their CD4 counts are 350 cells/mm^3 or even lower, the study suggests that diagnosing people earlier (when CD4 counts are higher) is becoming increasingly important.

Raltegravir non-inferior to efavirenz

New data based on larger numbers of trial participants, presented to ICAAC in October, continue to suggest that raltegravir (*Isentress*), the new integrase inhibitor manufactured by Merck, is at least equivalent to efavirenz (*Sustiva*) in terms of potency, and results in fewer central nervous system (CNS) side-effects during the first eight weeks of treatment.

A smaller, phase II trial based on just 200 people over 96 weeks reported similar results at the International AIDS Conference in Mexico City in August 2008. In this larger, phase III study, 281 people starting treatment for the first time were randomised to take raltegravir (400mg, twice daily) and 282 were randomised to take efavirenz (600mg daily), both in combination with tenofovir and FTC (*Truvada*).

At week 48, 86% of participants on raltegravir and 82% of those on efavirenz had a viral load below 50 copies/ml. CD4 cell count increases were 189 cells/mm^3 in the raltegravir-treated patients compared to 163 cells/mm^3 amongst those who were treated with efavirenz.

Although nearly everyone on either drug reported at least one adverse event during the 48 weeks of the study, those judged to be drug-related were much less common in those on raltegravir than the people on efavirenz. When the investigators examined CNS symptoms at week eight, at least one had occurred in 52% of the participants on efavirenz, compared with 20% on raltegravir

In a separate presentation, data were presented that suggested that raltegravir may act against HIV in a manner quite distinct from existing antiretrovirals, allowing for the drug to remain effective against HIV for a period much longer than the actual metabolic half-life of the drug itself. In fact, test-tube studies showed that 48 hours after infection, HIV was still not replicating in cells that had been exposed to raltegravir, even after they were 'washed' clean of active drug.

Only 40% might benefit from new maturation inhibitor, bevirimat

Bevirimat is an investigational maturation inhibitor being developed by Panacos Pharmaceuticals. It targets a late stage in the HIV lifecycle, as new viruses are being prepared for release from infected cells. The drug interferes with the maturation of these viruses. A previous ten-day phase II study found potent anti-HIV effect and encouraging tolerability in small groups of treatment-experienced patients.

The drug's development history has been chequered, however. A 400mg tablet resulted in unexpectedly low levels in the blood and, although trials using an oral solution had better results, responses were still uneven. The participants who did best in the latest two-week study were those who took a 300mg liquid dose and who were screened for key polymorphisms (naturally occurring genetic variations) in the HIV *gag* gene. These key polymorphisms (Q369, V370 and T371) had previously been identified as resulting in poorer responses to the drug.

In other words, some people have HIV that is naturally resistant to bevirimat. Should it become approved, screening for these key polymorphisms will be necessary before anyone starts taking the drug. When 1034 patients were screened for these key polymorphisms, about 60% of those people were found to have at least one of them, although they do not appear to be more common in treatment-experienced patients.

This suggests that, should bevirimat overcome its formulation problems and become approved in the future, the drug may only be useful for 40% of HIV-positive people. However, it may still have a role to play in the HIV arsenal and could be particularly helpful for highly treatment-experienced individuals attempting to put together a new potent regimen.

More ICAAC highlights

Is Truvada more effective than Kivexa?

A systematic review of previous clinical trials suggests that the dual-nucleoside backbone of tenofovir/FTC (*Truvada*) results in better outcomes than abacavir/3TC (*Kivexa*), when combined with a boosted protease inhibitor, in patients taking treatment for the first time. Some of the apparent advantage of *Truvada* may be due to better tolerability, rather than potency, and may not hold true for people who are screened for abacavir hypersensitivity.[1]

Since ICAAC, however, *Kivexa* was downgraded from a 'preferred' to an 'alternative' NRTI backbone in newly updated US HIV treatment guidelines. The move was due to concerns that treatment with abacavir may increase the risk of heart attack, and because of evidence showing poorer virological outcomes in patients with a high viral load. Although draft UK guidelines had also downgraded *Kivexa*, the final version, published this summer, reinstated it to equal first choice with *Truvada*.

