ISSN 2046-9373

htb south

HIV treatment bulletin +south

htb south: volume 7 number 2

april–june 2014

CONTENTS

EDITORIAL 2

CONFERENCE REPORTS 3

21st Conference on Retroviruses and Opportunistic Infections (CROI)

- No HIV transmissions with undetectable viral load: interim PARTNER study results show need for longer follow-up
- PrEP injections every three months may protect against exposure from anal sex
- ARV pipeline: doravirine, GSK-744 and BMS-068
- Viral load rebound rate of 35% using ritonavir-boosted PI monotherapy: results of five-year PIVOT study
- Dual therapy less effective at high viral load: NEAT 001 study with raltegravir/darunavir/r
- Atazanavir, raltegravir and darunavir virologically equivalent in naive patients but significant differences for tolerability: results from ACTG 5257
- Pharmacokinetic targets for efavirenz might be too high
- Abacavir link to cardiovascular events in high-risk patients maintained in D:A:D study
- NNRTI resistance found in 12% of people stopping treatment with undetectable viral load: implications for stock-outs
- HIV related infections remain the leading cause of maternal deaths in South Africa despite the availability of ART
- Lower newborn bone mineral content with maternal tenofovir use
- Paediatric pipeline: CROI 2014 update on new antiretrovirals for children
- Efavirenz maintenance therapy effective in children exposed to nevirapine prophylaxis
- Xpert TB test has advantages but does not reduce morbidity
- Moxifloxacin and rifapentine: we need better trials
- Trials show further benefits for cotrimoxazole in children and adults
- Reports of a second baby possibly cured of HIV: uncertainty remains
- Updates on SB728-T, a CCR5-targeting gene therapy

TREATMENT ACCESS 24

- FDA approvals of generic ARVS
- Medicines Patent Pool adds dolutegravir

GUIDELINES 25

- UK guidelines for HIV-related cancers: 2014 edition published online
- Strong recommendations in WHO guidelines are often based on lower quality evidence than indicated in GRADE approach

PAEDIATRICS 26

- FDA approves raltegravir for children older than 4 weeks

EPIDEMIOLOGY 26

- Life expectancy in South Africa is increasing, but drug-resistant TB is a threat

BASIC SCIENCE AND CURE RESEARCH 28

- The prognostic value of interleukin-6 and D-dimer levels in primary HIV infection
- HIV reservoir: CD4 T stem cells may facilitate long-term persistence
- Update published on the first Berlin patient
- Poor CD4 T cell recovery despite HIV suppression linked to increased morbidity and mortality
- The relevance of the CD4/CD8 ratio in the ART era
- First human trial of AAV as a delivery vehicle for HIV neutralising antibodies gets underway

ON THE WEB 33

FUTURE MEETINGS 34

- Conference listing 2014/15

HIV i-BASE 34

DONATE 35

Published by HIV i-Base

htb south

HIV TREATMENT BULLETIN SOUTH

HTB South is a quarterly journal published by HIV i-Base.

http://www.i-Base.info

To order copies send an email to: subscriptions@i-Base.org.uk Editor: Polly Clayden

Contributing Editor: Simon Collins

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

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources. HIV South is supported by The Monument Trust. Nathan Geffen is renumerated from this grant.

HIV i-Base, 57 Great Suffolk Street, London SE1 0BB T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489

http://www.i-Base.info

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formerly known as DrFax.

EDITORIAL

This issue of HTB South includes first reports from the 21st Conference on Retroviruses and Opportunistic Infections (CROI) that was held in Boston from 3-6 March.

As usual, there is so much to report from this key meeting.

We lead with the interim analysis from the PARTNER study, starting to properly quantify the residual risk of transmission on ART plus the potential for future PrEP to come from slow-release injections, perhaps every three months.

ARV reports include three phase-2 studies on pipeline compounds from different classes: doravirine, GSK-744 and BMS-068. Results from three large ARV strategy trials also provide datasets on choice of initial and maintenance therapy: PIVOT, NEAT001 and ACTG 5257, plus a report on whether the target dose for efavirenz could be set lower.

Studies on PMTCT report on the high rate of maternal death during pregnancy in South Africa and a caution about low bone mineral density in infants exposed to tenofovir that are not infected.

Paediatric news covers an exciting pipeline of new formulations and the safety of switching to efavirenz for babies initially treated with lopinavir/r. Also from South Africa, a tempering of expectations from clinical practice from access to Xpert TB testing.

Cure research included the headline news about a second baby who may be cured and a detailed review on the current evidence supporting the gene therapy to modify CD4 cells.

We also include six basic science reviews including new results on the prognostic value of IL-6 and D-dimer, HIV persistence and cure research, management of immunologic non-responders and the value of the CD4:CD8 ratio - thanks to reports from Gareth Hardy and Richard Jefferys best-on-the-net blog.

The Southern African HIV Clinicians Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinicians Society has grown to a membership of over 15,000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinicians Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit:

http://www.sahivsoc.org

Tel: + 27 (011) 341 0162 Fax: +27 (011) 341 0161

CONFERENCE REPORTS

21st Conference on Retroviruses and Opportunistic Infections (CROI)

3 – 6 March 2014, Boston

Introduction

This year the Conference on Retroviruses and Opportunistic Infections - the leading HIV conference on basic and clinical science - was held in Boston from 3-6 March 2014.

While the meeting mostly looked and felt like CROI, the strains of the ongoing legal wrangle with the previous secretariat are taking time to work through - most notable for a scandolous and spiteful decision to inactivate the previous 20-year online conference archive.

It is exciting that the CROI committee are now partnering with IAS-USA to ensure the meeting is secure for the future, and dates for the 2015 meeting are already online.

This year though, the access to abstract and posters for people who were either unable to attend and for reference afterwards is patchy, which makes linking references in HTB reports more difficult.

Webcasts from the conference are now online - an essential aspect of CROI's historical lead as an educational resource - and CROI has also released an app via both Apple and Google that will allow presentations to be viewed on mobile devices after the conference ends.

Some posters are also available online as PDF files, but abstracts from the conference are not yet online as html pages and many can only be accessed by downloading a PDF file of the abstract book.

http://www.croi2014.org/electronic_materials

Abstract book (a sturdy 61MB PDF file)

http://croi2014.org/sites/default/files/uploads/CROI2014_Final_Abstracts.pdf (PDF)

The programme itself though was as packed as ever, and as usual we will spread out reports over (at least) two issues of HTB.

Reports in this issue of HTB are:

- No HIV transmissions with undetectable viral load: interim PARTNER study results show need for longer follow-up
- PrEP injections every three months may protect against exposure from anal sex
- ARV pipeline: doravirine, GSK-744 and BMS-068
- Viral load rebounds in 35% of people using PI/r monotherapy: results of five-year PIVOT study
- Dual therapy less effective at high viral load: NEAT 001 study with raltegravir/darunavir/r
- Atazanavir, raltegravir and darunavir virologically equivalent in naive patients but significant differences for tolerability: results from ACTG 5257
- Pharmacokinetic targets for efavirenz might be too high
- Abacavir link to cardiovascular events in high-risk patients maintained in D:A:D stud
- NNRTI resistance found in 12% of people stopping treatment with undetectable viral load: implications for stock-outs
- HIV related infections remain the leading cause of maternal deaths in South Africa despite the availability of ART
- Lower newborn bone mineral content with maternal tenofovir use
- Paediatric pipeline: CROI 2014 update on new antiretrovirals for children
- Efavirenz maintenance therapy effective in children exposed to nevirapine prophylaxis
- Xpert TB test has advantages but does not reduce morbidity
- Moxifloxacin and rifapentine: we need better trials
- Reports of a second baby possibly cured of HIV: uncertainty remains
- Updates on SB728-T, a CCR5-targeting gene therapy

CROI 2014: PREVENTION

No HIV transmissions with undetectable viral load: interim PARTNER study results show need for longer follow-up

Simon Collins, HIV i-Base

The PARTNER study is an international observational study that estimates the risk of HIV transmission within HIV serodifferent couples who do not use condoms, when the HIV positive person is on ART and has an undetectable viral load.

This is not a question of merely academic interest - it is central to defining the safety of programmes that already emphasise the impact of treatment as prevention. It is also essential for people making their own decisions about levels of risk.

Results presented at CROI 2014, by Alison Rodger from University College London, from a planned interim analysis, reported that no linked transmissions have so far occurred after almost 900 couple years of follow-up. These results come from 586 heterosexual and 308 gay male couples. [1]

An entry criterion for the study is to not routinely use condoms. Sexual behaviour questionnaires are included in order to have greater certainty over the range for the residual risk of transmission for different types of sex. Although HIV treatment dramatically reduces this risk, this knowledge is based on very limited data, largely from heterosexual studies, and often when condoms continued to be used.

By November 2013, PARTNER had enrolled 1,110 couples. Median time on ART was almost five years (IQR: 1.9-11.4) and couples reported having sex without condoms for a median two years (IQR:

0.5-6.3). Follow-up results included almost 44,500 times when sex was without condoms and over 21,000 times when this was from anal sex, (see Table 1). Couples had sex a median of 45 times a year without using condoms (IQR: 16-90).

For inclusion in this analysis, the positive partner needed to have a viral load <200 copies/mL. Although some HIV negative people became positive during the study, the phylogenetic analyses key to the results, showed these were not linked to their HIV positive partner. Sex with partners outside the partnership during follow-up period, also not using condoms, was reported by 34% of HIV negative gay men and 3% of heterosexual HIV negative partners.

Estimating risks is dependent not simply on the number of transmissions that may or may not occur, but in the statistical calculations for how confident the researchers are that the same results might not just occur by chance. This is the upper limit of the 95% confidence interval (95% CI), based on the standard assumption that a 5% possibility of the same results occurring by chance is acceptable.

Based on current analysis, the rate of within-couple HIV transmissions during eligible couple-years for the study as a whole was zero. However, the upper limits of the 95%CI were 0.40 per 100 couple years of follow-up (CYFU) for the study as a whole, 0.96/100 CYFU for anal sex (in gay and straight couples combined) and 1.97/100 CYFU for receptive anal sex with or without ejaculation (for gay couples).

The estimated transmission risk across the study per act, ranges from around 1 in 5,000 for an HIV negative man having vaginal sex to 1 in 2,000 for an HIV negative man having receptive anal sex.

A non-technical explanation of these risks, based on the PARTNER results so far, is that the risk of transmission occurring for one couple over ten years (based on having sex 45 times a year) could be as high as 4% for the average participant, and that the risk from anal sex could be as high as 9%. For receptive anal sex this reaches 32% risk over ten years. There is also a 2.5% chance that these risks could be higher.

If participants in the study had not been on ART, approximately 15 transmissions would have been expected in the straight couples and 86 transmissions in the gay couples, based on two meta-analyses of per act risk.

The data from PARTNER is already more substantial than the four other previous studies that have looked at this question. However, these upper estimates are dependent on the current number of years of follow-up and the study is only partly completed. If similar results continue, then the upper estimates will reduce further, but this is dependent on having this data.

In addition to the final results from the participants currently enrolled in PARTNER, an extension of the study called PARTNER 2 is looking to enroll an additional 450 gay male couples to achieve approximately 2000 patient years of follow up for anal sex. This will generate similar levels of confidence to the risk from vaginal sex.

The researchers have also produced online resources that help explain the implications of these results. [2, 3]

Simon Collins is a community representative on the Steering Committee of the PARTNER Study.

Table 1: Risk behaviour by the HIV negative partner and approximate estimated rates of HIV transmissions within couples

HIV status and sexual orientation of couples	Type of sex without a condom by HIV negative partner	Linked trans-missions (n)	Couple-years of follow up (CYFU)	Approx. no. of sex acts without condoms	Risk per contact (95% CI)*	Rate per 100 CYFU (95% CI)	10 year risk (95% CI)
Study overall	All types of sex (VL <200)	0	894	44,450	0 (0 - 0.00008)	0 (0-0.40)	0 (0 - 3.9%)
	All types of sex (VL < 50)	0	836	41,480	0 (0 – 0.00009)	0 (0-0.43)	0 (0 – 4.2%)
	Anal sex	0	374	21,030	0 (0 – 0.00017)	0 (0-0.96)	0 (0 – 9.2%)
Straight couples (man positive)	Sex	0	288	13,730	0 (0 – 0.00028)	0 (0-1.25)	0 (0 – 11.7%)
	Vaginal sex with ejaculation	0	191	8,910	0 (0 – 0.00043)	0 (0-1.88)	0 (0 – 17.1%)
	Vaginal sex without ejaculation	0	174	6,380	0 (0 – 0.00060)	0 (0-2.07)	0 (0 – 18.7%)
Straight couples (woman positive)	Sex	0	298	14,300	0 (0 – 0.00027)	0 (0-1.21)	0 (0 – 11.4%)
	Vaginal sex	0	272	14,150	0 (0 – 0.00027)	0 (0-1.32)	0 (0 – 12.4%)
Gay male couples	Anal sex	0	308	16,420	0 (0 – 0.00023)	0 (0-1.17)	0 (0 – 11.0%)
	Receptive anal sex (with or without ejaculation)	0	182	7,750	0 (0 – 0.00050)	0 (0-1.97)	0 (0- 17.9%)
	Insertive anal sex	0	262	11,750	0 (0 – 0.00033)	0 (0-1.37)	0 (0 – 12.8%)

COMMENT

It is important to be able to explain the concept of confidence intervals related to risk, even though this is not always easy in non-technical terms. Without substantive data from observed rates in prospective studies such as PARTNER, however, it is nearly impossible.

These results do not prove the safety of having sex without a condom when viral load is undetectable: they provide the most reliable evidence to date on the level of risk for people who have already been having sex without condoms, sometimes for many years. Other factors affecting risk, include genetic predisposition to HIV infection and STIs could both make risks higher on an individual rather than population-based level.

These results are nevertheless extremely positive. They support modelling data indicating that new infections, especially among gay men, are likely to be driven by people who are not yet diagnosed, and are often due to high viraemia in primary infection.

References

1. Rodger A et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 153LB.
   http://www.croiwebcasts.org/console/player/22072
2. Q&A fact sheet and resource on the interim results from the PARTNER Study.
   http://www.chip.dk/PARTNER/Press/tabid/487/Default.aspx
3. An online interview with the principal investigator of the PARTNER study is posted on the community IFARI youtube channel.
   http://www.youtube.com/user/AccessHIV

PrEP injections every three months may protect against exposure from anal sex

Simon Collins, HIV i-Base

A new study presented at CROI 2014 by Chastity Andrews from the Aaron Diamond AIDS Research Centre and colleagues looked at defining protective drugs levels of GSK-744 needed to protect from multiple rectal exposures. [1]

Data in macaques has already reported that the investigational integrase inhibitor GSK744 is at least as effective as tenofovir when used as PrEP, and that this includes protection similar to sexual transmission from anal sex.

The promising potential for next generation PrEP has also been shown by pharmacokinetic data showing that the long-acting injection formulation of GSK744 has a sufficiently long half-life for the potential for injections to provide protection for as long as three months.

A group of 12 macaques were given a single GSK744 IM injection and exposed to SHIV weekly until infection occurred. Treated animals were protected for up to 7-16 exposures compared to 1-7 exposures for the control group.

Estimates for protective drug levels were calculated relative to the plasma GSK744 protein-adjusted IC90 (PAIC90) value. No infections occurred from the 59 challenges when plasma levels were more than three-fold higher than the PAIC90 (100% protection). This compared with 1 of 22 challenges when plasma levels were between 1-3 fold higher than the PAIC90 (97% protection) and 11 of 43 challenges when plasma levels were lower that the PAIC90. In placebo animals, 12 of 26 challenges resulted in infection.

No integrase-associated mutations were seen in infected animals at the time of infection, though longer follow-up will be important to confirm durability of this finding, given the long plasma half-life of GSK-744.

Importantly, similar drug levels in humans are achieved from a single 800 mg IM injection of GSK-744, suggesting that three-monthly injections may be achievable for future use as PrEP.

Similar levels of protection against vaginal exposure were presented in a pigtail macaques study presented by J. Gerardo Garcia-Lerma from the US CDC, Atlanta. This study reported protection results in six animals given GSK-744 with six controls, using monthly injections also detailed in a second late-breaker poster. [2, 3]

References

1. Andrews CD et al. Correlating GSK1265744 plasma levels to prevention of rectal SHIV transmission in macaques. 21st CROI, 3-6 March 2014, Boston. Oral abstract 39.
   http://www.croiwebcasts.org/console/player/22066
2. Garcia-Lerma JG et al. Monthly GSK744 long-acting injections protect macaques against repeated vaginal SHIV exposures. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 40LB and poster 941LB.
   http://www.croiwebcasts.org/console/player/22067
3. Andrews CD et al. GSK1265744 long-acting protects macaques against repeated high-dose intravaginal challenges. Late breaker poster 941LB.

CROI 2014: ANTIRETROVIRALS

ARV pipeline: doravirine, GSK-744 and BMS-068

Simon Collins, HIV i-Base

HIV is still a fruitful market for new drug development and CROI 2014 included oral presentations of phase 2 data on three important pipeline compounds: doravirine, GSK-744 and BMS-068.

Doravirine (MK-1439)

Doravirine (MK-1439) is a once-daily NNRTI in development at Merck which in previous studies reported -1.3 log reductions in viral load after 7 days monotherapy. Doravirine retains activity (less than 3-fold resistance) to major NNRTI-associated mutations, including K103N, Y181C, G190A and E138K, indicating likely lack of cross-resistance to rilpivirine and etravirine.

Results from a randomised, double-blind, phase 2 dose-finding study in treatment naïve patients looked at 20, 50, 100 and 200 mg doses compared to a control group using efavirenz 600 mg. [1] All patients also used tenofovir/FTC. There were approximately 40 people in each arm, stratified by baseline viral load above or below 100,000 copies/mL.

Baseline characteristics included median age 37 years (range 19-69); 90% men; 74% white, 20% black, 17% Hispanic. Approximately half

the participants were from North America, 38% from Europe and 14% from Asia-Pacific. Median CD4 and viral load was approximately 380 cells/mm3 (range 83–1140) and 4.6 log copies/mL (range 2.8–6.1), respectively, with 30% having viral load >100,000 copies/mL. Distribution was roughly similar between arms, although a higher percentage of people with CD4 counts <200 cells/mm3 were in the 25 mg doravrine group (17% vs ~10% in other arms).

Results for the primary endpoint of viral suppression <40 copies/mL at week 24, were 80%, 76%, 71% and 78% vs 64% for the increasing doravirine doses vs efavirenz arms respectively. When using a cut-off of <200 copies/mL the results were: 85%, 85%, 92% and 90% vs 81%, respectively. CD4 increases were +137 for the combined doravirine groups vs +121 for the efavirenz arm.

Virological non-responders using the <40 copy cut off (n=1, 5, 6 and 5 vs 5) were undetectable using the <200 copy cut-off, all with reported >90% adherence. One person from the 25 mg doravirine arm had viral rebound although resistance results were not yet available. Response rates in patients with baseline viral load >100,000 copies/mL were 90%, 67%, 50% and 58% vs 54% using the <40 cut-off and 90%, 83%, 100% and 100% vs 92% using the <200 cut-off.

Neither viral efficacy nor tolerability results appeared to show a dose-related response. Few patients discontinued doravirine due to side effects than for efavirenz (approximately 2.5% vs 4.8%) and serious side effects were not considered drug-related (including, interestingly, suicidal ideation in a patient taking efavirenz). Most CNS-related side effects were more common with efavirenz.

Laboratory abnormalities were generally grade 1/2 with lipids and liver marker changes higher in the efavirenz group.

Participants in this study using doravirine have now been rolled over to the selected dose of 100 mg once-daily, for continued follow-up compared to efavirenz, out to 96 weeks.

GSK-774: dual maintenance therapy with rilpivirine

Although the headline news for GSK-744 (the follow-on integrase inhibitor to ViiV's dolutegravir) were grabbed for data on the slow-release formulation for use as PrEP, [2, 3] results using daily oral dosing of 744 were presented from a phase 2 dose-finding study in treatment naïve patients. [4]

The half-life of GSK-744 is approximately 40 hours for the oral formulation and 40 days for the long-acting injection. In earlier studies, oral dosing of 5 mg and 30 mg GSK-744 produced a -2.0 log drop in viral load after 10 days monotherapy.

The current study compared 10 mg, 30 mg and 60 mg doses of oral GSK-744 compared to 600 mg efavirenz control (approximately 60 patients in each arm), all with investigator selected 2RTIs, with a roll over at week 24 to oral dual therapy using GSK-744 plus 25 mg rilpivirine.

This was generally a group in early infection. Baseline demographics included median age 32 (no range given); >95% men; race: 65% white, 30% African-American, 15% Hispanic [stet - totals >110%]. Median CD4 count was approximately 400 cells/mm3 (<5% <200 cells/mm3) with mean viral load of 4.2 - 4.4 log copies/mL (approximately 12% >100,000 copes/mL. No data on the range or variance for the baseline data were included in the presentation, limiting the ability to interpret the results. Choice of NRTIs was roughly 60% tenofovir/FTC vs 40% abacavir/3TC.

Results at week 24 were previously presented at the EACS conference in October 2013 with viral suppression <50 copies/mL in 88% vs 74% with efavirenz, and a selection of the 30 mg dose for weeks 24-48. [5]

At week 48, after 24-weeks dual maintenance treatment, viral suppression <50 copies/mL (ITT snapshot) was 93% for 744/rilpivirine vs 94% with efavirenz + 2NRTIs, with similar responses across arms and only a single discontinuation due to virologic failure (in the efavirenz arm). However, two patients had protocol defined virological failure in the dual therapy arm. One patient in the 10 mg arm was suppressed <40 copies/mL at week 40 but had resistance to both drugs with Q148R and E138Q at week 48. This person had suboptimal plasma levels of GSK-744 from week 2-36 and to rilpivirine from week 26-26. This was possibly related to a calorie-restricted diet (650 calories/day from week 40-48). No drug resistant mutations were found in the second person who had been randomised to the 30 mg arm.

The lower response rates in the efavirenz control group were largely due to higher CNS-related side effects, responsible for 13% discontinuation (compared to 2%, 2% and 7% with GSK-744). However, headache was more commonly reported with GSK-744 (22% vs 11% with efavirenz), although these were predominantly grade 1/2, with no discontinuations.

Responses by choice of NRTI were slightly higher with tenofovir/FTC vs abavacir/3TC (84% vs 79% in the GSK-744 and 72% vs 70% in the efavirenz groups).

Future clinical studies will use dual long-acting formulations of GSK-744 and rilpivirine as injection-based ART, although an induction period using oral dosing is still likely due to safety concerns in the event of a hypersensitivity reaction.

BMS-663068: attachment inhibitor

BMS-068 (a prodrug of BMS-626529) is an attachment inhibitor that binds to gp-120 blocking conformational changes that allow CD4 attachment, making it active irrespective of viral tropism (although notably not to sub-type AE or Group O). After 8 days monotherapy, BMS-068 reduced viral load by -1.6 logs in both treatment-naïve and -experienced patients.

The current study included randomised patients to one of four twice (BD) or once (QD) daily doses of BMS-068: 400 mg BD, 800 mg BD, 600 QD and 1200 QD) and an atazanavir/r QD control group. There were 50 people in each arm (including 10 patients in each arm using 7 days monotherapy) and background therapy was with raltegravir plus tenofovir for all patients. Sensitivity to BMS-529 was an entry criteria (requiring IC50 < 100 nM and ~ 5% screening failures were due to higher IC50s). This was an international study with sites in the USA, Mexico, Peru and Germany. [6]

Approximate baseline characteristics included median age 39 years, 60% men and 40% women, 65% sub-type B and 15% sub-type C, with race categorised as ~ 60% non-white. Mean CD4 and viral load was ~ 250 cells/mm3 (with ~ 40% < 200) and 4.7 log copies/mL (with ~ 40% >100,000). Approximately 30% patients had one of more resistant mutation to one or more classes (but sensitivity to all study drugs was an entry criteria).

Although discontinuations ranged from 11–22%, these were largely due to withdrawal of consent, loss to follow-up, pregnancy or poor adherence, with very few dues to either lack of efficacy or side effects.

Viral response rates from 8 days of monotherapy were dose-related, ranging from -0.69 log (400 mg BD) to -1.47 log (1200 mg QD). Unlike other ART classes, a transient small increase in viral load occurred during the first two days of treatment prior to the viral load drop.

At week 24, viral load suppression to <50 copies/mL (ITT analysis) was achieved by 80%, 69%, 76% and 72% across the BMS-068 arms compared to 74% in the atazanavir/r control. When stratified by baseline viral load, all groups except the 1200 mg QD group had at least 15-20% lower response rates at above compared to below 100,000 copies/mL. No pattern in response was seen by sensitivity to BMS-068 by IC50 levels (+/-0.1 vs +/-1.0 vs +/-10 nM). CD4 increases were similar across all arms.

In the BMS-068 arms, none of the 15 serious adverse events (in 123 people) were attributed to the study drugs (with four discontinuations due to 1 non-specific EKG changes, 2 TB cases and 1 tenofovir-associated acute renal failure).

All participants on BMS-068 have now been rolled over to the 1200 mg QD dose for continued follow up.

References

Unless indicated otherwise, all references are to the Programme and Abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2014, Boston. CROI 2014 links are to webcasts.

1. Morales-Ramirez JO et al. Safety and antiviral effect of MK-1439, a novel NNRTI (+FTC/TDF) in ART-naive HIV-infected patients. 21st CROI, 3-6 March 2014, Boston. Oral late-breaker abstract 92LB.
   http://www.croiwebcasts.org/console/player/22172
2. Andrews C et al. Correlating GSK1265744 plasma levels to prevention of rectal SHIV transmission in macaques. 21st CROI, 3-6 March 2014, Boston. Oral abstract 39.
   http://www.croiwebcasts.org/console/player/22066
3. Garcia Lerma JG et al. Monthly GSK744 long-acting injections protect macaques against repeated vaginal SHIV exposures. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 40LB.
   http://www.croiwebcasts.org/console/player/22067
4. Margolis D et al. 744 and rilpivirine as two-drug oral maintenance therapy: LAI116482 (LATTE) week 48 results. 21st CROI, 3-6 March 2014, Boston. Oral late-breaker abstract 91LB.
   http://www.croiwebcasts.org/console/player/22171
5. Margolis D et al. Once-daily oral GSK1265744 (GSK744) as part of combination therapy in antiretroviral naïve adults: 24-week safety and efficacy results from the LATTE study (LAI116482). 14th EACS, 2013, Brussels. Oral abstract PS7.1.
   http://www.eacsmobile.org/libraryEntry/show/38282193537098395
6. Lalezari J et al. Attachment inhibitor prodrug BMS-663068 in ARV-experienced subjects: week 24 analysis. 21st CROI, 3-6 March 2014, Boston. Oral abstract 86.
   http://www.croiwebcasts.org/console/player/22166

Viral load rebound rate of 35% using ritonavir-boosted PI monotherapy: results of five-year PIVOT study

Simon Collins, HIV i-Base

A long-term strategy study sponsored by the Medical Research Council (MRC) in the UK reported low rates of serious complications and the potential to reduce drug costs. However, more than a third of people on the ritonavir-boosted PI monotherapy group had viral load rebound compared to only 3% of people on standard combination therapy.

The PIVOT study randomised 587 UK patients who already had an undetectable viral load on stable treatment to either PI/r monotherapy or triple therapy. It included four years of follow up (median 44 months, maximum 59 months) and the primary endpoints was loss of future treatment options based on development of drug resistance. Participants in the monotherapy arm were restarted on triple therapy if they had three viral load results >50 copies/mL (including a retested sample), or due to side effects or patient choice. Approximately 80% of people in the boosted PI monotherapy arm used darunavir/r, with 14% using lopinavir/r and 7% using another PI.

Baseline characteristics included median age 44 years (IQR 38-49), 23% women, 60% gay men; 68% white, 28% black, 4% other. Baseline CD4 count and CD4 nadir were 513 cells/mm3 (IQR 392 – 682) and 178 cells/mm3 (IQR 86 – 250), respectively. Median time on ART was 4.0 years (IQR 2.2 – 6.7), having used a median of 4 individual drugs (IQR 3 – 6). Approximately half of participants were using PI-based and half using NNRTI-based treatment at enrolment.

Although loss of treatment options was low in both arms, more people lost treatment options on the PI/r vs the triple therapy arm. These results were 6 (2.1%) vs 2 (0.7%) people [difference 1.4% (95%CI -0.4 to 3.4%), p = 0.15] after 36 months and 6 (2.1%) vs 4 (1.8%) people [difference -0.2% (95%CI -2.5 to 2.46%), p = 0.85] at the end of the trial.

However, viral load rebounded much more frequently in the monotherapy group (35% vs 3.2%; difference 31.8% [95%CI 24.5% to 39.0%], p < 0.001). Patients with viral rebound all became undetectable again, either spontaneously or after the addition of two NRTIs.

There were no significant differences between arms by CD4 response (p=0.21), numbers of serious complications (p=0.15) or change in neurocognitive function (change in mean NPZ-score, p=0.86). However, there were less grade 3/4 serious events in the monotherapy group [n=137 vs 159 (46% vs 55%; difference, -8.4%; 95%CI -16.4% to 0.3%), p=0.043].

Although the poster included no details on the higher numbers of deaths in the monotherapy arm (n=6 vs 1), these were apparently largely related to cancers and not attributed to treatment strategy.

Finally, although the results reported overall mean (SE) drug costs of £21,260 (700) vs £30, 230 (860), with the PI/r monotherapy treatment saving £8,970 (-6,790 to -11,160) per person over five years, this did not take account of additional monitoring and costs associated with changing treatment in those patients with viral rebound.

COMMENT

The very high rates of viral rebound in people using PI/r monotherapy makes it unlikely that this study will change prescribing guidelines. Given the volume of data generated from the extensive follow-up it is also frustrating that so little information was included in the poster.

It is unclear why there was no analysis for whether virological failure was related to prior treatment history, choice of boosted PI, adherence (including not taking meds with food), or other factors and it is unclear why details of deaths in the study were not included.

Cost differences based on drug costs alone, rather that as part of a more detailed analysis of total management costs are unhelpful.

A more comprehensive presentation of the results will be presented as an oral session at the upcoming BHIVA conference in Liverpool.

References

Paton N et al. Randomised controlled trial of a PI monotherapy switch strategy for long-term HIV management. 21st CROI, 2014, Boston. Late breaker poster abstract 550LB.

Dual therapy less effective at high viral load: NEAT 001 study with raltegravir/ darunavir/r

Simon Collins, HIV i-Base

An experimental dual therapy combination of an integrase inhibitor plus a boosted-PI was non-inferior at week 96 compared to PI-based triple therapy, but was less effective in patients starting with a high viral load.

Francois Raffi, from University Hospital, Nantes, presented results from a European independent investigator collaboration comparing twice-daily raltegravir (n=401) to once-daily tenofovir/FTC (n=404) in combination with once-daily darunavir/ritonavir (800 mg/100 mg) in treatment-naive patients.

This was the NEAT001 study (ANRS143 in France), and the first from a EU network of independent investigators, with 78 sites in 15 countries. NEAT001 is a randomised, phase 3, open-label, 96 week study with a composite primary endpoint of time to virological or clinical failure. It is a non-inferiority study with an absolute difference of 9% defined for failure of raltegravir by ITT analysis. Entry criteria included CD4 count <500 cells/mm3, hepatitis B negative and having no major drug resistance mutations.

Virological failure was defined as <1 log reduction by week 18 or viral load >400 copies/mL at week 24, or if viral load was >50 copies/mL at or after week 32. Clinical endpoints included any new or recurrent serious event.

Participants were largely male (88%) and white (82%) with median age 37 years. At baseline, median viral load was 4.8 (IQR 4.2, 5.1) log copies/mL with 36% vs 32% having >100.000 in the raltegravir vs tenofovir/FTC arms respectively (and 6% vs 5% with >500,000). Median CD4 count was 340 (IQR 260, 394) vs 325 (IQR 248, 401) respectively with approximately 15% having a count <200 cells/mm3.

There were more discontinuations prior to week 96 in the raltegravir arm (n=38 vs 22), mainly driven by greater loss to follow-up (n=24 vs 15), although there were also more deaths (n=4 vs 0) compared to the tenofovir/FTC arm. Although numerically the raltegravir arm had a greater probability of reaching the primary endpoint at week 96, with 17.4% vs 13.7% having treatment failure, this supported a non-inferiority result with an adjusted between-arm difference of 3.7% (95% CI: -1.1 to 8.6%), p=0.12).

This difference was driven by more patients having viral load >50 copies/mL after week 32 (n=32 vs 22). At week 96, 89% vs 93% patients had viral load <50 copies/mL in the raltegravir and darunavir/r arms respectively. Serious AIDS-related events occurred in 5 vs 3 people and serious non-AIDS event occurred in 7 people in each arm.

In a planned stratified analysis, raltegravir was inferior in more advanced patients. Primary endpoint results at week 96 when baseline CD4 count was <200 cells/mm3 were 39.0% vs 21.3%, p=0.02 with a trend to non-inferiority when baseline viral load was >100,000 copies/mL (36% vs 27%; p=0.09).

No resistance was detected in 13/15 patients with virological failure and genotypic results in the tenofovir/FTC arm compared to five major mutations in 28/36 patient with results with raltegravir. This included one case of K65R and five patients with N155H. In questions after the presentation, 4/5 of these patients were said to have had baseline viral load "considerably higher than 500,000 copies/mL".

The differences in serious side effects were numerically higher in the raltegravir arm, but differences were not statistically significant. There were 89 vs 75 events (in 73 vs 61 patients; incidence rate 10.2 vs 8.3/100 PY, p=0.17).

The four deaths in the raltegravir arm were from Burkitt's lymphoma, DRESS syndrome, melanoma and suicide, with the single death in the tenofovir/FTC arm from morphine overdose. Life threatening events occurred in 8 vs 4 patients (CK increase (n = 5), hepatitis, Hodgkin lymphoma, pancreatitis vs CK increase (n = 2), myocardial infarction and gGT increase).

Changes in fasting lipids were more significant in the raltegravir group (TC p<0.001, LDL-c p=0.02, HDL-c p<0.001 and TG p=0.49) but there were no significant different in TC:HDL-c ratio (p=0.7). Grade 3/4 creatinine kinase elevation occurred in 6.2% vs 5.0% and grade 3/4 ALT increase in 3.0 vs 1.0% of the raltegravir vs tenofovir/FTC arms respectively.

Creatinine clearance measured by eGFR at week 96 increased by 0.9 in the raltegravir group compared to dropping by -3.8 in the tenofovir/FTC arm (p=0.02) with the drop occurring in the first four weeks of treatment.

Reference

Raffi F et al. First-line raltegravir (RAL) + darunavir/ritonavir (DRV/r) is non-inferior to tenofovir/emtricitabine (TDF/FTC) + DRV/r: the NEAT 001/ANRS 143 randomised trial. 21st CROI, 3–6 March 2014, Boston. Late breaker oral abstract 84 LB.
http://www.croiwebcasts.org/console/player/22164

Atazanavir, raltegravir and darunavir virologically equivalent in naive patients but significant differences for tolerability: results from ACTG 5257

Simon Collins, HIV i-Base

Primary results from the ACTG 5257 study shifted the assumed relative parity between three of the preferred first-line combinations in US DHHS guidelines. Raphael Landovitz from University of California Los Angeles, presented results at CROI 2014 from this large randomised open label study with over 1800 treatment naive participants. [1]

The study was designed based on a hypothesis of equivalence for the three groups, with 90% power to define any pair-wise comparison.

Equivalence was defined based on cumulative incidence of events at 96 weeks if the 97.5% CI for results fell within +/–10% margin. Superiority required the upper limit of the 97.5% CI to be greater than 10% and the lower limit greater than zero. All three study groups used tenofovir/FTC as background. Atazanavir/r (300 mg/100 mg) and darunavir/r (800 mg/100 mg) were dosed once-daily and raltegravir (400 mg) was twice-daily.

Overall, the study performed better than the study projections, with lower rates of virological (25% vs 16%) and tolerability (10% vs ~7%) failure and less loss-to-follow-up (12% vs 5%), in the projected vs actual rates, respectively. While all arms performed well, significant differences were seen for some comparisons in the primary endpoint of time to virological failure or cumulative time to discontinuation due to toxicity.

Baseline characteristics were well balanced between arms. Mean age was 37 years and 24% of participants were women. Ethnicity was 42% black, 36% white, and 22% Hispanic. Median CD4 and viral load were 308 cells/mm3 (IQR 170-425, with 30% <200) and 4.6 log copes/mL (IQR 4.1-5.1, with 30% >100,000, including 7% >500,000), respectively.

Approximately 8% of patients were lost to follow up over two years, with 92% of patients in the 96 week analysis.

Viral suppression to <50 copies/mL was achieved by 88%, 94% and 89% (ITT analysis, tolerability change allowed) and 63%, 80% and 73% (ITT analysis, off-ART = failure) of the atazanavir/r, raltegravir and darunavir/r arms respectively.

In pairwise comparisons, equivalence was demonstrated for the three regimens: atazanavir/r vs raltegravir (difference 3.4%; 97.5% CI: –0.7%, 7.4%); atazanavir/r vs darunavir/r (diference –2.2%; 97.5% CI: –6.7%, 2.3%), and darunavir/r vs raltegravir (difference 5.6%; 97.5% CI: 1.3%, 9.9%).

In the analysis of cumulative incidence of tolerability failure, darunavir/r and raltegravir were non-inferior (difference 3.6%; 97.5% CI: 1.4%, 5.8%). However, atazanavir/r was inferior to both darunavir/r (difference 9.2%; 97.5% CI 5.5%, 13%) and raltegravir (difference 13%; 97.5% CI: 9.4%, 16%).