Treatment affects bones

A sub-study of the SMART trial found greater losses of bone mineral density in people who stayed on continuous antiretroviral therapy, compared to those who periodically interrupted their treatment. The study also found that people on continuous treatment were almost five times more likely to experience a serious fracture during the follow-up period than those who interrupted treatment.[2]

No increased cancer risk for vicriviroc

Earlier concerns over the apparent increased risk of cancer seen in some earlier clinical trials of the experimental CCR5 antagonist, vicriviroc, appear to have been dispelled. After 192 weeks of vicriviroc use, with a mean duration of 96 weeks' use in 205 treatment-experienced patients, toxicities were reported to appear "infrequently and sporadically", with no specific toxicities clearly related to vicriviroc use. In particular, incidence of cancers did not increase over time.[3]

Elvucitabine comparable to 3TC

After 48 weeks of treatment, a 10mg once-daily tablet dose of the experimental NRTI elvucitabine appears comparable to 3TC (lamivudine, Epivir) in terms of anti-HIV activity, CD4 cell response, side-effects and safety in people taking antiretrovirals for the first time.[4]

For further details visit www.aidsmap.com

news in brief

adherence

Modern treatments more forgiving of less than perfect adherence

It's long been thought that the minimum level of adherence needed for HIV treatment to have a good chance of success is 95%. However, this information was based on studies involving people who were taking combinations of HIV drugs including unboosted protease inhibitors that are no longer recommended.

Now a study from Spain suggests that adherence to currently approved treatments (that include either an NNRTI or a ritonavir-boosted protease inhibitor) need not be quite as rigid in order to achieve - and keep - an undetectable viral load.

Levels of adherence in the study were high, and only 83 of the 1059 people in the study experienced an increase in their viral load to detectable levels. These people took about 76% of doses of their HIV treatment. The investigators found an almost 50% risk of viral load becoming detectable for people who took between 70% to 80% of their doses. This increased to a greater than 75% risk for people who took fewer than 70% of their doses.

However, there was just a 9% risk of viral load increasing to detectable levels for people who took between 80 and 90% of their doses, compared to people who took at least 90% of their doses. Eighty to ninety per cent is the equivalent of missing no more than one dose in five of a once-daily combination. Ninety per cent adherence is the equivalent of missing one dose in ten – a substantial difference in the frequency of missed doses.

"Our data show that virologic success is possible with less than 95% adherence", wrote the investigators. However, since the investigators found that even with 90% adherence a minority of people experienced increases in their viral load (1% for those taking an unboosted protease inhibitor, 0.5% for those taking a boosted protease inhibitor and 1.4% for those taking an NNRTI) they concluded that the goal should still be to achieve "the highest rate of adherence possible".

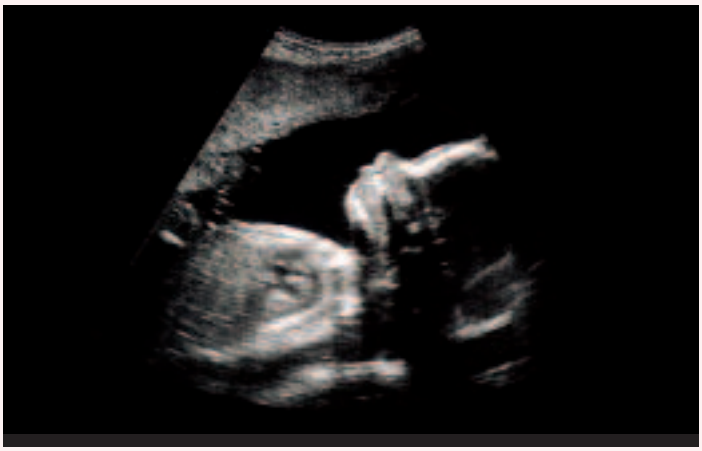
pregnancy

No increased cancer risk from antiretroviral exposure in womb

There has been a lot of research to see if using HIV treatment during pregnancy harms the developing baby. The results aren't consistent, and although some research has found that HIV treatment might increase the chances of having a premature baby with a low birth weight, other research has not. Although AZT exposure in the womb has, on rare occasions, led to biological abnormalities after birth (specifically, mild anaemia and other blood disorders), its impact on cancer is unknown.