This was driven by side effects that are already well-described with 16% vs 1% vs 5% in the atazanavir/r, raltegravir and darunavir/r arms respectively stopping treatment for this reason (n = 25 vs 2 vs 14 for gastrointestinal; 47 vs 0 vs 0 for increased bilirubin/jaundice and 4 vs 0 vs 0 for kidney stones). Of the 47 cases of jaundice/bilirubin, 8 were early switches and 30 were already virologically suppressed to <50 copies/mL.

Approximately 75-80% of patients with virological failure had results from genotype testing, with primary mutations (mainly M184V and other NRTIs) detected in 2.8%, 3.3% and 2.0% of the atazanavir/r, raltegravir and darunavir/r arms, respectively. However, 11/18 patients with detected resistance in the raltegravir group, had integrase mutations, with or without additional NRTIs.

Results were also presented for two tolerability substudies. Both PI/r arms had significantly higher increases in LDL-cholesterol and trgilycerides (p<0.001), unlinked to ritonavir exposure.

Approximate CD4 increases were similar between arms (+284 (IQR 270, 300), though slightly, non-statistically, lower with darunavir/r (+256, IQR 240, 271).

C O M M E N T

This was a very large study and this may mean that some of the statistically significant findings might be less important clinically. The dataset is also likely to lead to numerous future analyses, relating to cardiovascular, metabolic, skeletal, lipids, biomarkers, behavior, adherence and key subgroup differences.

While the incidence of atazanavir-related side-effects occurred at a similar rate to that reported in phase 3 studies the other discontinuations occurred at a lower rate than the study expected.

References

Unless stated otherwise, references are to the Programme and Abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2014, Boston.

1. Landovitz RJ et al. Efficacy and tolerability of atazanavir, raltegravir, or darunavir with FTC/tenofovir: ACTG 5257. 21st CROI, 3-6 March 2014, Boston. Oral abstract 85.
   http://www.croiwebcasts.org/console/player/22165
2. Ofotokun I et al. Darunavir or atazanavir vs raltegravir lipid changes are unlinked to ritonavir exposure: ACTG 5257. 21st CROI, 3-6 March 2014, Boston. Poster abstract 746.
3. Brown T et al. Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir. 21st CROI, 3-6 March 2014, Boston. Late breaker 779 LB.

Pharmacokinetic targets for efavirenz might be too high

Polly Clayden, HIV i-Base

Results from a substudy of ENCORE1 – looking at 400 vs 600 mg efavirenz daily – challenge the current pharmacokinetic (PK) targets for treatment success of this drug. [1]

ENCORE1 is an ongoing trial in treatment-naïve adults randomised to receive either reduced (400 mg), or standard (600 mg) dose efavirenz, both with TDF/FTC. At 48 weeks 400 mg efavirenz was virologically non-inferior to 600 mg. Viral suppression was high with 90% vs 86% <50 copies/mL in the 400 mg vs 800 mg arms, respectively. [2]

A poster presented at CROI 2014 – authored by Laura Dickinson and Rebekah Puls from University of Liverpool and University of New South Wales, on behalf of the substudy group – showed findings from an intensive PK analysis comparing efavirenz plasma exposures between the two doses in a subset of trial participants.

Sampling was undertaken at steady state between 4 to 8 weeks of treatment: pre-dose, 2, 4, 8, 12, 16 and 24 hours post dose. Efavirenz plasma concentrations were determined by LC-MS/MS with lower and upper limits of quantification of 0.025 and 10 mg/L.

The investigators also performed genotyping for CYP2B6 516G>T and 983T>C in order to evaluate the influence of host genetics on efavirenz exposure.

Forty-six participants (28 and18 from the 400 and 600 mg groups respectively) were enrolled at four study sites in South Africa, Thailand, UK and Argentina. Fifteen participants were women and 37% African, 22% Asian and 41% white. Mean age, weight and baseline CD4 were: 36 years, 71 kg, and 289 cells/mm3 respectively.

The results of the PK evaluation are summarised in Table 1.

Table 1: Efavirenz PK parameters ENCORE 1 (n=46)

Parameter GM (90% CI)	400 mg	600 mg	GMR (90% CI)	p
AUC0-24 (mg.h/L)	38.0 (34.4-54.0)	54.2 (47.8-75.8)	0.70 (0.54-0.91)	0.007
CL/F (L/h)	10.5 (10.2-13.2)	11.1 (9.96-15.0)	0.95 (0.73-1.23)	0.857
Cmax (mg/L)	2.65 (2.46-3.36)	4.09 (3.72-5.23)	0.65 (0.52-0.81)	0.002
C12 (mg/L)	1.50 (1.36-2.25)	2.05 (1.81-2.92)	0.73 (0.55-0.97)	0.029
C24 (mg/L)	1.12 (1.01-1.72)	1.52 (1.33-2.47)	0.73 (0.54-1.01)	0.065

The evaluation revealed AUC0-24, Cmax and C12 were significantly lower for 400 mg efavirenz compared to 600 mg. C12 and C24 were below the previously calculated minimum effective concentration (MEC) of 1.0 mg/L in 25 (46%) and 6 (28%) of participants receiving 400 and 600 mg efavirenz respectively.

Genotype data were available for 44/46 participants: 52%, 35% and 9% were CYP2B6 516 GG, GT and TT respectively and 93%, 2% and 0% were CYP2B6 TT, TC and CC respectively.

Multivariate analysis found CYP2B6 516 G>T, dose and participants weight were independently associated with AUC0-24; and CYP2B6 516 G>T and dose with C24 (both p=0.0001).

Overall 78% of participants had viral load <50 copies/mL at 48 weeks (missing data classified as detectable).

The investigators noted that because the sample size was small, a formal PK-pharmacodynamic (PD) evaluation was not possible. At 48 weeks 5/28 (18%) participants had detectable viral loads in the 400 mg group of which two were <1.0 mg/L for C12 and C24. In the 600 mg group 5/18 (28%) had detectable viral loads and one was below the MEC at C24.

The investigators concluded that participants in the substudy receiving 400 mg efavirenz had comparable viral suppression to 600 mg – as in the main ENCORE1 study – despite significantly lower exposure and higher proportions of C12 and C24 below the suggested MEC.

"These data challenge the currently defined PK targets for therapeutic success", they wrote.

COMMENT

PK-PD modelling of the data from ENCORE1 is currently ongoing to help better understand predictors of efavirenz PK and response in a heterogeneous population.

Since the announcement of the trial results last year, there has been a great deal of discussion about recommending the reduced dose of efavirenz, particularly in low-income countries where the resulting cost savings would be considerable. Questions about whether or not 400 mg will be robust enough in the third trimester of pregnancy and in the presence of concomitant treatment for TB have delayed recommendations from WHO and national guidelines.

A forthcoming research letter to AIDS from Hill et al cites five studies that include 235 women treated with 600 mg efavirenz in pregnancy in which drug concentrations were not significantly affected and there were high rates of viral load suppression in the mothers at the time of delivery. [3] The authors conclude that the results suggest that pregnancy has slight if any clinically important effects on efavirenz PK.

For rifampicin, there have been a number of short-term PK studies with 600 mg efavirenz showing reduction in efavirenz plasma concentrations. It is unclear how useful these results are when efavirenz has not reached steady state. Longer-term studies in HIV positive people have shown increased Cmin or no effect. [4] In order to determine whether the PK interaction between rifampicin and EFV is different using the 400mg dose (there may be different induction effects) a new PK study is probably needed.

It seems that to recommend 400 mg efavirenz widely PK studies with rifampicin and in pregnant women will have to be conducted. One question will be, what target to aim for treatment success?

It is also important to remember that in the early DMP-266 005 trial of efavirenz there was no difference in viral suppression between people receiving 200, 400 and 600 mg at 16 weeks. [5]

In the UK, there is talk of exploring the 200 mg dose.

References

1. Dickinson L et al. Efavirenz (EFV) 400 Versus 600 mg daily: results of the ENCORE1 intensive PK substudy 21st CROI. 3-6 March 2014. Boston. Poster abstract 510.
http://croiconference.org/sites/all/abstracts/510.pdf (PDF)
2. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. The Lancet. Early online publication. 10 February 2014.
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62187-X/abstract?rss%3Dyes
3. Hill A et al. Does pregnancy affect the pharmacokinetics of efavirenz? AIDS. Forthcoming 2014.
4. Hill A. Presentation to WHO adult ARV group. March 2014/personal communication.
5. Haas D et al. A phase II, double-blind, placebo-controlled, dose-ranging study to assess the antiretroviral activity and safety of efavirenz (DMP-266) in combination with open-label zidovudine (ZDV) with lamivudine (3TC) at 24 weeks (DMP 266–005). 5th CROI. February 1998. Chicago. Poster abstract 698.

CROI 2014: SIDE EFFECTS

Abacavir link to cardiovascular events in high-risk patients maintained in D:A:D study

Simon Collins, HIV i-Base

A poster at CROI 2014, presented by Caroline Sabin from University College London and colleagues, presented follow-up results from D:A:D since the initial findings in 2008 of a link between abacavir use and risk of myocardial infarction (MI) in people with high cardiovascular risk. [1]

Given the high profile given to the initial results, abacavir should have been less likely to be prescribed in high CVD risk patients, with any confounding bias now working against seeing a continued association.

UK guidelines no longer recommend using abacavir in HIV positive people who have a high risk of cardiovascular disease (CVD), defined as >20% 10-year Framingham score. [2] This is based on results from cohort studies that have reported an association, the largest of these being the prospective D:A:D study that was designed to look at ARVs and CVD and that first reported this associated at CROI in 2008. [3]

In this study, logistic regression models were used to compare CVD and abacavir use before and after March 2008.

When stratifying abacavir use, people at moderate or high CVD risk were more likely to use abacavir before March 2008 (aOR 1.14; 95%CI: 0.90, 1.44) and less likely to use it afterwards (aOR 0.74; 95%CI: 0.48, 1.13), p=0.007 for interaction. After March 2008, people at moderate/high CVD risk on abacavir were more likely to discontinue abacavir than those at low/unknown CVD risk (relative rate (RR) 1.49 [95% CI 1.34-1.65]).

In the new analysis, the rate of MI with current use of abacavir was 0.47 (95%CI: 0.42-0.52) compared to 0.21 (95%CI: 0.19-0.22) without, with abacavir associated with a 98% increase in MI (RR 1.98; 95%CI: 1.72-2.29). There was no difference in the early and late periods and results were unchanged after adjusting for other CVD-related factors.

COMMENT

It is notable that the D:A:D group took five years after the initial findings to accumulate sufficient new data to reassess this association.

Reference

Sabin C et al. Is there continued evidence for an association between abacavir and myocardial infarction risk? 21st CROI, 3-6 March 2014, Boston. Poster abstract 747 LB.

CROI 2014: RESISTANCE

NNRTI resistance found in 12% of people stopping treatment with undetectable viral load: implications for stock-outs

Simon Collins, HIV i-Base

Although stopping ART is not recommended, this still occurs due to drug stock-outs in some countries and retrospective data from the UK HIV Drug Resistance Database (HDRD) highlighted the risk this has for developing drug resistance.

Valentina Cambiano from University College London and colleagues analysed drug resistance mutations in rebound viraemia in people who interrupted NNRTI-based treatment when their viral load was consistently undetectable <200 copies/mL for at least six months and who had no prior evidence of NNRTI resistance.

Of 208 eligible patients with a resistance test after stopping treatment, 39% were on efavirenz and 61% on nevirapine. Background therapy was most commonly with 3TC (85%) and/or AZT (63%) and treatment was stopped after a median of 12 months on ART (IQR: 5-32 months).

At the first resistance test after stopping treatment, 25/208 patients (12%, 95% CI: 8-17) had one or more major NNRTI mutations, with no indication of a reduced rate in the 20/208 people who staggered the interruption, though small numbers meant that there were wide confidence intervals around these estimates. In these patients, the resistance test was taken after a median of 12 months (IQR: 3-20).

The most common mutations were K103N (64%) and G190A (12%), with K101E, V108I, Y181C, L100I, V106A, Y188L and P225H found in 8% (n=2) or less. In multivariate analysis, the only independent predictor of NNRTI resistant mutations was a lower CD4 count nadir (RR per 100 cells higher = 0.67; 95% CI: 0.53-0.85; p=0.001).

The authors concluded that in this largest study to date, NNRTI resistance was common occurring in 12% of patients tested. Although this was a retrospective analysis, this may underestimate the risk given the time taken between stopping treatment and testing for drug resistance.

COMMENT

These results are important in countries where the drug supply is less secure, and when using NNRTI-based ART with AZT and/or 3TC. Further research is needed to determine whether the longer half-life of tenofovir has a protective impact on NNRTI resistance in this context.

This also highlights the lack of research into the clinical outcomes of people who do not have access to an assured and continuous supply of ARVs. While stock-outs are commonly reported, research into the outcomes is not.

A recent paper in HIV Medicine reported resistance data after stopping atazanavir/r-based combinations (largely related to poor

adherence), and suggested a benefit of PI/r-based combinations when stock-outs are common. This was a retrospective analysis of 110 patients in Ireland and although minor PI mutations were common, viral load was resuppressed after restarting atazanavir/r. [2]

Reference

1. Cambiano V et al. Detection of NNRTI resistance mutations after interrupting NNRTI-based regimens. 21st CROI, 3–6 March 2014, Boston. Poster abstract 593.
   http://croiconference.org/sites/all/abstracts/593.pdf (PDF)
2. Tinago W et al. Characterisation of associations and development of atazanavir resistance after unplanned treatment interruptions. HIV Medecine (2014), 15 (4) 224-232. DOI: 10.1111/hiv.12107.
   http://www.ncbi.nlm.nih.gov/pubmed/24215370

CROI 2014: PREGNANCY AND WOMEN'S HEALTH

HIV related infections remain the leading cause of maternal deaths in South Africa despite the availability of ART

Polly Clayden, HIV i-Base

HIV remains the leading cause of maternal death in South Africa despite a steep decline in vertical transmission, according to data presented at CROI 2014.

Researchers from University of the Witwatersrand and Anova Health Institute conducted a review of maternal deaths at Chris Hani Baragwanath hospital. The hospital is an academic tertiary centre and a district referral facility serving a population of approximately two million people from a mixture of urban and informal settlements in Johannesburg. Coceka Mnyani presented the data on behalf of the group.

The study was conducted between 1997 and 2012 during which time the number of deliveries at the hospital increased from approximately 16,000 a year to over 20,000 – where the rate currently stands. The prevalence of HIV was very high in the mothers giving birth, reaching a peak of 30.7% in 2004 compared to 23.6% in 2012. In 2012 the rate of vertical transmission was 1.5%, compared to 6.9% in 2007.

The researchers considered time trends in their analysis coinciding with PMTCT and ART guideline changes in South Africa (see Table 1).

Table 1. Changes in PMTCT/ART availability in South Africa 1997 to 2012

1997-2002	No PMTCT interventions
2003-2008	sdNVP for PMTCT ART from 2003, CD4 threshold 200 cell/mm3
2009-2010	AZT for PMTCT From 2010, ART CD4 threshold 350 cells/mm3
2011-2012	ART availability within antenatal clinics

There were 589 maternal deaths during the 15-year period. The researchers found that the leading cause of death throughout the four time periods was from non-pregnancy related infections reported in over a third of the mothers who died. The next biggest causes of maternal death were hypertensive disorders and obstetric haemorrhage.

Of the women in the study tested for HIV, 70.7% (285/403) were HIV positive. The HIV testing rate of pregnant women increased over time from less than 50% in 1997 to 2002 to over 80% in 2011 to 2012. The proportion of mothers with HIV that died also increased during the study period: 31% in 1997 to 2002, 53.9% in 2003 to 2008, 53.5% in 2009 to 2010 and 65.8% in 2011 to 2012.

There were 285 deaths among the HIV positive women with a mean age of 29.3 years at time of death. The median CD4 count of the women was very low with 74.6% less than 200 cells/mm3 and only 9% greater than 350 cells/mm3.

Despite the availability of ART, the number of women receiving it remained very low: 10%, 13% and 11% during 2003 to 2008, 2009 to 2010 and 2011 to 2012 respectively. For the few women who were started on ART for their own health (n=13) the median duration of treatment was quite long at 56 weeks but 44.4% had defaulted at the time of death. The median duration of ART was four weeks for those who started in pregnancy.

The majority (80.7%) of deaths among HIV positive women occurred post partum with 78.8% in the first week. Non-pregnancy related infections remained the leading cause of death – responsible for 62% of deaths in HIV positive women. The majority of infections were respiratory particularly community acquired pneumonia and pulmonary TB. Obstetric haemorrhage, pregnancy related sepsis, medical and surgical disorders and hypertensive disorders caused 9.1%, 6.7%, 5.3% and 4.6% of deaths in HIV positive women who died.

Dr Mnyani concluded that HIV related infections remain the leading cause of maternal deaths in South Africa despite the availability of ART. Contributing factors include women presenting late and defaulting treatment, and starting ART is often delayed.

The study has been extended to December 2014 to assess the impact of the extended ART programme and the recent availability of efavirenz-based fixed dose combinations for all HIV positive women.

COMMENT

Depressing news – these findings are similar to those reported before the widespread availability of ART. In South Africa, gains in prevention of childhood HIV are not reflected in maternal mortality rates.

Targeted interventions to decrease the high rate of HIV-related maternal deaths are urgently needed.

Reference

Mnyani CN et al. A 15-Year Review of Maternal Deaths in a Background of Changing HIV Management Guidelines. 21st CROI. 3-6 March 2014, Boston. Oral abstract 67.
http://www.croiwebcasts.org/console/player/22141

Lower newborn bone mineral content with maternal tenofovir use

Polly Clayden, HIV i-Base

Maternal tenofovir disoproxil fumarate (TDF) use is associated with a significant reduction of bone mineral content in neonates in a multisite study from the United States and Puerto Rico.

TDF is currently recommended for pregnant women in BHIVA, US DHHS and WHO guidelines. Little is known about the effect on infant bones with this strategy.

George Siberry from the NIH presented findings from a study conducted to compare the bone mineral content of newborns exposed and not exposed to TDF in utero.

This research was part of the SMARTT (Surveillance Monitoring of ART Toxicities) component of the PHACS (Pediatric HIV Cohort Study). HIV positive women are enrolled during pregnancy and their uninfected infants at 0 to 2 weeks.

The TDF substudy enrolled two groups of HIV-exposed, uninfected newborns of at least 36 weeks gestational age (infected infants were excluded) at 14 US and 9 Puerto Rican sites. The TDF group included infants whose mothers received this drug for eight weeks or more in the third trimester. The non-TDF group included infants whose mothers did not receive TDF in pregnancy at any time.

A whole body dual-energy X-ray absorptiometry (DXA) was performed within four weeks of birth to measure bone mineral content of the infant and analysed with and without including the head. Analysis of the scans was standardised and conducted centrally.

The study had 80% power to detect a mean difference of 7% or 0.5 standard deviations of bone mineral content between arms. This gave a target sample size of 75 to ensure at least 63 evaluable per arm. Dr Siberry noted that the study did not depend on defining bone mineral content as normal or abnormal as there are no such infant norms available.

There were 74 evaluable infants in the TDF and 69 in the non-TDF group. TDF use among the mothers varied by site, p<0.001. Mothers in the TDF group were more likely to be married, 31% vs 22%, p=0.04 and to have received boosted protease inhibitors, 86% vs 64%, p=0.005. Otherwise the groups were similar for demographics, infant weight z-score, p=0.38, length z-score, p= 0.21) and gestational age, p=0.6. In the third trimester similar proportions of mothers with available data had CD4 $\geq$250 cells/mm3 and viral load <400 copies/mL in each group.

The most widely used regimens in the TDF group were TDF/FTC/boosted atazanavir (52%) and TDF/FTC/boosted darunavir (16%). AZT/3TC/boosted lopinavir (41%) and AZT/3TC/abacavir (21%) were most widely used in the non-TDF group.

The unadjusted mean infant whole body bone mineral content was 7.9 g lower (12.2%, 0.5 SD; p=0.002) in the TDF group: 56 g vs 63.8 g. The effect persisted in the multivariate model (adjusted for site, infant gestational age, body length, ethnicity, age at DXA; maternal boosted PI use, age and smoking) whole body bone mineral content was 6.4g (95% CI 2.1 to 10.7) lower in the TDF group, p=0.004. Results were similar when whole body bone mineral content did not include the head in the analysis.

Dr Siberry noted that maternal CD4 and viral load were unlikely to have a role in mediating this association as these values were similar in each group and the investigators found no link to infant body mineral content.

He suggested that the study was limited as it was non-randomised with possible residual confounding including PI use and high rates of triple NRTIs in the non-TDF group. The advantages are that the children will be followed up for years to come as part of SMARTT.

COMMENT

The big question – asked after the presentation – is what to do with these data? Dr Silberry stressed that these results alone are not enough to change current recommendations for TDF use in pregnancy. "But this is the first study to address long standing concerns about the effect of maternal TDF on infant bones and provides some evidence that these concerns might have been well placed", he said. He suggested that results from longitudinal studies are needed to better understand this phenomenon.

As well as continued follow up in SMARTT, a substudy of the IMPAACT 1077 PROMISE maternal and infant survival trial (IMPAACT P1084S) is looking at the effects of TDF on the bone and kidneys of HIV positive women during pregnancy and breastfeeding. [2]

The study will also look at bone health and kidneys in the infants of these women and includes several sites in Africa. It is randomised to compare TDF exposed and unexposed infants and results should be available in 2016.

References

1. Siberry et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate. 21st CROI. 3-6 March 2014. Boston. Oral abstract 71. http://www.croiwebcasts.org/console/player/22145
2. Clinical trials.gov. Study of effects of tenofovir on bone health and kidneys during pregnancy and breastfeeding. http://clinicaltrials.gov/ct2/show/NCT01066858

CROI 2014: PAEDIATRIC CARE

Paediatric pipeline: CROI 2014 update on new antiretrovirals for children

Polly Clayden, HIV i-Base

Several posters at CROI 2014 reported data on antiretrovirals in the paediatric pipeline. These included the new integrase inhibitor class – which might be a useful option for children in the future.

Rilpivirine

Rilpivirine is an NNRTI, approved for treatment adults 18 years old and above with viral load less than 100,000 copies/mL. PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278),

is an ongoing, open label, 48-week phase 2 trial looking at rilpivirine pharmacokinetics (PK), safety and efficacy in treatment naïve adolescents aged 12 to 18 years. [1]

Part one of this trial aimed to find a rilpivirine dose providing comparable exposure to that in adults. Part two is assessing safety and efficacy at 12 and 24 weeks (with an extension of up to 240 weeks) and will be reported at a later date. Rilpivirine steady-state PK plus preliminary four-week safety and efficacy data (with a 25 mg once daily dose) from part one were shown.

Participants (n=25) were enrolled from sites in India, Thailand, Uganda and South Africa. All were treated with rilpivirine in combination with two NRTIs, taken with a meal.

They were a median age of 15 years (range 13 to 17); 56% were girls; 48% were aged 12 to 15 years and 52% were 15 to 18. The majority (84%) were black African and the remainder Asian. Their viral load was a median of 4.9 log copies/mL (range 3.3 to 5.8). In 72% of participants viral load was ≤100,000 copies/mL, 20% 100,000 to 500,000 copies/mL and 8% ≥ 500,000 copies/mL.

Samples were collected predose, 2, 4, 5, 6, 9, 12 and 24 hours after an observed rilpivirine dose, between 2 and 4 weeks of treatment. Plasma concentrations were determined by liquid chromatography-tandem mass spectrometry with a lower limit of quantification of 1.0 ng/mL.

PK data were available for 23 participants. Geometric mean AUC24h, C0h and Cmax were 1750 (range 887-3573) ng*h/mL, 70.6 (range 20.03-191.0) ng/mL and 102.3 (range 48.5-182.0) ng/mL, respectively. Geometric mean PK parameter ratios adolescents:adults (pooled phase 3 ECHO/THRIVE PK substudy) were respectively 0.98, 1.21 and 0.88. Ratio of >0.80 and <1.25 had been predetermined to demonstrate comparability in rilpivirine PK parameters between adults and adolescents.

The investigators observed no apparent relationship between rilpivirine PK parameters and weight, age or between sexes.

At 4 weeks, all but two participants (92%) had >1 log drop in viral load from baseline. The mean decrease in viral load from baseline was 2.3 log copies/mL (n=24). For participants with a baseline viral load <100,000 copies/mL or >100,000 copies/mL, the mean decrease in viral load was 2.6 (n=17) and 2.2 (n=7) log copies/mL, respectively. The mean increase in CD4 count from baseline was 105 cells/mm3 (n=21).

None of the participants discontinued the study drugs due to adverse events (AEs) by week 4. AEs were similar to those reported in adults.

Dolutegravir

Dolutegravir is an integrase inhibitor approved for treatment naïve and experienced adults and adolescents 12 years old and above.

It is being evaluated for children in IMPAACT 1093 – an ongoing, phase 1/2, open label PK, safety and efficacy study in children and adolescents in age de-escalated cohorts. Preliminary data in children aged 12 to 18 years were included with the adult regulatory submissions for dolutegravir leading to the recent FDA and EMA approval.

Twenty-four week data were shown for children aged 6 to 12 years and 48-week data for children and adolescents aged 12 to 18 years.

In the first study, 11 treatment experienced but integrase inhibitor naïve children with viral load ≥ 1000 copies/mL were enrolled in an intensive PK evaluation. Participants received dolutegravir tablets (10, 25, 50mg) dosed at 1 mg/kg once daily (based on weight bands) added to a stable, failing ART regimen, with optimised background therapy added after the PK evaluation, which was performed between days 5 and10. [2]

Children were a median age of 10 years (IQR 8 to 11); 36.4% girls; 36% African American, 27% white, 18% Asian and 36% Latino. Their median baseline viral load was 5.0 log10 copies/mL (IQR 3.5 to 5.3) and median CD4 645 cells/mm3 (IQR 325 to 732). They had received prior ART for a median duration of 9.3 years and just over half were triple class experienced.

PK targets were AUC0-24 37 to 67 ug*h/ mL and C24 0.77 to 2.26 ug/mL.

Five children (≥40 kg) received 50 mg, 2 (30 to < 40 kg) received 35 mg and 4 (20 to <30 kg) received 25 mg dolutegravir once daily. This achieved adequate dolutegravir geometric mean AUC(0-24) and C24 of 50.46 (63%) ug*h/mL and 0.92 (89%) ug/ mL respectively.

In ITT analysis 82% achieved virological suppression <400 copies/mL and 64% <50 copies at 24 weeks. There were no discontinuations due to AEs. Adolescents, aged 12 to 18, had also previously achieved PK comparable to those in adults with the paediatric weight band dose of 1 mg/kg once a day.

The second study from IMPAACT 1093 showed safety and efficacy in 23 adolescents at 48-weeks. [3]

This group were a median age of 15 years (IQR 12 to 16); 78% female; 52% African American, 35% white and 26% Latino. Median baseline viral load was 4.3 log copies/mL (IQR 3.9 to 4.6) and CD4 was 466 cells/mm3 (IQR 297 to 771). About a third were triple class experience and two participants had previously used T-20.

Nineteen participants (≥ 40 kg) received 50 mg dolutegravir once daily and four (30 to <40kg) received 35 mg.

At 48 weeks, 74% of participants achieved virologic suppression <400 copies/mL and 61% <50 copies/mL. There were no Grade 4 AEs, serious AEs or discontinuations due to AEs.

Elvitegravir

Elvitegravir is an integrase inhibitor approved by the EMA (for use with a boosted protease inhibitor) and in regulatory review with the FDA for adults. It is given with a booster and mostly used in the fixed dose combination (FDC) elvitegravir/cobicistat/FTC/TDF.

Two paediatric formulations are in development – a 50 mg tablet and a 5 mg/mL suspension. Data from a single dose PK evaluation of the two formulations boosted compared to the 150 mg adult formulation (all boosted by ritonavir) in healthy volunteers were presented at CROI 2104. [4]

The study design was prospective, open-label, crossover, randomised with multiple cohorts in healthy adults. Cohort 1 (n=30) compared the paediatric tablets (3 X 50 mg) to the adult tablet (reference). Cohort 2 (n=26) compared the paediatric suspension (30 mL) to the reference. Cohort 3 (n=18) evaluated multiple dose PK of both formulations. All formulations of elvitegravir were given with 100 mg ritonavir within 5 minutes of a standard meal.

Intensive PK sampling was performed over 48 hours post dose. Bioequivalence was assessed in cohorts 1 and 2 using standard definition: geometric mean ratios and 90% confidence interval of 80% to 125% (>85% power). Only descriptive PK was assessed in cohort 3.

In cohorts 1 and 2, elvitegravir exposures were within the defined bioequivalence bounds for both the pediatric tablet and suspension formulations vs reference. For the tablet GMR% of adult tablets for AUCinf ng*h/mL, AUC48h ng*h/mL and Cmax ng/mL were respectively: 100 (90% CI 93.8 to 107), 99.6 (90% CI 93.2 to 106) and 100 (90% CI 93.1 to 107). For the suspension these values were: 109 (90% CI 102 to 118), 111 (90% CI 103 to 120) and 108 (90% CI 98.7 to 118).

In cohort 3, ritonavir boosted elvitegravir PK after multiple doses was comparable between the paediatric tablet and suspension formulations and with historical steady state data, including mean trough concentrations (elvitegravir Ctau) ~8.5 and 9.2-fold, respectively, above the IC95 (44.5 ng/mL).

These formulations will be evaluated in children in an ongoing phase 2/3 study.

Cobicistat

Cobicistat is a CYP3A inhibitor with no antiretroviral activity that is approved for adults as a booster of atazanavir 300 mg or darunavir 800 mg by the EMA. It is also a component of the FDC elvitegravir/cobicistat/FTC/TDF.

A 50 mg pediatric immediate release tablet and as a 20 mg pediatric dispersible tablet are in development. Both were compared to the 150 mg adult tablet formulation (reference) in healthy volunteers.

The PK study was designed in the same way as the previous elvitegravir one for cohorts 1 and 2, with the same predefined bioequivalence bounds. Cohort 1 (n=32) evaluated the paediatric immediate release tablets (3 X 50 mg) and cohort 2 (n=30) the paediatric dispersible tablet (7.5 X 20 mg – tablet divided using a pill cutter) vs reference. [5]

In cohorts 1 and 2, cobicistat exposures were within the defined bioequivalence bounds for both the paediatric immediate release and dispersible tablets. For the immediate release tablet GMR% of adult tablets for AUCinf ng*h/mL, AUC48h ng*h/mL and Cmax ng/mL were respectively: 95.0 (90% CI 88.9 to 101), 95.0 (90% CI 88.9 to 101) and 100 (90% CI 92.8 to 108). For the dispersible tablet these values were: 96.6 (90% CI 90.1 to 104), 96.6 (90% CI 90.0 to 104) and 108 (90% CI 86.8 to 97.4).

Both formulations will also be evaluated in an ongoing phase 2/3 study.

Elvitegravir/cobicistat/FTC/TDF

Elvitegravir and cobicistat were also evaluated in treatment naïve adolescents aged 12 to 18 years as components of the adult FDC or single tablet regimen (STR) containing elvitegravir 150 mg, cobicistat 150 mg, FTC 200 mg and TDF 300 mg (E/C/F/TDF).

In this study, 14 adolescents weighing ≥35 kg with viral load ≥1000 copies/mL, CD4 counts ≥100 cells/mm3 and eGFR >90 mL/min received one E/C/F/TDF tablet once daily.

The participants were from the United States, Thailand and South Africa and had a mean age of 16 years (range 13 to 17). Their mean baseline viral load was 4.83 log copies/mL (71% were ≤ 100,000 copies/mL) and CD4 count was 441.5 cells/mm3.

Intensive PK was performed at steady state (day 10). Samples were collected predose, 2, 4, 4.5, 5, 8 and 12 hours post dose. The primary endpoint was EVG AUCtau. Exposures were compared to population PK-based exposures in adults from E/C/F/TDF Phase 2 and 3 trials (ANOVA). Viral load, AEs and routine laboratory tests were evaluated through week 12.

At Day 10 this revealed elvitegravir geometric least squares mean (GLSM) AUCtau 130% (90% CI 105 to 162) of the adult level and GLSM Cmax of 142% (90% CI 116-173%). The GLSM Ctau was 410 ng/mL, 106% of the adult level (90% CI 70.0 to 160), which is 9.2 times the protein-adjusted IC95 of 44.5 ng/mL.

The investigators reported cobicistat, TDF and FTC exposures that were similar to those observed in adults. At 12 weeks, 100% of participants had viral load < 400 copies/mL and 64.3% <50 copeis/mL, and median CD4 count was 627 cells/mm3.

Median serum creatinine increased 0.06 mg/dL by week 12, similar to that seen in adults and consistent with cobicistat's inhibition of tubular creatine secretion. There were no discontinuations due to AEs.

Study of E/C/F/TDF in adolescents and children continues.

References

Unless indicated otherwise, all references are to the Programme and Abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2014, Boston.

1. Crauwels H et al. Rilpivirine pharmacokinetics in HIV-1-infected adolescents: A substudy of PAINT (phase II trial). Poster abstract 900. http://croiconference.org/sites/all/abstracts/900.pdf
2. Viani RM et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV+ children. Poster abstract 901. http://croiconference.org/sites/all/abstracts/901.pdf
3. Viani RM et al. Safety and efficacy of dolutegravir in HIV treatment-experienced adolescents: 48-week results. Poster abstract 906LB. http://croiconference.org/sites/all/abstracts/906LB.pdf
4. Custodio JM et al. Bioequivalence of two paediatric formulations vs adult tablet formulation of elvitegravir. Poster abstract 902. http://croiconference.org/sites/all/abstracts/902.pdf
5. Custodio JM et al. Bioequivalence of two paediatric formulations vs adult tablet formulation of cobisistat. Poster abstract 908. http://croiconference.org/sites/all/abstracts/908.pdf
6. Gaur A et al. Pharmacokinetics, efficacy, and safety of an integrase inhibitor STR in HIV-infected adolescents. Poster abstract 909. http://croiconference.org/sites/all/abstracts/909.pdf

Efavirenz maintenance therapy effective in children exposed to nevirapine prophylaxis

Polly Clayden, HIV i-Base

Children exposed to nevirapine prophylaxis who are initially suppressed on lopinavir/ritonavir-based therapy can safely switch to efavirenz-based maintenance therapy, according to data presented at CROI 2014.

Lopinavir/ritonavir is recommended as first-line therapy for infants and young children in resource-limited settings. This is partly to overcome NNRTI resistance following nevirapine prophylaxis,

which is still widely used in PMTCT programmes globally. However, treatment with lopinavir/ritonavir has a number of shortcomings including: cost, palatability, managing concomitant TB treatment and potential metabolic complications.

The NEVEREST 3 trial was designed to find out whether switching nevirapine-exposed children who start on lopinavir/ritonavir-based ART (and are stable) to efavirenz-based maintenance therapy is equivalent virologically to staying on lopinavir/ritonavir.

Ashraf Coovadia from Rahima Moosa Mother and Child Hospital in Johannesburg, presented data from NEVEREST 3 on behalf of colleagues from University of the Witwatersrand, Johannesburg; Columbia University, New York; and Institute of Communicable Diseases, Johannesburg.

This was a 48-week, non-inferiority, open label, randomised trial, enrolling 300 children; two were lost before starting the trial and 294 completed follow up.

Children who had been exposed to nevirapine prophylaxis, initiated lopinavir-based therapy <24 months of age and suppressed <50 copies/mL at enrollment. They were randomised to switch to efavirenz or stay on lopinavir/ritonavir. Children had regular viral load, CD4 and other laboratory tests, growth measurements and clinical assessments throughout 48 weeks follow up.

Primary endpoints were: viral load >50 copies/mL at any time during follow up; and confirmed viral failure >1000 copies/mL. The non-inferiority margin was 10% ie the study was powered to exclude this difference between arms in virologic efficacy.

At baseline, children were an average of 4.1 years of age, just over half were girls, they had initiated ART at about 9 months and had been on treatment for about 3.5 years. About 60% received abacavir, 35% d4T, and the remainder AZT; all children received 3TC.

Both primary endpoints were non-inferior in the efavirenz arm vs lopinavir-ritonavir. A higher proportion of children in the lopinavir/ritonavir than the efavirenz arm had viral rebound >50 copies/mL: 28% vs 17%, difference +11% (95% CI 1.6 to 20.5), p=0.03. Similar proportions had viral failure >1000 copies/mL: 2% vs 2.6%, difference 0.6% (95% CI -4.1 to 2.8) p=0.68. Professor Coovadia noted that this rate of viral failure was exceptionally low.

At 48-weeks there was a greater increase in CD4 percentage in the efavirenz arm vs lopinavir/ritonavir: to 37% vs 34%, p<0.001. Professor Coovadia remarked that this might mean very little clinically.

There were no deaths in either arm, hospital admissions were rare but two children had efavirenz related seizures that stopped after discontinuing the drug. There was a spike in reported sleep difficulties and nightmares in the efavirenz arm, with 28% of children reporting this at 4 weeks, but there was no difference between the arms at 8 weeks. There were no differences by arm in behavioral problems assessed by the Strengths & Difficulties Questionnaire (SDQ). Weight- and height-for-age were in the normal range and similar across arms. Laboratory abnormalities and other complications were rare.

In conclusion, the investigators wrote: "We advise consideration of such a switch strategy in treatment programmes particularly in resource constrained settings."

COMMENTS

These results are welcome, not least as Professor Coovadia pointed out where "practice is preceding what the science shows" – programmes are already switching children from lopinavir/ritonavir to efavirenz in this situation.

WHO and national guidelines are clear in recommending that young infants and children start on lopinavir/ritonavir-based treatment. They are also clear that older treatment naïve children should start on efavirenz. What is less clear is whether children initiated on lopinavir/ritonavir should switch to the preferred regimen for older children once they become older. Professor Coovadia suggested that there would need to be a lot of discussion about what these results mean for guidelines and programmes.