Now researchers in France have found that the exposure babies have to HIV treatment in the womb or shortly after birth does not increase the risk of cancer. The results come from a very large study involving almost 10,000 babies whose mothers were HIV-positive and received various types of HIV treatment. Overall, the researchers found that the risk of cancer in these babies was no greater than that seen in the general French population.

There were, however, ten cancers, and five of these were cancers of the central nervous system. This was more than would be expected. Researchers found that using 3TC (lamivudine, *Epivir*) and ddI (didanosine, *Videx*) together seemed to increase the risk of this, but the numbers were so small they couldn't be sure. This combination of drugs is not routinely recommended, and the researchers emphasise how effective treatment to prevent mother-to-child transmission is. Importantly, during 20 years of use, neither AZT nor other antiretrovirals have been associated with cancer in adults or children who take them.



news in brief

anti-hiv drugs

More people in UK now eligible for darunavir

A decision by medicines regulators in Europe means that many more UK patients will now have the option of taking the ritonavir-boosted protease inhibitor, darunavir (*Prezista*). Originally approved only for use in highly pre-treated individuals who had taken more than one regimen containing a protease inhibitor, the twice-daily dose of 600mg (with 100mg ritonavir) is now approved for all treatment-experienced people.

Somewhat confusingly, regulators in the US recently approved once-daily darunavir (at a dose of 800mg with 100mg ritonavir) for people taking HIV treatment for the first time and, although this is not yet the case in the UK and Europe, the situation may change next year.

In addition, results of a small study suggest that once-daily darunavir may soon be an option for treatment-experienced individuals, although a larger study examining the safety and effectiveness of once-daily darunavir for the treatment experienced would be required before this is approved in either the US or Europe.

cancer

Cancer risk related to immune system strength

Researchers with the D:A:D cohort have uncovered another benefit of keeping the immune system strong in people with HIV: a lowered risk of dying from any type of cancer, including both AIDS-defining cancers (Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical cancer), and non-AIDS-related cancers (including lung, gastrointestinal, anal and liver cancer and cancers of the blood, such as leukaemia and lymphoma).

The study, originally intended to try and see if HIV treatment caused side-effects, notably lipodystrophy, involved over 23,000 people. With so much data (104,921 person-years of follow-up), researchers were also able to use the information they had gathered to see what effect HIV treatment has on the risk of cancer.

In total, 305 people died of cancer (112 died of an AIDS-defining cancer, while 193 died of a non-AIDS-defining cancer), but the investigators found that there was a very low risk of dying of any type of cancer if a person had a reasonably strong immune system (i.e. a CD4 count over 500 cellls/mm^3). Unsurprisingly, non-AIDS-defining cancer deaths due to lung and liver cancer were linked to smoking and active hepatitis B virus infection, respectively.

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A 'functional cure'?

Examining the excitement over a bone marrow transplant that 'eradicated' HIV, by Edwin J Bernard

Last month, the world's press reported that a 42-year-old American man living in Berlin had been 'cured' of his HIV infection following a bone marrow transplant two years earlier.

We last examined the elusive 'cure' for HIV almost three years ago, following media reports of so-called "miracle man" Andrew Stimpson and his premature claims that he was 'cured' of HIV in November 2005.[1]

Is this latest case just another example of media hype?

A tantalising possibility?

Between 1982 and 1996, reports of over 30 bone marrow transplants in HIV-positive individuals with advanced disease were published. In some cases, individuals required chemotherapy and radiation and subsequent bone marrow transplants for non-Hodgkin's lymphoma. In other cases, researchers actively enrolled individuals with AIDS at a time when there appeared to be no other options and replaced their bone marrow with those from healthy transplanted donors – in some cases these were not humans, but baboons – in order to attempt to repopulate the individual's immune system with healthy, HIV-free blood cells.