Hopefully, with more widespread uptake of maternal ART in pregnancy, nevirapine prophylaxis exposure for children will soon be a thing of the past, and treatment recommendations will not need to take this into consideration.

Authors note – about halfway through the presentation Professor Coovadia gives one of the best explanations of non-inferiority I have heard and deserves a plain English award! It is worth checking out the webcast for that too.

Ref: Coovadia A et al. Virologic efficacy of efavirenz maintenance therapy in nevirapine prophylaxis-exposed children. 21st CROI, 3-6 March 2014, Boston. Oral abstract 73.
http://www.croiwebcasts.org/console/player/22147

CROI 2014: TB COINFECTION

Xpert TB test has advantages but does not reduce morbidity

Nathan Geffen, CSSR

South Africa consumes more than half the Xpert MTB/RIF cartridges used worldwide and the device has been rolled out widely with the support of the Minister of Health.

It was hoped that Xpert would reduce morbidity and mortality because it is faster and more sensitive than sputum microscopy. However, although two recently published trials indicate that the Xpert has brought no mortality or morbidity benefit, there are still advantages to using this diagnostic.

In February, Grant Theron and the TB-NEAT team published the results of a randomised trial in The Lancet. [1] Participants with suspected TB (one or more symptoms according to WHO criteria) were randomised to what was effectively an onsite TB diagnostic test using the Xpert or smear microscopy. The primary outcome was TB morbidity measured using Karnofsky performance and a scale developed in 2008 by a Scandanavian team called TBscore. [2]

The TBscore scale is from 0 to 13, with lower scores being healthier, in contrast to Kanofsky performance. All the facilities either had laboratories on site or close by. The sites were located in Cape Town, Durban, Harare, Lusaka and Mbeya. Two sputum samples were collected from patients, one used either for the Xpert or microscopy test and the other for lab culture confirmation using MGIT.

The study was powered to detect a one-point difference in TBscore and 10 point difference in Kanofsky score.

From April 2011 to 30 March 2012, over 1,500 patients were recruited, of whom 758 were assigned to microscopy and 744 to Xpert. At baseline the median age was 37 (IQR: 30-46), 43% of participants were women, 26% had previous TB and 60% were HIV-positive, of whom 26% were on ART. Baseline Kanofsky score was 70 (IQR: 60-90) and TBScore was 5 (IQR: 4-7).

In the microscopy group, 114 were smear-positive of whom 91 were culture-positive, 20 were culture-negative and three culture-contaminated. 111 began treatment. Of the 643 smear-negative cases, 91 were culture-positive, 540 culture-negative and 12 culture-contaminated. (One patient had no microscopy done and was culture-negative.) Of these 212 were put on treatment after chest radiography and other considerations.

In the Xpert group, 184 were positive for TB. Of these 154 were culture-positive, 27 culture-negative and three culture-contaminated, and 182 participants began treatment. Of the 559 Xpert negative cases, 31 were culture-positive, 517 were culture-negative and 11 were culture-contaminated. (One patient had no Xpert result and was culture-negative.) After chest radiography and other considerations a further 139 participants began treatment.

Sensitivity of the Xpert [83%, 95%CI: 77-88] was significantly better than microscopy [50%, 95%CI: 43-57] with $p < 0.0001$. Specificity was similar on both tests: 97% [95%CI: 95-98] for microscopy vs 95% [95%CI: 93-97] for Xpert.

There was no difference in median [IQR] TBscore between the two groups at two months (TBscore: 2 [0-3] in microscopy vs 2 [0.25-3] in Xpert) or six months (1 [0-3] vs 1 [0-3]), nor for Kanofsky performance (80 [70-90] vs 90 [80-90]) at two months, or six months (100 [90-100] vs 100 [90-100]).

Nevertheless, there was a measured benefit to the Xpert. People in the Xpert group were more likely to get a same-day diagnosis (24% vs 13%; $p <0.0001$) and same-day treatment initiation (23% vs 15%; $p=0.0002$).

At CROI 2014, Gavin Churchyard presented the primary endpoint results of the XTEND study that looked at a similar question in a different way. [3]

This was a randomised cluster-controlled trial. Twenty South African clusters were randomly chosen either to use the Xpert or smear microscopy (10 clusters each). A cluster was defined as two clinics served by the same lab. In contrast to the TB-NEAT study, the diagnostic test was done at a supporting laboratory located away from the clinics. The primary outcome was mortality in adults investigated for TB.

Participants in this study provided one sputum sample if they were at an Xpert site and two sputum samples if they were at a microscopy site. Health workers could upon request take additional sputum samples for culture and perform X-rays.

Just under 5,000 participants were screened, 2,541 in the Xpert arm and 2,431 in the microscopy one, of whom 2,344 and 2,368 were enrolled respectively. In the Xpert arm, 20 people withdrew and 36 withdrew from the microscopy arm leaving 2,324 and 2,332 participants for analysis.

At baseline the median age was 36 and 62% were female. There were differences in self-reported HIV status between the arms. In the Xpert clusters, 73% said they knew their status vs 79% in the microscopy arm, but in both arms 62% of those with known status said they were HIV-positive. Median CD4 count was just over 300 in both arms.

The participants in the microscopy arm appear on average to have been less healthy at enrollment with significantly more having a body mass index (BMI) less than 18.5 (8.7% in the Xpert clusters vs 12.4% in microscopy). TB symptoms were also significantly worse in the microscopy arm with, for example, 9.8% reporting no symptoms in the Xpert arm vs 6% in the microscopy arm.

Deaths were high across the study with 4% of participants on the Xpert arm dying vs 5% on the microscopy arm but adjusted for age group, sex, BMI, number of TB symptoms and HIV status there was no difference between the arms. A Kaplan-Meier graph shows a constant risk of death in both arms across the six month follow-up period. Having multiple TB symptoms, low BMI, being male and older were all predictive of risk of death ($p < 0.001$ for all these).

Reporting being HIV positive and not being on ART conferred an adjusted odds ratio of death of 3.32 (95%CI: 2.03-5.41) over reporting being HIV negative. For participants who reported being HIV positive and on ART this was 1.79 (95%CI: 0.99-3.21). Interestingly, for participants who reported unknown status the adjusted odds ratio of death over those reporting being HIV negative was 2.41 (95%CI: 1.47-3.98; $p <0.001$).

Katherine Fielding presented the secondary endpoint results from the study. Diagnostic results were obtained for 97% of participants. On the Xpert arm 9.2% tested positive for TB vs 7.8% on the microscopy arm. Adjusted for age, sex, BMI and number of TB symptoms the prevalence ratio was 1.49 [95%CI: 1-2.23] times higher in the Xpert arm, suggesting much greater sensitivity by the Xpert diagnostic.

Loss-to-follow-up might be expected to be higher in the microscopy arm because of the longer time to diagnose patients and get them on treatment. But it was 17% in the Xpert arm by day 28 compared to 15% in the microscopy arm. When adjusted for BMI and number of TB symptoms there was no difference between the study arms.

Of the 200 participants with positive results in the Xpert arm, 4% (n=8) were positive for rifampicin resistance.

Overall, 541 participants (11.6%) were treated for TB over the six month follow up period, 10.8% on the Xpert arm and 12.5% on the microscopy one. The adjusted risk ratio showed no difference between the arms (1.04: 95%CI: 0.76-1.43).

A post-hoc analysis reported that 71% people treated for TB were microbiologically confirmed to have TB, either by Xpert or culture (385/541), again without any significant difference between arms.

During question time it was suggested that nurses in the microscopy sites had to make a greater effort to diagnose their patients and keep them in care, which compensated for the Xpert's better sensitivity and faster turnaround time.

COMMENT

While it is disappointing that the Xpert did not confer a morbidity or mortality benefit, it's advantages include quicker and easier diagnosis with less work for health workers. Churchyard's group will publish a cost-effectiveness analysis later this year.

The need for a highly sensitive and specific affordable point-of-care TB test remains urgent.

References

1. Theron G et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. The Lancet, 383 (9915); 424-435. (1-7 February 2014).
   http://www.ncbi.nlm.nih.gov/pubmed/24176144
2. Wejse C et al. TBscore: Signs and symptoms from tuberculosis patients in a low-resource setting have predictive value and may be used to assess clinical course. Scandinavian Journal of Infectious Diseases 2008; 40(2): 111-20.
   http://www.ncbi.nlm.nih.gov/pubmed/17852907
3. Churchyard G et al. Effect of Xpert MTB/RIF on early mortality in adults with suspected TB: a pragmatic randomized trial. 21st Conference on Retroviruses and Opportunistic Infections, 3-6 March 2014, Boston. Oral Abstract 95.
   http://www.croiwebcasts.org/console/player/22178
4. Fielding KL et al. Xpert as the First-Line TB Test in South Africa: Yield, Initial Loss to Follow-Up, Proportion Treated. 21st Conference on Retroviruses and Opportunistic Infections, 3-6 March 2014, Boston. Oral Abstract 96LB.
   http://www.croiwebcasts.org/console/player/22178

Moxifloxacin and rifapentine: we need better trials

Nathan Geffen, CSSR

Data on TB drugs was mostly disappointing at CROI 2014, but none more so than the results of the RioMAR trial. This was not because of any shortcomings found with the drugs, but because the trial itself was plagued with logistical problems and was eventually terminated with only half the necessary number of participants enrolled. [1]

Susan Dorman of Johns Hopkins presented the results of RioMAR. This was a phase II randomised open-label trial at three sites in Rio de Janeiro, Brazil. Its aim was to compare the standard drug-susceptible regimen (isoniazid, rifampin, pyrazinamide and ethambutol) against a regimen comprising isoniazid, rifapentine (7.5mg/kg used to determine whether the patient received a 300 or 450mg pill), pyrazinamide and moxifloxacin (400mg) taken daily during the eight-week intensive phase of treatment. There was no food guidance on the administration of drugs.

The primary outcomes were proportion of participants with sputum-negative results, as determined by liquid culture (MGIT) or Löwenstein–Jensen in solid media, at the end of the intensive phase, as well as safety and tolerability. A secondary endpoint was time to sputum conversion.

Last year the results of the RIFAQUIN trial were presented at CROI 2013. That trial found that a regimen using moxifloxacin and rifapentine instead of isoniazid and rifampicin, and in which the two intervention drugs were taken once-weekly in the continuation phase, was non-inferior. Unfortunately, a shorter four month arm had significantly worse outcomes than the study's standard six-month treatment arms. [2]

This however was a superiority trial and there was no treatment shortening arm. Target enrollment was 216 smear-positive adults. Patients with HIV were allowed to enroll but not if they had CD4 counts less than 350 cells/mm3. Interestingly patients would not be allowed to start ART during the intensive phase. This was because the grant for the trial was submitted a decade ago and started seven years ago when practice at the time was not to start ART during the intensive phase. Nevertheless, this all turned out to be theoretical because in the end the trial recruited no patients with HIV.

The study was stopped early. The trial ran out of funding because of slow enrollment, drug procurement delays and what Dorman described as "other operations issues". The trial was unable to obtain free drugs from the pharmaceutical manufacturers.

Only 121 participants were enrolled, 59 on the control and 62 on the intervention arm. After removing patients in both arms who did not have culture-confirmed TB, or those in the control arm who had resistance to the standard regimen, there were 53 and 61 patients in each arm in a modified intent-to-treat analysis.

Median age at enrollment was 30 and median BMI was 20 (IQR: 19-23). There were more women in the control (39%) than the intervention arm (24%).

As to be expected when only half the target is enrolled, there were no significant differences in most measures. In the control arm, nine patients discontinued their regimen for safety and tolerability reasons versus twelve in the intervention arm. There were six and five grade 3 or higher adverse events in the control and intervention arms respectively, which was not significant.

Dorman divided the primary endpoint result into patients whose sputum was tested using Löwenstein–Jensen versus MGIT (though many patients received both). For Löwenstein–Jensen the proportion of patients who were sputum-negative at the end of the intensive phase was the same in both arms (44 of 51 participants in the control vs 51 of 60 participants). This was also the case in a per-protocol analysis. For MGIT, the proportion of sputum conversions was 30 of 42 participants in the control versus 39 of 46 on the intervention arm. While the intervention arm appeared slightly better using MGIT, this didn't reach statistical significance (p=0.13).

On a per-protocol analysis using MGIT, the intervention arm did significantly better (23 of 35 sputum conversions vs 34 of 36, p=0.01; difference: 23%, 95%CI difference: 6.3-39.8%), but this data appears to be over-analysed.

For the secondary outcome of time to sputum conversion, there was no difference in solid media, but there was a significant difference for MGIT (7 weeks vs 5.6; p=0.01). However, Dorman did not clarify if this was measured by intention to treat or per-protocol.

COMMENTS

Dorman ended her presentation saying that the combination of rifapentine and moxifloxacin warrants additional study, but this trial was the opportunity to for that study. When trials are terminated by a DSMB either because of futility or an unexpected result, that is part of the clinical trial process and advances our knowledge. But this trial was terminated for reasons that were entirely organisational. Patients dedicated their time and took the risk of participating in this trial at least in part to advance the treatment of TB. But they have never got the benefit of a proper result. This kind of outcome can undermine patient confidence in future clinical trials.

That a trial of this size took ten years to set up, run and complete is also questionable. Perhaps if this trial had recruited in much of sub-Saharan Africa or Haiti, which have an abundance of TB patients, it likely would have been up and running, fully recruited and finished with results published in a fraction of the time.

Moxifloxacin has two promising uses. It might help shorten drug-susceptible TB treatment to four months and it is already used in regimens for MDR-TB. But the evidence of safety and efficacy is not yet compelling, nor do we know the optimal dosing for second-line treatment. There are 17 moxifloxacin phase II or higher TB trials listed on clinicaltrials.gov. What they collectively tell us about this promising drug mainly is confusing. For the most part these appear to be a collection of small haphhazard trials. More co-ordination is needed in the TB world. We need larger better-run trials that answer clearer questions quicker.

A supply of ten 400mg moxifloxacin pills is about R226, much too high for drug-susceptible TB treatment but affordable for MDR-TB (by comparison linezolid is nearly R6,000 for ten 600mg pills). [3]

Last year we explained in HTB in our review of the RIFAQUIN trial that the high price of rifapentine renders it inaccessible to most of the world's TB sites. It's not clear that much progress reducing the price has been made since then. Unless the price comes down dramatically, it has no place in first-line treatment in most of the world. According to our article last year, the price of rifapentine is about R450 to R650 per month versus R38 for the entire standard first-line TB regimen. Further clinical trials of first-line treatment using it are of limited value unless the price issue is resolved.

References

1. Conde MB et al. 2014. A Phase 2 trial of a rifapentine plus moxifloxacin-based regimen for pulmonary TB treatment. 21st Conference on Retroviruses and Opportunistic Infections, Boston, 3-6 March. Oral abstract 93. http://www.croiwebcasts.org/console/player/22176?mediaType=slideVideo&
2. Geffen N. 2013. RIFAQUIN trial proves new TB regimen. HTB South, April 2013. http://i-base.info/htb-south/2254
3. TAC. Private sector single exit medicine prices on Sunday 16th March 2014. http://www.tac.org.za/community/node/2021

CROI 2014: COTRIMOXAZOLE

Trials show further benefits for cotrimoxazole in children and adults

Nathan Geffen, CSSR

Cotrimoxazole is more than forty years old and costs a few dollars per patient per month. Amazingly, new benefits continue to be found for this broad-spectrum antibiotic. Results from three randomised clinical trials of cotrimoxazole, one for adults and two for children, have recently been presented.

Cotrimoxazole prevents malaria in adults on ART with high CD4 counts

At CROI 2014, Christina Polyak of the Military HIV Research Unit at Walter Reed presented the results of a randomised non-inferiority trial of cotrimoxazole prophylaxis (CTX) conducted in Homa Bay District Hospital in Western Kenya. [1] This is a malaria endemic area.

The World Health Organisation (WHO) recommends CTX for all adults with HIV with CD4 counts < 350 cells/mm3. In settings with high HIV prevalence and limited resources, the WHO recommends CTX for all adults with HIV. The Kenyan guidelines follow this recommendation. However these guidelines were developed prior to the scale-up of ART. The threshold for discontinuing CTX is undefined after patients start ART.

Discontinuing CTX means a reduced pill burden for patients, potentially less drug toxicity and less resistance, as well as lower costs. The aim of this study was to find out if continuing CTX reduces morbidity in people on ART whose immune systems have recovered. An earlier trial in Uganda found reduced diarrhea and malaria in patients on ART with CD4 counts higher than 200 cells/mm3. [2] An ongoing study in Uganda called COSTOP is also looking at this question. [3]

The study described by Polyak was a non-blinded, non-inferiority randomised trial, open to HIV-positive participants on ART over 18 with CD4 counts of 350 cells/mm3 or more. Pregnant women and people on second-line ART were excluded. Participants were provided bed nets and water filters. The primary endpoint was a composite measure of morbidity (malaria, pneumonia and diarrhaea) and non-trauma mortality. Severe adverse events were a secondary endpoint.

The study took place from February 2012 to September 2013. Patients were followed up for a year.

Of 538 people assessed, 500 were randomised, with exactly 250 allocated to CTX and 250 allocated to stop CTX. 245 patients in each arm completed follow-up.

There were no significant differences between the arms at baseline. About 70% were female, average age was 40, median CD4 count was just under 600 cells/mm3, median time on ART was 4.5 years and nearly 90% of participants reported using bed nets.

The CTX arm did significantly better on the primary endpoint (34 cases at an incidence of 13.4 / 100 person years vs 77 cases at an

incidence of 30.4 per 100 person years; incidence rate ratio [IRR]: 2.27, 95%CI: 1.52-3.38; p < 0.001).

This was driven solely by malaria (1 case vs 33; IRR: 33.02, 95%CI: 4.52-241.02; p < 0.001). Only one malaria case – in the stop CTX arm – was serious and required hospitalisation. There were no significant differences in mortality, diarrhea or pneumonia. For diarrhea, there were 25 cases in the CTX arm versus 34 in the discontinuation one, but the IRR does not show a trend (p=0.24).

There was no significant difference in serious adverse events. There were actually fewer on the CTX arm (9 vs 19; IRR: 2.0, 95%CI: 0.9-4.44; p=0.088).

Polyak pointed out that the study had limitations. It was unblinded which might have affected clinician care decisions and patients off CTX might have sought care more often. Also the study was confined to an endemic malaria area, had very high retention and was short.

Cotrimoxazole trials in children on ART

The WHO recommends CTX for children without HIV born to mothers with HIV, from six weeks until the end of breastfeeding.

ARROW

In January, the ARROW trial team published the results of an open-label randomised non-inferiority trial in the NEJM. [4] This trial showed the benefit of children with HIV continuing to take CTX. Children in Uganda and Zimbabwe older than three were included if they had been on ART for more than 96 weeks, were using insecticide treated bed nets in malaria areas and had not had Pneumocystis jirovecii pneumonia. 382 and 376 children were randomised to stop or continue CTX respectively.

At baseline, the children had been on ART for a median of just over two years (IQR: 1.8 to 2.3). median age was nearly eight years (IQR: 4.6 to 11.1), and median CD4 percentage was 33% (IQR: 26 to 39). Median follow-up was just over two years (IQR: 1.8 to 2.2).

Children who stopped CTX had higher rates of hospitalisation or death than those who continued (72 [19%] vs. 48 [13%]; HR: 1.64; 95%CI: 1.14-2.37; p=0.007). But deaths were not significantly different: two in the stopped CTX arm vs three in the CTX arm. The malaria hospitalisations in the stopped CTX arm were 49, while there were 21 in the CTX arm. There were 53 hospitalisations for other infections in the stopped CTX arm and 25 in the CTX arm.

There were significantly more grade 4 adverse events in the CTX stop group (HR: 2.04; 95% CI 0.99-4.22; p=0.05). Most of these were due to anemia (12 vs 2).

A poster at CROI also showed that children on CTX in ARROW had lower inflammatory biomarkers than those in the stopped CTX arm. [5]

Young Ugandan children trial

At CROI a late-breaker poster by Jaco Homsy and colleagues showed the results of a CTX trial in Uganda. [6] The children in this trial were younger than in ARROW and HIV uninfected for the most part. The trial design is complex.

The trial enrolled 203 HIV-exposed infants who were between six weeks and nine months old. They were prescribed daily CTX until breastfeeding ended and their HIV status was confirmed. After breastfeeding, 185 children remained in follow-up and without HIV. They were randomised to continue or stop CTX until two years old. At two, the 91 children who continued CTX were randomised again to continue or discontinue CTX until they were four years old.

Also followed up for comparison were 48 children with HIV on continuous CTX prophylaxis and 100 children unexposed to HIV who never received CTX prophylaxis.

Of the 185 HIV-exposed children 152 (82%) and 146 (79%)were followed to ages four and five respectively.

CTX to age four resulted in a 43% reduction in malaria(IRR: 0.57; 95%CI, 0.49-0.66; p<0.001). Throughout the trial, malaria incidence was lowest among children who received CTX and highest among HIV-negative unexposed children who did not receive CTX prophylaxis. There were no significant differences in serious adverse events, hospitalisations, or deaths among HIV-exposed, HIV-unexposed, and HIV-infected children. There was no evidence of malaria incidence rebound in the year following stopping CTX at age two or four, but incidence increased significantly from age four to age five among children who stopped CTX at age four.

In the 203 HIV-exposed children on CTX there were 142 malaria episodes and a malaria incidence of 1.35 episodes per person year.

In the 48 children children on CTX who were infected with HIV there were also 142 malaria episodes and a malaria incidence of 1.93 per person year.

In the 100 HIV unexposed children not on CTX there were 674 malaria episodes and a malaria incidence of 4.63 per person year.

HIV-exposed children who continued CTX to age four had a 47% lower risk of malaria compared to children who stopped CTX at age two or after the end of breastfeeding.

COMMENT

These trials show that CTX reduces malaria in both adults and children with HIV. CTX also reduces malaria in children exposed to HIV until at least the age of four, probably beyond. It also reduces other infections that require hospitalisation in children with HIV.

New WHO guidelines will likely consider the results of these trials and recommend continued CTX for adults and children with HIV or exposed to HIV in malaria endemic areas. Children with HIV in non-malarial areas might also benefit from CTX.

These trials suggest CTX might be an effective malaria prophylactic irrespective of HIV status. One question put to Christina Polyak at CROI was whether there could be a perception of AIDS exceptionalism. The implication was why offer CTX to people with HIV stable on ART for the prevention of malaria and not people without HIV? Also what are the public health consequences of mass prophylaxis against malaria using cotrimoxazole and the possible development of population resistance over time, perhaps not only for malaria? These are complex questions that researchers and patients have to grapple with.

References

1. Polyak CS et al. 2014. CTX Prophylaxis discontinuation among ART-treated adults: a randomised non-Inferiority trial. 21st Conference on Retroviruses and Opportunistic Infections, Boston, 3-6 March. Oral abstract 98. http://www.croiwebcasts.org/console/player/22181?mediaType=slideVideo&

2. Campbell JD et al. HIV-infected Ugandan adults taking antiretroviral therapy with CD4 counts <200 cells/IL who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. Clin Infect Dis. 2012 Apr;54(8):1204-11. doi: 10.1093/cid/cis013. http://www.ncbi.nlm.nih.gov/pubmed/22423133
3. Munderi P. 2010. Safety of discontinuing co-trimoxazole prophylaxis among Ugandan adults on antiretroviral therapy (ART). (COSTOP) http://www.controlled-trials.com/ISRCTN44723643/
4. Bwakura-Dangarembizi M et al. A Randomized Trial of Prolonged Co-trimoxazole in HIV-Infected Children in Africa. N Engl J Med 2014; 370:41-53. http://www.nejm.org/doi/full/10.1056/NEJMoa1214901
5. Prendergast AJ et al. Lower inflammatory biomarkers in children randomised to prolonged cotrimoxazole prophylaxis. 21st Conference on Retroviruses and Opportunistic Infections, Boston, 3-6 March. Poster abstract 914. http://croiconference.org/sites/all/abstracts/914.pdf
6. Homsy J et al. Four year cotrimoxazole prophylaxis prevents malaria in HIV-exposed children: a randomised trial. 21st Conference on Retroviruses and Opportunistic Infections, Boston, 3-6 March. Poster abstract 860LB. http://croiconference.org/sites/all/abstracts/860LB.pdf

McNeil Jr. also appears to misunderstand Persaud's description of HIV antibody test results, writing: "because the most sensitive blood tests can find no virus capable of replicating, she describes the baby as 'having sero-reverted to H.I.V.-negative.'" Seroreversion refers to antibody responses, not the "sensitive blood tests" used to look for HIV, and it is common for infants treated early with ART to lose HIV antibody responses even when viral genetic material remains detectable. Persaud's description therefore does not represent some sort of special designation for this case.

The webcast of Persaud's talk is now available on the CROI 2014 webcast site.

Source: TAG Basic science blog. Reports of a second baby possibly cured of HIV: uncertainty remains. (06 Mar 2014).

Ref: Persaud D et al. Very Early Combination Antiretroviral Therapy in Perinatal HIV Infection: Two Case Studies. 21st Conference on Retroviruses and Opportunistic Infections, 3-6 March 2014, Boston. Oral Abstract 75LB. http://www.croiwebcasts.org/console/player/22149

CROI 2014: ERADICATION AND CURE RESEARCH

Reports of a second baby possibly cured of HIV: uncertainty remains

Richard Jefferys, TAG

One of the headline news stories during CROI 2014 related to a conference presentation by Deborah Persaud from Johns Hopkins University in which she described the case of an HIV-infected baby who was treated within four hours of birth and who now shows no detectable HIV after nine months of follow up.

The diagnosis of HIV infection was established by a positive HIV DNA test and detectable viral load measurements of 217 copies/mL in the blood (36 hours after birth) and 32 copies/mL in the cerebrospinal fluid (on day 6, sampled as part of a work up for meningitis). Crucially, the infant remains on antiretroviral therapy (ART) so it is as yet unknown if they have been cured.

According to news stories, doctors may consider interrupting ART if tests continue to show an absence of detectable HIV when the child reaches two years of age.

The recent report of viral load rebound after ART interruption in two adults in Boston who had no detectable HIV after receiving stem cell transplants emphasises the need to be cautious about assuming a cure has been achieved based only on virological assays. Many news articles have neglected to appropriately emphasise this point; in Donald G. McNeil Jr.'s piece in the New York Times he states there is now "little doubt that the treatment works" – but there is considerable doubt about this. An unproven, possible second case in addition to the Mississippi child (reported by Persaud at CROI last year and recently published) does not constitute scientific proof that early ART can be curative; rather, these cases raise the hope that it could be, at least in some instances, and provide justification for the conduct of a clinical trial currently being planned by the IMPAACT network.

Updates on SB728-T, a CCR5-targeting gene therapy

Richard Jefferys, TAG

Recently there have been two widely publicised updates relating to SB728-T, a gene therapy for HIV infection developed by Sangamo BioSciences.

On Wednesday March 5th the New England Journal of Medicine (NEJM) published results from a phase I study conducted by Pablo Tebas and colleagues at the University of Pennsylvania [1], and on the following day at CROI 2014 Gary Blick presented new data derived from subsequent trials. [2]

The therapy is technologically complex: it involves extracting CD4 T cells from HIV-positive individuals and then modifying them with a method that aims to disable the gene that encodes the CCR5 receptor (which most HIV variants use as a foothold to gain entry into cells). The CD4 T cells are then expanded in number and ultimately infused back into the individual, typically with around 10% successfully modified so that they no longer express CCR5. The method for disabling the CCR5 gene involves an enzyme called a zinc finger nuclease (ZFN), which targets and breaks the DNA containing the gene; cellular repair enzymes then stitch the DNA back together in a way that prevents the gene from making a functional CCR5 receptor. The ZFN is delivered into the CD4 T cells by an adenovirus vector during the laboratory modification procedure. The goal of the therapy is to create a population of CD4 T cells that are resistant to infection by HIV.

The results described in NEJM relate to a clinical trial begun in 2009. There were 12 participants, all receiving antiretroviral therapy (ART): six classified as immunological responders with CD4 T cell counts above 450 and a nadir of no lower than 300, and six immunological non-responders with relatively low CD4 T cell counts despite HIV suppression (between 200 and 500 after a minimum of two years of ART). The primary purpose of the study was to evaluate the safety of a single infusion of gene-modified CD4 T cells, with secondary analyses including CD4 T cell count changes, persistence (and trafficking to gut mucosa) of modified cells, and viral load measurements.

CD4 T cell counts increased in all participants, although the paper notes there was variation between individuals, with seven experiencing large increases and the remainder more modest changes. After 36 weeks of follow up, the median increase was 615 cells. CD4/CD8 ratios, which are typically slow to improve on ART alone, rose significantly from a median of 0.99 at baseline to 2.62 after one week, before declining to 1.14 at week 36. Tracking the gene-modified CD4 T cells is complex, because only approximately 25% show a consistent, quantifiable genetic signature associated with the CCR5 gene disruption; the number measured by this technique is therefore multiplied by four to estimate the total. The median number of gene-modified CD4 T cells in blood was 250 cells per cubic millimeter one week after infusion, representing 13.9% of CD4 T cells, but declined thereafter with an average half-life of 48 weeks. Modified CD4 T cells remain detectable in the blood of all participants, and in the individual followed for the longest period (3.5 years), the level is now 13 cells per cubic millimeter, representing 1.7% of circulating CD4 T cells. Among 11 participants who agreed to repeat rectal biopsies, the median frequency of gene-modified cells was 0.8% of rectal mononuclear cells at day 21 after infusion with subsequent measurements ranging from 0.2-0.4%.To assess effects on viral load, ART was interrupted in the six immune responder participants four weeks after the CD4 T cell infusion. The duration of the interruption was set at 12 weeks, but in two cases ART was restarted early (due to concern about rapidly rising viral load and three consecutive viral loads over 100,000 copies, respectively). In three of the four remaining individuals, viral load rebounded but subsequently declined to levels similar to their historical pre-ART setpoints at the end of the interruption. In the final participant, a surprising result was observed: viral load rebounded but declined to undetectable levels just before ART was resumed (the viral load graph in the paper appears to indicate there may have been a slight, temporary blip after treatment was begun again, but this is not clarified in the text). Subsequent analyses revealed that this individual is heterozygous for the CCR5 delta-32 mutation, meaning that in his CD4 T cells one copy of the CCR5 gene is already disabled (each cell contains two CCR5 genes, one on each set of chromosomes). As a result, in CCR5 delta-32 heterozygotes there is less work for the gene therapy to do: it only has to disable one CCR5 gene in each CD4 T cell in order to completely abrogate expression of the CCR5 receptor.

The need to disable two CCR5 genes per cell in most recipients adds an additional wrinkle to attempts to measure the number of CD4 T cells modified by the approach. Because laboratory studies indicate that approximately 33% of modified CD4 T cells have both CCR5 genes disabled, the estimated number of modified cells has to be multiplied by 1/3 to reach an approximate number of CD4 T cells that completely lack CCR5 receptor expression. In CCR5 delta-32 heterozygotes, the multiplier is 2/3. Using these formulas, the researchers were able to demonstrate a statistically significant inverse correlation (rho = -0.90, P=0.037) between the estimated numbers of CD4 T cells lacking CCR5 and the viral load decline during the ART interruption, although this is not reported in the paper itself but rather in figure S7 of the supplementary appendix. [3]

Side effects from the administration of the CD4 T cells were generally mild to moderate infusion reactions comprising transient fever, chills, myalgia, arthralgia, and headache. In one case these symptoms were severe enough to lead to a visit to the emergency room within 24 hours after the infusion. A temporary garlic-like body odor was common after infusion due to the metabolism of the substance DMSO, which is used as a cryopreservative during the storage of the extracted CD4 T cells.

The media coverage of the NEJM paper has generally failed to note that the data are not new; Carl June first presented the trial at CROI in 2011. The results have informed the design of several subsequent studies being conducted by Sangamo BioSciences, including those covered in the presentation by Gary Blick at CROI 2014. Specifically, the apparent correlation between numbers of gene-modified cells and viral load reductions spurred an evaluation of whether the immunosuppressive drug cyclophosphamide (Cytoxan) could be used to deplete CD4 T cells prior to the infusion and thereby enhance the uptake of the modified CD4 T cells (essentially create immunological “space” for the new cells to expand into).

Blick reported results involving three different Cytoxan doses: 200mg, 500mg and 1000mg per meter squared. There were three, six and three participants in each dose group respectively. Two individuals receiving 500mg withdrew consent due to nausea and vomiting, and the protocol was subsequently amended to allow prophylactic antiemetic treatment prior to Cytoxan administration. Six weeks after receiving the CD4 T cell infusions (ranging from around 8-35 billion cells), participants underwent a 16-week ART interruption, with the exception of an individual in the 200mg group whose viral tropism (CCR5 vs. CXCR4) could not successfully be evaluated. Blick reported that the highest numbers of gene-modified CD4 T cells were seen in recipients of the 1000mg Cytoxan dose. Initial CD4 T cell count increases also appeared to be somewhat greater in this group. However both of these measures seemed to decline to levels that overlapped with the other groups by the end of the ART interruption. In terms of viral load, one individual in the 1000mg Cytoxan dose group experienced a decline of close to 2 logs from the peak during ART interruption, while another saw a drop to around 1 log below their pre-ART baseline; in other cases the drops were in the 0.3-1 log range. Two participants in the highest dose group remain off ART, based on protocol criteria that allowed the interruption to be continued if viral load stayed beneath 10,000 copies and CD4 T cell counts were maintained above 500 (the wisdom of this is could be questionable given evidence that cumulative exposure to detectable viral load is associated with an increased risk of mortality [4]; levels of inflammatory biomarkers in these individuals were not reported). No statistical comparisons of the viral load outcomes between the different dose groups were provided in the presentation.

Based on these very limited numbers, Blick speculated that perhaps the highest Cytoxan dose is allowing the number of gene-modified CD4 T cells to get close to a level where a functional cure might be achieved. An additional arm administering 1,500mg of Cytoxan (preceded by prophylactic antiemetics) has now been added to the study. Blick also mentioned an individual under his care who is a participant in another Sangamo BioSciences clinical trial, which enrolled only CCR5 delta-32 heterozygotes (a design based on the promising data described in the NEJM paper). This person has now been off ART for over 31 weeks and continues to maintain viral load at or below the limit of detection (Sangamo BioSciences has previously provided updates on this individual via press releases at 7, 14 and 20 weeks of follow up). [5, 6, 7] The complete data from this trial has not yet been presented or published.

Overall the results are encouraging, but preliminary. Many media stories have emphasized the exciting possibility of achieving ART-free containment of HIV, but it’s important to note that, as of now, there is only one CCR5 delta-32 heterozygous study participant who

has maintained viral load levels beneath detection for an extended period. Because the CCR5 delta-32 heterozygote described in the NEJM paper restarted ART, it is not known if viral load would have remained controlled in that case. For the two individuals in the Cytoxan study who remain off ART, further follow up and additional studies are needed to assess if the relatively low but detectable viral load is leading to elevated inflammation, as is typical in untreated HIV infection, or if the gene therapy is ameliorating those effects.

The mechanism of viral load control also needs to be better understood; Dale Ando from Sangamo BioSciences has presented evidence that improved HIV-specific CD8 T cell responses may be playing a role, possibly suggesting that, in some cases, gene-modified HIV-specific CD4 T cells have been created that are protected from HIV infection and therefore able to provide appropriate help to CD8 T cells. As yet however, no data on HIV-specific CD4 T cell responses has been reported (at least to my knowledge). Because the play of chance would influence how many HIV-specific CD4 T cells are extracted and successfully modified by SB728-T for a given individual, this could be a potential contributor to the heterogeneous outcomes seen in the trials, along with other immunological factors such as variation in HLA genes that affect the quality and targeting of virus-specific CD4 and CD8 T cells responses. A better understanding of these issues might help further refine the approach in order to improve success (e.g. perhaps combining with therapeutic vaccination to try and boost HIV-specific T cell immunity prior to ART interruption). Although it's only given for a short period, Gary Blick's report indicates Cytoxan may have some drawbacks as an adjunctive modality.

Researchers are also pursuing the possibility of introducing CCR5 modification at the level of stem cells (based on the cure achieved in Timothy Brown, who received a stem cell transplant from a CCR5 delta-32 homozygote), although there are significant barriers to making this type of delivery possible in people who do not have cancer diagnoses requiring stem cell transplantation.

Some community members with long memories were surprised to see Blick presenting these data. In the past Blick has been involved in studies of a controversial purported therapy called extracorporeal hyperthemia (a procedure for heating the blood outside the body that was associated with some recipient deaths), which briefly drew publicity, and harsh criticism, in the early 1990s. [8] Blick is still listed as holding patents on hyperthermia, both as a treatment for HIV and hepatitis C.