Although most died due to HIV – or transplant-related complications – soon after the procedures, two individuals were found to have undetectable HIV RNA and DNA levels in the weeks and months following the procedures. A review of these reports, written in 1997 and published in 1999, suggested that bone marrow transplantation offered the tantalising possibility of a 'cure' for HIV.[2]

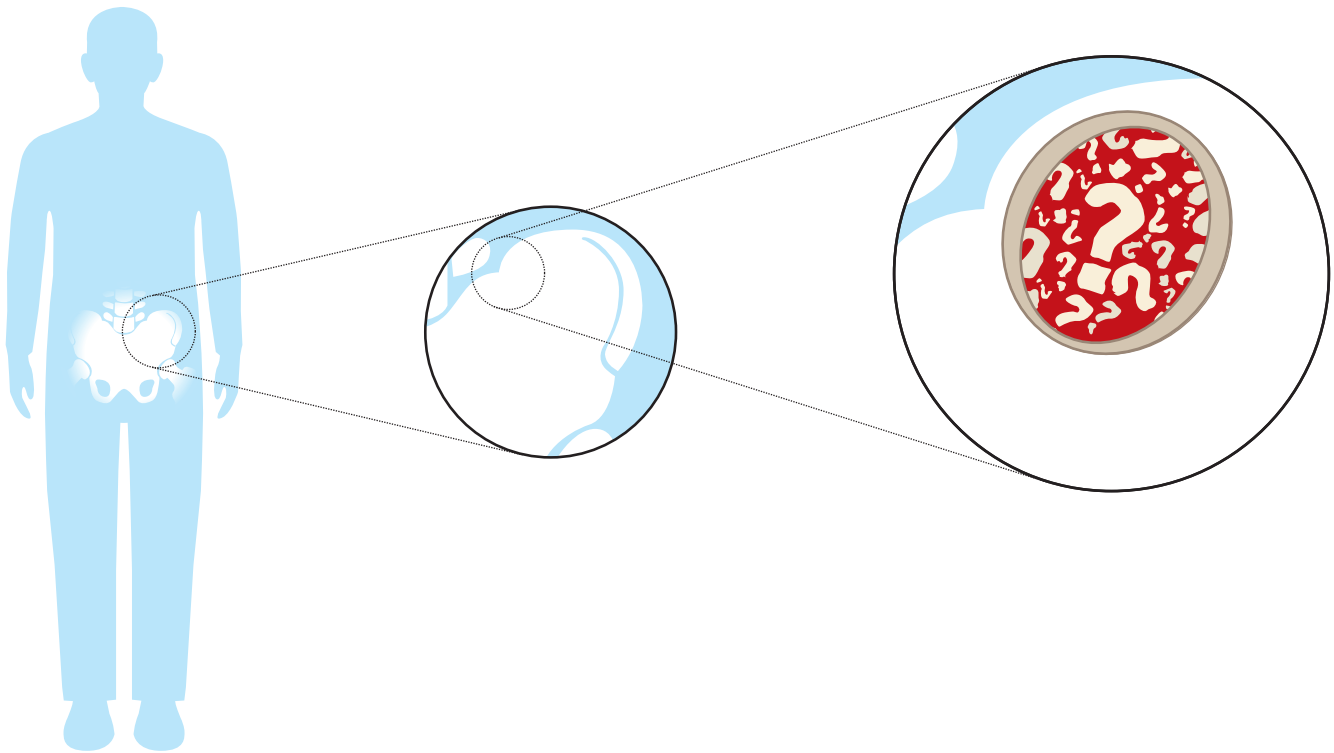
Then, last year, French researchers reported on the case of an HIV-positive individual who had required a bone marrow transplant to treat acute myeloid leukaemia. As well as experiencing severe graft-versus-host disease (when the immune cells from the donated marrow attack the body of the transplant patient), the man was found to still have detectable viral load following a post-transplant treatment interruption, and he died 191 days post-transplant. Doctors concluded that eradication of HIV from the body was unlikely utilising this method.[3]

A promising approach

Unlike the previously reported cases, the most recent case differs in two important ways:

- unusually, despite the high-risk nature of the procedure, the patient is still alive two years following the transplant
- a transplant donor was sought who specifically had two copies of the natural genetic mutation (also known as a polymorphism) delta32 CCR5.