References

1. Tebas P et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. NEJM 2014; 370:901-910 (6 March 2014). DOI: 10.1056/NEJMoa1300662.
   http://www.nejm.org/doi/full/10.1056/NEJMoa1300662
2. Blick G et al. Cyclophosphamide enhances SB-728-T engraftment to levels associated with HIV-RNA control. 21st CROI, 3-6 March 2014, Boston.
   http://www.croiwebcasts.org/console/player/22278
3. Tebas P et al (ibid). Supplementary material.
   http://www.nejm.org/doi/suppl/10.1056/NEJMoa1300662/suppl_file/nejmoa1300662_appendix.pdf (PDF)
4. Mugavero M et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. Clin Infect Dis. Nov 1, 2011; 53(9): 927–935.
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189165/
5. Sangamo Sciences press statement (12 September 2013).
   http://investor.sangamo.com/releasedetail.cfm?ReleaseID=790503
6. Sangamo Sciences press statement (28 October 2013).
   http://investor.sangamo.com/releasedetail.cfm?ReleaseID=800686
7. Sangamo Sciences press statement (6 December 2013).
   http://files.shareholder.com/downloads/SGMO/3004478797x0x711926/e9e5b790-5f95-4275-9e05-81da7df099f5/SGMO_News_2013_12_6_General_Releases.pdf (PDF)
8. Cimons M. US officials criticize hyperthermia AIDS treatment: Health inquiry finds no benefit from the controversial procedure, nor does it find any reason to encourage further experiments. Los Angeles Times. September 05, 1990
   http://articles.latimes.com/1990-09-05/news/mn-561_1_aids-treatment

TREATMENT ACCESS

FDA approvals of generic ARVS

The US Food and Drug Administration (FDA) has granted tentative (or full) approval for the following new generic ARV products so far in 2014.**

Drug and formulation	Manufacturer, Country	Approval date
atazanavir (100 mg, 150 mg, 200 mg and 300 mg) capsules	Aurobindo, India	31 Jan 2014
3TC/AZT (150 mg/300 mg tablet) **	Hetero Labs, India	3 Feb 2014
tenofovir/FTC (300 mg/200 mg) tablets	Cipla, India	26 Feb 2014
tenofovir/3TC (300 mg/ 300 mg) + copackaged nevirapine (200mg)	Hetero labs, India	14 Mar 2014
atazanavir/ritonavir (300 mg/100 mg) tablets	Emcure, India	17 Mar 2014

** full approval, otherwise all tentative approval; FDC: Fixed Dose Combination

Tentative approval means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Full approval means the patent has expired for the original compounds and the product can be used in the US.

An updated list of generic tentative approvals (now at 170) is available on the FDA website:

http://www.fda.gov/oia/pepfar.htm

A list of generic ARVs now available for use inside the US is also online:

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118944.htm

Source: FDA list serve (various dates, as approved).

Medicines Patent Pool adds dolutegravir

Polly Clayden, HIV i-Base

On 1st April the Medicines Patent Pool (MPP) announced two licence agreements with ViiV Healthcare for dolutegravir. According to their press release, the adult agreement will allow access to generic formulations of dolutegravir in countries where 93% of HIV positive adults live, and the paediatric one in countries where 99% of HIV positive children live.

They note that this announcement comes only two months after the EMA approved the drug for adults and adolescents age 12-18, and eight months after the US FDA's approval.

In February 2013, the MPP and ViiV announced a collaboration on paediatric antiretrovirals and a licence for abacavir. The paediatric licence for dolutegravir will expand as the drug gains EMA/FDA approval for formulations in development for younger age groups.

C O M M E N T

Despite only being recently approved, WHO included dolutegravir in the list of products for pre qualification in January. Meanwhile studies are underway or planned in younger children, pregnant women and with TB treatment that will help to inform the use of this drug in resource limited settings.

This news from the MPP should also help to shorten the time between approval for rich countries to use in poor ones.

http://www.medicinespatentpool.org/medicines-patent-pool-viiv-healthcare-sign-licence-for-the-most-recent-hiv-medicine-to-have-received-regulatory-approval/

Source: http://i-base.info/htb-south/2632

GUIDELINES

UK guidelines for HIV-related cancers: 2014 edition published online

BHIVA guidelines for HIV-associated malignancies 2014 are now available online.

They aim to provide guidance on best clinical practice in the treatment and management of adults with HIV infection and malignancy. The scope includes the management of diagnosed malignancies in people living with HIV but does not address screening for malignancies in this population. This is covered elsewhere in other BHIVA guidance where evidence is available to support it.

The guidelines are aimed at clinical professionals directly involved with, and responsible for, the care of adults with HIV infection, and at community advocates responsible for promoting the best interests and care of HIV positive adults.

The guidelines should be read in conjunction with other published BHIVA guidelines.

Reference

BHIVA. British HIV Association guidelines for HIV-associated malignancies 2014.

http://www.bhiva.org/Malignancy-2014.aspx

Strong recommendations in WHO guidelines are often based on lower quality evidence than indicated in GRADE approach

Polly Clayden, HIV i-Base

In an article in the Journal of Clinical Epidemiology, 6 January 2014, researchers from the United States and Canada write that WHO guidelines frequently make strong recommendations, based on low or very low confidence estimates.

They note that guideline panelists can be reluctant to offer weak/conditional/contingent recommendations despite GRADE guidance warning against strong recommendations when confidence in effect estimates is low or very low.

The researchers conducted a study to evaluate the strength of recommendations and confidence in estimates in WHO guidelines that used the GRADE approach and graded both strength and confidence.

They reviewed WHO guidelines from January 2007 to December 2012 for this study. After identifying those that used GRADE, they looked at the classifications of strong and weak alongside the associated confidence in estimates: high, moderate, low, and very low.

The researchers identified 116 published WHO guidelines of which 43 (37%) used GRADE. From these there were 456 recommendations, of which 289 (63.4%) were strong and 167 (36.6%) were conditional/weak.

They found that 95 of the 289 strong recommendations (33.0%) were based on evidence "warranting low confidence in estimates" and 65 (22.5%) on evidence "warranting very low confidence in estimates". Overall, they said 55.5% of strong recommendations were based on low or very low confidence in estimates.

They concluded that: "Further study to determine the reasons for such high uncertainty recommendations is warranted".

Reference

Alexander PE et al. World Health Organisation recommendations are often strong based on low confidence in effect estimates. Journal of Clinical Epidemiology. Published online 6 January 2014.

http://www.jclinepi.com/article/S0895-4356(13)00434-4/abstract

PAEDIATRICS

FDA approves raltegravir for children older than 4 weeks

On 20 December 2013, the FDA approved a new oral suspension formulation of raltegravir (Isentress) for use in paediatric patients aged 4 weeks and older, weighing at least 3 kg to less than 20 kg.

The indication is for use in combination with other antiretroviral agents for the treatment of HIV-1. Each single-use packet for oral suspension contains 100 mg of raltegravir which is suspended in 5 mL of water giving a final concentration of 20 mg/mL.

A new document as part of the patient labeling includes detailed information about dosing of both this suspension and the previous paediatric chewable formulation. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and have specific guidance.

Merck expects to have the raltegravir oral suspension commercially available by the third quarter of 2014.

The revised label for all formulations are now posted on the FDA website under the brand name Isentress.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

EPIDEMIOLOGY

Life expectancy in South Africa is increasing, but drug-resistant TB is a threat

Nathan Geffen, CSSR

Life expectancy in South Africa is increasing rapidly. Deaths from HIV and TB are declining because of the antiretroviral treatment programme and improved TB treatment outcomes. This is the essence of what we learn from two recent reports and a Department of Health slideshow.

In March, Statistics South Africa released the mortality data for 2011. [1] A few days later the Medical Research Council (MRC) released its second Rapid Mortality Surveillance Data report. [2] Adding to this rich data, a presentation by Norbert Ndjeka of the National Department of Health has been made available on the Health-e website. [3]

The Stats SA publication reports the registered deaths in the country. It shows a continuing trend of declining annual deaths in South Africa. It estimates that well over 90% of adult deaths are registered but more time is needed to estimate the percentage of recorded child deaths.

In 1997 there were just over 317,000 recorded deaths. This rose to over 500,000 by 2002 and peaked at 613,000 in 2006. Then deaths began declining. In 2011 there were about 505,000 deaths, about the same number as 2002.

In 1997, the median age of death was 51. This dropped steadily to a low of just under 43 in 2004 and then began increasing again. In 2011 it crossed 50 for the first time since 1997.

This good news is echoed by the MRC report. Monthly, since 1999 the MRC has collected the deaths registered on the National Population Register. This is a subset of deaths registered with Stats SA that includes only people who had South African birth certificates or identity documents. As with the Stats SA data, the adult death data is much more complete than children. Various technical adjustments, beyond the scope of this article, have been made to the data.

Using the census data to estimate the total population, the MRC calculates life-expectancy at birth. The report states, "The estimates for 2012 show that the average life expectancy in South Africa has reached 61 years, an increase of 7 years since the low in 2005." On average, women live a lot longer than men. Life-expectancy in 2012 for women was 64 but only 58.5 in men. The odds of a person aged 15 dying before their 60th birthday declined from 46% in 2009 to 38% in 2012.

The report explains that this is because of a "significant decline in the mortality of those under the age of 1, but is also due to a decline in adult mortality probably as a result of greater than expected roll-out of ARVs."

Although not stated in the report, the decline in mortality in infants is likely because of the programme to prevent transmission of HIV from mother-to-child and because in recent years guidelines have

provided for infants diagnosed with HIV to start treatment immediately, which significantly reduces mortality. [4]

In 2011, a Department of Health committee set 59 as the target life-expectancy for 2014. Unbeknown to the committee at the time, this had already been exceeded. All this is excellent news. However, we can't be complacent. Tens of thousands of people continue to die of AIDS and life-expectancy has still not reached 1990s levels. The other worry is TB. It is the biggest cause of death in the country; mortality due to this disease rose through the late 1990s and 2000s because people with HIV are so prone to becoming deathly ill with it.

For the most part the news on TB is improving. Ndjeka's presentation shows that in 2007 there were nearly 354,000 TB notifications. This peaked at just under 406,000 notifications in 2009 and has since declined to just under 345,000 in 2012, even lower than in 2007. The Stats SA report also shows a decline in recorded TB deaths, from nearly 70,000 in 2009 to just over 54,000 in 2010. While the death certificates used by Stats SA are not reliable for determining totals for cause of death, and actual TB deaths were certainly much higher than recorded, the decline in TB as a cause of death is consistent with the rest of the data.

The one disturbing TB trend is this: in 2007 there were 7,350 confirmed cases of multi-drug resistant TB. This rose to 14,161 in 2012, of which fewer than half had started treatment according to Ndjeka's slides.

For extensively drug-resistant TB, the number of laboratory confirmed cases rose from 85 in 2004 to 1,574 in 2011. There was a tiny drop in 2012.

Survival rates are poor for drug-resistant TB: nearly 20% of multi drug-resistant TB patients die of their illness and nearly half of extensively drug-resistant ones according to Ndjeka's presentation. But its possible that these are underestimates. Mortality from drug-resistant TB is hard to gauge and some studies report higher rates than this.

The number of drug-resistant TB patients are still not large, but these are only confirmed cases. The growth of drug-resistant TB is clearly happening. While there are new TB drugs in the pipeline and completely new TB treatment regimens on the horizon, progress is slow. In the meanwhile people with drug-resistant TB have to face about two years of treatment on drugs with awful side-effects, including deafness, and limited evidence of efficacy.

Ndjeka's presentation shows the response to TB in Umzinyathi district in Kwazulu-Natal in a positive light. But with a plethora of reports on stockouts, the NHLS again in the news for being in financial crisis and a multitude of reports of problems in the health system, it is hard to be confident that we are adequately confronting the drug-resistant TB problem.

Other interesting data

Some other interesting facts can be found in the Stats SA and MRC reports.

Unnatural deaths (violence, suicides, accidents) were just under 46,000 in 2011, the lowest since at least 1997, the earliest year for which the report gives this statistic. The highest in this period was nearly 54,500 in 2007.

Recorded diabetes deaths have been steadily climbing, reaching 21,612 in 2010. But in 2011, diabetes deaths dropped slightly. Is this an indication that diabetes deaths as a proportion of the population have reached a plateau?

The World Health Organisation defines a maternal death as a woman dying while pregnant or within 42 days of the termination of pregnancy, from any cause related to the pregnancy, but excluding accidents or "incidental causes". [5] If that's a mouthful, it's edited; the actual definition is even wordier. It's hard to estimate maternal mortality, in part because it's hard to classify and also because the number of pregnancies and live births are not easy to calculate. Nevertheless, the MRC does its best. In 2008 there were 280 maternal deaths for every 100,000 live births. This rose to 304 in 2009 and then dropped to 269 in 2011. The Health Department's target for 2014 is 252 per 100,000 live births. Whatever the real figure, maternal deaths are far too high.

References

1. Statistics South Africa. Mortality and causes of death in South Africa, 2011: Findings from death notification. http://beta2.statssa.gov.za/publications/P03093/P030932011.pdf
2. Dorrington R et al. Rapid mortality surveillance report 2012. Burden of Disease Research Unit, Medical Research Council, February 2014. http://www.mrc.ac.za/bod/RapidMortalitySurveillanceReport2012.pdf
3. Ndjeka N. 2014. Multi-drug Resistant Tuberculosis: Strategic overview on MDR-TB care in South Africa. http://www.health-e.org.za/wp-content/uploads/2014/03/Strategic_overview_of_MDR_TB_RSA.pdf
4. Violari A et al. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med 2008; 359:2233-2244. http://www.nejm.org/doi/full/10.1056/nejmoa0800971
5. World Health Organisation. Maternal mortality ratio (per 100 000 live births). http://www.who.int/healthinfo/statistics/indmaternalmortality/en/

BASIC SCIENCE AND CURE RESEARCH

The prognostic value of interleukin-6 and D-dimer levels in primary HIV infection

Gareth Hardy, HIV i-Base

Inflammatory and thrombotic markers are attracting increasing attention for their potential as predictive markers of HIV disease progression, prompted by results from the SMART study in 2008, which addressed the efficacy of structured interruptions in ART, and raised considerable interest in two of these markers. [1]

In SMART, levels of interleukin-6 (IL-6) and D-dimer in plasma at study entry were highly predictive of disease progression or subsequent death. This relationship with mortality included any cause of death, including AIDS and non AIDS-related causes such as cardiovascular disease, hepatic and renal disease or substance abuse. The striking association with all-cause mortality generated huge interest in both their prognostic significance and their potential mechanistic role in disease pathogenesis. In other studies, plasma IL-6 and D-dimer have been associated with non-AIDS related co-morbidities of HIV infection, even during effective ART. [2]

IL-6 is an inflammatory cytokine. D-dimer are small protein subunits that result from the degradation of fibrin following blood clots. Such clots form in blood vessels during cardiovascular disease and may be facilitated by inflammatory cytokines.

New results by researchers investigating the predictive value of these markers during primary HIV infection have been published in 27 March 2014 edition of AIDS. Elizabeth Hamlyn and colleagues looked at patients taking part in the SPARTAC trial to assess whether various factors were associated with levels of IL-6 or D-dimers in plasma at seroconversion, and whether plasma IL-6 and D-dimers were predictive of time to the study's primary endpoint. [3]

The SPARTAC trial assessed whether 12 weeks ART, 48 weeks ART or no ART, initiated during primary HIV infection, had any impact on the subsequent time to initiate ART or reach a CD4 count below 350 cells/mm3. Primary HIV infection was defined as being within the first 6-months of infection.

Hamlyn and colleagues assessed IL-6 and D-dimer levels in the plasma of 200 participants from the SPARTAC trial at study baseline (before initiation of ART). There was a strong correlation between the plasma levels of IL-6 and D-dimers ($r = 0.31$, $p<0.001$) at this time point. The levels of both markers in plasma increased with older age. For IL-6 this was equivalent a 19% increase per 10 year increase of age and for D-dimer a 16% increase per 10 years of age. D-dimer was also strongly associated with viral load at baseline ($p<0.001$), equivalent to a 10% increase per log(10) increase in viral load.

There was no relationship between plasma IL-6 and viral load at baseline. There was also no baseline association between either marker and CD4 count, time since seroconversion, sex/risk group, or body mass index.

Longitudinal analysis of IL-6 and D-dimer levels were then conducted for 73 individuals who were randomised to the "no ART" trial arm, for a median of 225 weeks. During this time, 48 of these patients reached the trial primary endpoint: initiation of long-term ART or a CD4 count below 350 cells/mm3. While baseline D-dimer and IL-6 levels were both associated with a shorter time to the primary endpoint in univariate analysis (hazard ratio 1.41 for IL-6 and 3.12 for D-dimer), the association between baseline D-dimer and time to end point was lost in multivariate analysis, after adjusting for baseline age, viral load and IL-6 levels. Only baseline IL-6 levels were independently associated with time to endpoint (hazard ratio 1.38).

This study demonstrates that IL-6 levels during primary HIV infection independently predict disease progression, after controlling for age, viral load and CD4 count at baseline. It should be noted that a possible association between D-dimer levels during primary infection and disease progression should not be completely ruled out, as the numbers of subjects in longitudinal analysis in this study were very small.

References

1. Kuller LH et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med, 2008, Volume 5. e203. http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050203#pmed-0050203-st001
2. Duprez DA et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One, 2012, Volume 7. e44454. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0044454
3. Hamlyn E et al. Interleukin-6 and D-dimer levels at seroconversion as predictors of HIV-1 disease progression. AIDS (2014), 28 (6): 869–874. http://journals.lww.com/aidsonline/pages/articleviewer.aspx?year=2014&issue=03270&article=00008&type=abstract

HIV reservoir: CD4 T stem cells may facilitate long-term persistence

Gareth Hardy, HIV i-Base

A report in Nature Medicine is important for suggesting that a recently discovered and little understood subset of CD4 T cells are a long-term hiding place for the HIV reservoir.

Maria Buzon and colleagues at the Massachusetts General Hospital and Massachusetts Institute of Technology, in Boston, describe their analysis of the HIV reservoir in different T cell subsets before and after several years of ART [1].

T cells are divided into different maturational subsets according to their exposure to antigen.

These are:

- naive T cells (T_{NA}), which have never encountered antigen;
- central memory T cells (T_{CM}), which have encountered antigen and undergone clonal expansion, but which are in a resting non-activated state;
- effector memory T cells (T_{EM}), which have encountered antigen and are activated, providing effector functions such as cytokine release; and
- terminally differentiated T cells (T_{TD}), which are memory cells that have reached the end of their capacity to divide.

Over the last 5 years or so, evidence has accumulated that there is an additional maturational subset of T cells with stem cell-like

properties, called stem central memory T cells (TSCM). These cells may form the first and most long-lived developmental stage of memory T cells as they can subsequently differentiate into either TCM or TEM cells. TSCM are highly resistant to cell death, they live for extremely long periods and they maintain their pool size through proliferation and self-renewal.

Considering these characteristics, Buzon and colleagues hypothesised that TSCM cells might represent a nook that harbours a significant proportion of the long-term persistent HIV reservoir. In order to investigate this, the researchers measured the abundance of HIV DNA in each of the different T cell subsets over time, and conducted detailed comparisons of the genetic sequences of this DNA, and how they related to plasma viruses before and after ART.

Before assessing the contribution of TSCM cells to the HIV reservoir, they first determined that TSCM cells from uninfected donors could be infected with lab-adapted strains of HIV. The observation that TSCM cells can be infected with HIV, has also been made recently by others [2]. Buzon et al found that HIV-1 RNA can be found in TSCM cells from HIV-positive donors who were not on ART, demonstrating that HIV infection of TSCM cells occurs in vivo.