People who have acquired two copies of this mutation (from both parents) are usually protected against infection with HIV, although there have now been at least eight case reports where infection occurred in people with two mutant CCR5 genes.[4]



The case was first reported in February 2008 as a poster presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. The poster described an HIV-positive individual who had achieved an undetectable viral load on antiretroviral therapy for several years before being diagnosed with acute myeloid leukaemia. After radiation treatment and chemotherapy failed to successfully treat the leukaemia, he underwent stem cell therapy by having a bone marrow transplant.

Out of a total of 232 potential donors with the same HLA type (genetic markers that identify cells as 'self' and prevent the immune system from attacking them), one donor was also found to have two copies of delta32 CCR5.

The man was asked to stop his antiretroviral therapy the day before his bone marrow transplant, since doctors were concerned it might have interfered with his recovery from the procedure. However, 68 days following the transplant, he was found to still have an undetectable viral load in his blood and bone marrow. Follow-up tests 285 days later also found no virus in rectal fluids, where the virus is often present.

The investigators were careful not to call this a 'cure' in their poster presentation, instead suggesting that "this finding... encourages further investigations of the development of CCR5-targeted treatment options." [5]

A 'functional cure'

In September this year, the Foundation for AIDS Research (amfAR) arranged a meeting between German haematologist, Dr Gero Hütter - who had found the donor and performed the stem cell transplant - and ten experts in clinical AIDS, stem cell transplantation and HIV virology. Further details of the case were reported in an article published on the amfAR website on 5 November.[6]

The man had suffered a relapse of his leukaemia following his initial transplant and had required a second transplant using the same donor. However, he continued to have no detectable signs of HIV in his blood, bone marrow and rectum, and further investigations found no HIV in his lymph nodes or brain.

"To the limits of our ability to detect HIV," wrote amfAR's senior scientific consultant, Dr Jeffrey Laurence, "it appears that the virus has been eradicated from his body. At the very least this patient represents a functional cure: he is off all anti-HIV meds, has a normal T-cell count, and exhibits no evidence of virus."[7] However, the amfAR experts have arranged to examine further specimens from the patient, since they believe the distinct possibility remains that HIV has not been totally eradicated from his body.

The story was then picked up in the Wall Street Journal[8] on 7 November, and press interest grew so great that Dr Hütter and his colleagues at the Charité Clinic for Haematology and Oncology in Berlin held a press conference on 12 November, resulting in global coverage of the case.

Limiting factors

There is no doubt that the case is remarkable, even if experts are not satisfied that HIV has been completely and permanently eradicated. However, it is unlikely to be repeatable due to several important limiting factors:

- The number of potential donors is limited, since fewer than 1% of individuals in parts of the Middle East, Europe and Asia (and none in Africa, Asia and South America) have two copies of delta32 CCR5.[9] In addition, there are more than 100 HLA types. Taken together, the pool of potentially matching donors is very shallow indeed.

- Bone marrow transplants are expensive (costing up to US$250,000 according to amfAR), and result in a 10 to 30% mortality rate. Even Dr Hütter admits that they are so dangerous that "they can't be justified ethically" in anything other than life-threatening situations like late-stage leukaemia.[10]

- The patient received immunosuppressive treatment for 2 years after the transplant. Some experts think this has played a role in the failure of HIV to return.

However, this case report may aid ongoing research into treatments, such as gene therapy, that seek to eradicate HIV - although cost and safety issues are likely to continue to be limiting factors for the foreseeable future.

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