The investigators went on to assess the contribution of TSCM to the HIV reservoir in HIV-positive subjects who had been receiving ART for a median of 7 years. The amounts of HIV DNA present per cell were significantly higher in these donors TSCM cells than in any of the other T cell subsets: TNA, TCM, TEM or TTD cells. Despite this, the overall contribution of TSCM cells to the HIV reservoir size was calculated at only 8%. Most of the contribution to the reservoir was found in TCM and TEM cells. This likely reflects the very low frequency of TSCM cells in the overall T cell pool. While the numerical contribution of TSCM to the overall reservoir may be small, this does not have bearing on the potential contribution of these cells to reservoir persistence. Indeed, the researchers found that even when, in some individuals, the reservoir size in TCM and TEM cells was relatively limited, its size in TSCM cells was sustained at generally higher levels, increasing the contribution of TSCM cells to the overall reservoir in these subjects. The researchers propose that this suggests TSCM cells are "a not necessarily large but very stable and durable component of the CD4+ T cell reservoir".

Replication-competent virus could be recovered from TSCM cells from all HIV-positive donors whose cells were used for viral outgrowth assays. These donors had been on suppressive ART for a median of 28 months. The decay rates of HIV DNA were also found to be far more stable in TSCM cells than other T cell subsets over several years of ART. HIV DNA levels were assessed in 8 subjects who had initiated ART during primary HIV infection. Samples were collected for HIV DNA assessment at a median of 1 year after initiation of ART and a second time point of 9 years after ART. Rates of HIV DNA decline in TCM and TNA cells were slightly faster than TSCM cells, while rates in TEM and TTD declined significantly faster. Furthermore the contribution of infected TSCM cells to the reservoir significantly increased from 14% at the one year post-ART time point to 24% at the nine year time point, despite the fact that these cells did not change as a proportion of the overall T cell pool. In contrast the contribution of TEM to the reservoir significantly decreased from 35% to 26% during these two time points, despite the fact that TEM cells significantly increased as a proportion of the T cell pool, from 31% to 39%. This further suggests that the HIV reservoir in TSCM is stable and outlasts the reservoir in other T cell subsets.

Lastly, in three patients who had initiated ART during chronic infection, a number of proviral *Env* sequences were observed in both TCM and TSCM cells at the beginning of ART that were still present after 4-8 years of ART. No proviral sequences identified at the beginning of ART in TNA or TTD cells were observed again at later time points. Analysis of diversity in genetic sequences of both provirus and plasma virus found that there was a close relationship between proviral DNA sequences in TSCM and TCM after 6 – 12 years of ART and plasma virus sequences from early in infection. This suggests that HIV that infects TSCM early in the course of infection is retained in these cells for very long periods of time.

While this data is based on small numbers of patients, it supports the hypothesis that the TSCM cell population is a stable and durable niche for the HIV reservoir. Furthermore, TSCM may represent an increasing relative proportion of the HIV reservoir over years of ART, as the reservoir in other T cell subsets gradually declines.

References

1. Buzon MJ et al. HIV-1 persistence in CD4+ T cells with stem cell-like properties. Nat Med, Feb 2014, Volume 20, Issue 2. Page 139-42. http://www.nature.com/nm/journal/v20/n2/full/nm.3445.html
2. Tabler CO et al. CD4+ Memory Stem Cells (TSCM) are Infected by HIV-1 in a Manner Regulated in Part by SAMHD1 Expression. J Virol, 19 Feb 2014. Epub ahead of print. http://jvi.asm.org/content/early/2014/02/13/JVI.00324-14.abstract

Update published on the first Berlin patient

Richard Jefferys, TAG

In the late 1990s, a single case report about an individual displaying control of HIV viral load for nearly two years after interrupting antiretroviral therapy (ART) drew a huge amount of publicity, including a lengthy story in the New York Times magazine by Mark Schoofs in June of 1998. [1]

The case report was ultimately published in the New England Journal of Medicine on May 27, 1999. [2]

The man was dubbed "the Berlin patient" long before the moniker was also applied to Timothy Brown, the only adult considered cured of HIV infection. This first Berlin patient was under the care of Dr. Heiko Jessen, and he was treated with the unusual combination of ddI (Videx), indinavir (Crixivan) and the cancer drug hydroxyurea (which at the time was sometimes used both to potentiate ddI and for possible immune-modulating activity). Treatment was started during acute infection and subsequently interrupted twice for short periods before being completely discontinued. During the second interruption and after discontinuation, HIV viral load levels remained undetectable based on the assay in use, which had a cut-off of 500 copies/ml. The individual was reported to have strong HIV-specific CD4 T cell and CD8 T cell responses, suggesting cellular immunity might be responsible for the salutary outcome.

The case was influential in generating the hypothesis that treatment of acute infection followed by structured treatment interruptions might boost HIV-specific CD4 T cell and CD8 T cell responses and lead to post treatment control of HIV replication. The hypothesis was tested by the research group of Bruce Walker at Massachusetts General Hospital but – after early indications of promise – the hoped for result of prolonged control of HIV after ART withdrawal was not achieved. [3, 4]

Since that time, the fate of the original Berlin patient has been somewhat mysterious, with some published papers suggesting he had been lost to follow up. [5] One of the last public updates given was by Bruce Walker at the 2003 IAS conference in Paris; Walker noted he had visited Jessen en route to the meeting, and learned that the individual was maintaining good control of viral load, but also that it had turned out that he possessed the HLA B*57 allele that is strongly associated with elite control of HIV replication in the absence of treatment.

The New England Journal of Medicine recently published a letter from Heiko Jessen, Todd Allen and Hendrik Streeck that provides an update on the case. [6]

Titled "How a Single Patient Influenced HIV Research - 15-Year Follow-up, " it reveals that the individual has mostly maintained a low viral load off ART in the intervening years, with a mean level of 2, 812 copies and only one blip to 25, 000 copies. CD4 T cell count has remained relatively stable with a mean of 729 cells although a figure accompanying the paper indicates there have been a couple of dips below 500 (one accompanying the viral load blip some time ago, and one quite recently). The letter also notes that the individual has the HLA B*57 allele and concludes: "Although the early initiation of treatment may have long-term benefits for certain patients, a likely explanation for control of viral replication in this patient is genetic background, regardless of intervention. Thus, this case represents a cautionary tale of drawing broad conclusions from a single patient.",

Since not every HIV positive person with the HLA B*57 allele becomes an elite controller, this conclusion is perhaps debatable, but it is impossible to know whether or not this individual would have ultimately maintained a low viral load even without the short course of ART. What is certain is that he is not cured of HIV infection. Unfortunately, there may be some confusion about this because a forthcoming book is promoting the idea that, along with Timothy Brown, the original Berlin patient is, in fact, cured. [8]

Although there is some uncertainty about the appropriate application of the term "functional cure, " there is no definition that allows for persistently detectable HIV viral load. The commonly used terminology for cases like that of the first Berlin patient (as has been applied to members of the VISCONTI cohort) is "post treatment controller" or "virological remission." [9]

Extended follow up will be required to define to what extent individuals in this situation are protected from disease progression.

Source

TAG Basic Science Blog. Update published on the first Berlin patient. (13 February 2014).
http://tagbasicscienceproject.typepad.com

References

1. Schoofs M. The Berlin patient. New York Times. 21 June 1998. http://www.nytimes.com/1998/06/21/magazine/the-berlin-patient.html?pagewanted=all
2. Lisziewicz J et al. Control of HIV despite the discontinuation of antiretroviral therapy. N Engl J Med 1999; 340:1683May 27, 1999DOI: 10.1056/NEJM199905273402114. http://www.nejm.org/doi/full/10.1056/NEJM199905273402114
3. Resenberg E et al. Immune control of HIV-1 after early treatment of acute infection. Nature 407, 523-526 (28 September 2000) | doi:10.1038/35035103. http://www.nature.com/nature/journal/v407/n6803/full/407523a0.html
4. Kaufmann DE. Limited Durability of Viral Control following Treated Acute HIV Infection. PLoS Medicine. 26 October 2004. DOI: 10.1371/journal.pmed.0010036.
5. Shytaj L and Savarino A. A cure for AIDS: a matter of timing? Retrovirology 2013, 10:145 http://www.retrovirology.com/content/10/1/145. http://www.retrovirology.com/content/pdf/1742-4690-10-145.pdf (PDF)
6. Walker B et al. Prospects for immunotherapy of HIV infection: lessons from acute infection. 2nd IAS Conference on HIV Pathogenesis and Treatment. Abstract 12. http://www.iasociety.org/Default.aspx?pageId=11&abstractId=11004
7. Jessen H et al. How a Single Patient Influenced HIV Research - 15-Year Follow-up. N Engl J Med 2014; 370:682-683February 13, 2014DOI: 10.1056/NEJMc1308413. http://www.nejm.org/doi/full/10.1056/NEJMc1308413
8. Holt N. Cured: How the Berlin patients defeated HIV and forever changed medical science, http://www.nathaliaholt.com/Book.html
9. Saéz-Cirión A et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI study. PLoS Pathog 9(3): e1003211. doi:10.1371/journal.ppat.1003211. http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1003211

Poor CD4 T cell recovery despite HIV suppression linked to increased morbidity and mortality

Richard Jefferys, TAG

A subset of HIV positive people who initiate antiretroviral therapy (ART) and achieve suppression of HIV replication experience poor recovery of CD4 T cell numbers.

Terms used to describe this subset of individuals include "discordant responders" and "immunological non-responders" (INRs). As yet, there is no universally accepted definition of INRs and a variety of CD4 T cell thresholds are cited in the scientific literature (e.g. persistently below 200, 250 or 350 cells despite HIV suppression). Depending on the definition, estimates of the proportion of people starting ART who can be categorised as INRs are typically around 5-20%. In studies conducted to date, the most consistently reported risk factors for this outcome are low CD4 T cell counts at the time of ART initiation and older age. Several published studies have also reported that INRs have a greater risk of morbidity and mortality compared to HIV-positive individuals with more robust CD4 T cell gains.

Two new papers now add to the evidence that INRs face an increased risk of illness and death.

Frederik N. Engsig and colleagues conducted what may be the largest evaluation of the clinical impact of blunted CD4 recovery on ART, using data from participants in the Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Research Europe (COHERE). The study was published on January 22nd in Clinical Infectious Diseases. [1]

A total of 5,550 individuals were identified who had a CD4 T cell count of less than 200 at the time of achieving viral suppression and data available for analysis after three years of follow-up. Out of this group, 835 (15%) did not experience recovery of CD4 T cells to over 200 cells. The greatest risk for this outcome was among those aged over 50 and those with the lowest CD4 T cell counts at the time when viral load was initially suppressed.

Mortality risk in this group was significantly increased compared to the participants whose CD4 T cell counts rose above 200 cells,

with a hazard ratio of 2.60 (95% confidence interval 1.86-3.81) - a 2.6-fold increase in risk. The estimated 5-year cumulative mortality was 11.8% in those with CD4 counts <200 cells at the end of the follow up period compared with 4.1%, 2.2% and 2.2% in those with CD4 counts of 201-350, 351-500 and >500 cells, respectively. The researchers note that these results are in accordance with two prior smaller studies, which reported a 2.69-fold and 3.4-fold greater risk of mortality among INRs.

The second paper, published in PLoS One, involves an analysis of the EuroSIDA cohort by Alexander Zoufaly and colleagues. [2]

The criteria for designating INRs in this study was different, being based on the lack of a CD4 T cell increase from the baseline measurement among a cohort starting with 350 cells or less (rather than the failure to crest a specific threshold). A statistically significant, close to 2-fold increase in the risk of fatal and non-fatal non-AIDS events was documented, although when the analysis was adjusted to take into account current CD4 T cell count this was attenuated to a statistical trend suggesting a 1.43-fold increase. Notably, the researchers point out that the elevated risk did not appear to diminish with longer duration of viral suppression. The smaller difference in risk found in this study is likely related to the difference in definition of INRs, and the fact that the majority of participants were in the 200-350 CD4 T cell range at the starting point for the analysis.

The authors of both papers highlight the current lack of any interventions to reduce the risk of morbidity and mortality among INRs. Engsig and colleagues write: "since 15% of treated HIV positive individuals have CD4 count <200 cells/mm3 after long-term viral suppression, prognosis of such patients is a major concern… virally suppressed patients with low CD4 counts should be monitored closely for diseases not conventionally considered HIV-related, especially non-AIDS defining cancers and liver diseases." On the subject of potential therapies, the Zoufaly paper adds: "to date, strategies to directly influence immune reconstitution by adding interleukin-2 or by modifying cART regimens have failed to show benefit over viral suppression alone; therefore new strategies perhaps aiming at other mechanisms to boost functional CD4 cells or decreasing the levels of immune-activation (e.g. interleukin-7, probiotics) need to be tested in people who show incomplete immune reconstitution despite sustained viral suppression."

Unfortunately, as noted in the article on CD4/CD8 ratios (see below), a clinical evaluation of IL-7 in INRs appears unlikely to happen anytime soon due to the recent bankruptcy of the original manufacturer. TAG maintains a listing of clinical trials for people with suboptimal immune reconstitution despite HIV suppression [3], derived from the clinicaltrials.gov database, but currently the page offers a dismayingly limited array of options: there are a total of seven trials, and in only one case is there a smidgeon of published evidence that the intervention could be beneficial. And that intervention, umbilical cord mesenchymal stem cells, does not seem well suited to large-scale manufacturing. [4]

There is certainly interest in the scientific community in pursuing studies of new approaches, including a variety of anti-inflammatory/anti-immune activation strategies and probiotic/prebiotic combinations (based on promising findings in macaques [5]), but the current research funding environment is not helping efforts to translate these ideas into the clinic. Recent updates from the National Institutes of Health indicate that paylines for research grants are at historic lows: for established investigators, only the top 8% of grant proposals are being funded, and for new investigators, the top 12%. [6]

The consequences of a slowdown in scientific progress will be profound, and INRs are an example of a population with a great deal at stake.

Source

TAG Basic Science Blog. Poor CD4 T cell recovery despite HIV suppression linked to increased morbidity and mortality. (06 February 2014).

http://tagbasicscienceproject.typepad.com

References

1. Engsig FN et al. Long-term mortality in HIV positive individuals virally suppressed for more than three years with incomplete CD4 recovery. Clin Infect Dis. (2014). doi: 10.1093/cid/ciu038. (22 January 2014). http://cid.oxfordjournals.org/content/early/2014/01/22/cid.ciu038.abstract
2. Zoufaly A et al. Immuno-Virological Discordance and the Risk of Non-AIDS and AIDS Events in a Large Observational Cohort of HIV-Patients in Europe. PLoS ONE 9(1): e87160. doi:10.1371/journal.pone.0087160. (31 January 2014). http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0087160
3. TAG. Clinical trials for people with suboptimal immune reconstitution despite HIV suppression. (Last updated 06 February 2014). http://www.treatmentactiongroup.org/basic-science/publications/clinical-trials-people-suboptimal-immune-reconstitution-despite-hiv-suppression
4. Zheng Z et al. Safety and immunological responses to human mesenchymal stem cell therapy in difficult-to-treat HIV-1-infected patients. AIDS (2013) 27(8);1283–1293. doi: 10.1097/QAD.0b013e32835fab77. (15 May 2013). http://journals.lww.com/aidsonline/Abstract/2013/05150/Safety_and_immunological_responses_to_human.11.aspx
5. TAG Basic Science Blog. Probiotic/prebiotic supplement combination shows benefits in SIV-infected pigtailed macaques. (15 March 2013). http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2013/03/probioticprebiotic-supplement-combination-shows-benefits-in-siv-infected-pigtailed-macaques.html
6. NIAID paylines. (Updated 28 January 2014). http://www.niaid.nih.gov/researchfunding/paybud/pages/paylines.aspx

The relevance of the CD4/CD8 ratio in the ART era

Richard Jefferys, TAG

An inversion of the normal ratio between CD4 and CD8 T cells was noted in the very first case reports of individuals with AIDS, before HIV was even identified.

Although a number of studies subsequently reported an association between the CD4/CD8 ratio and risk of disease progression, CD4 T cell counts were more extensively researched and became the most commonly used surrogate marker of immune system health in HIV-positive people. In recent years, data has emerged from cohort studies of very elderly HIV-negative people indicating that, in this population, the CD4/CD8 ratio is a strong predictor of the risk of aging-associated diseases and mortality. This new information prompted the research group of Sergio Serrano-Villar at the University Hospital Ramón y Cajal in Madrid to evaluate whether measurement of the CD4/CD8 ratio may provide information about the risk of morbidity and mortality in HIV-positive people in the current era of antiretroviral therapy (ART).

Last year, Serrano-Villar and colleagues published preliminary studies showing associations between the CD4/CD8 ratio and levels of immune activation [1] and markers of immune system

aging [2] (immunosenescence) in HIV infection. In two new papers published in HIV Medicine and PLoS One, they now extend these findings and report statistically significant associations between the CD4/CD8 ratio and markers of age-associated disease and the clinical outcomes of non-AIDS-related morbidity and mortality in HIV-positive people. [3, 4]

The PLoS One study assesses the link between the CD4/CD8 ratio and several dissimilar non-AIDS diseases in people on ART, and reports a significant association in each case. Separate analyses of participants with low CD4 nadirs (<200 cells) and those with good CD4 recovery on ART (to >350 cells) find that CD4/CD8 ratios remain independently associated with non-AIDS events in each subgroup.

In discussing the implications of their findings, the researchers write: "patients with failure to increase the CD4/CD8 ratio despite achieving full immunovirological response to ART might benefit from screening programs and aggressive management of concomitant risk factors for age-associated disease." They also note that, since there appears to be a relationship between immune activation and the CD4/CD8 ratio, such individuals may be prime candidates for inclusion in clinical trials of interventions that aim to reduce immune activation and associated adverse clinical outcomes. However, several limitations to the study are acknowledged, and the authors stress that: "before using the CD4/CD8 ratio as a surrogate of serious non-AIDS-related illnesses, these results should be reproduced in larger and prospective studies."

As it currently stands, there are very few reports of therapies capable of improving low CD4/CD8 ratios in HIV-positive people on ART. IL-7 increases both CD4 and CD8 T cell numbers, and according to a new study published in PLoS Pathogens, may reduce markers of inflammation, but the clinical impact of this cytokine has yet to be evaluated. [5]

A further complication is that the company behind IL-7, Cytheris, recently went bankrupt, leaving the rights to its development for HIV in the hands of the French Agence Nationale de Recherche sur le SIDA (ANRS) and a small biotech named Cognate Biosciences. SB-728-T, a gene therapy under development by Sangamo Biosciences, has been reported to significantly improve CD4/CD8 ratios in people on ART, but the duration of the effect is unclear and the company appears uninterested in developing the approach for people with suboptimal immune reconstitution (their focus is on attempting to achieve control of HIV replication after ART interruption). The therapy is also complex to administer because it involves the extraction, expansion and genetic modification of CD4 T cells, followed by reinfusion. A letter from TAG and many other community activists and organizations asking the company to continue to study the potential of SB-728-T to promote immune reconstitution fell on deaf ears. [6]

Although not directly connected to the work of Sergio Serrano-Villar and colleagues, another study on the topic of the CD4/CD8 ratio in HIV infection was published online by the Journal of Immunology this past Monday. [7]

Marcus Buggert and a Swedish research team used a bioinformatics approach to explore the connections between several of the laboratory measures used to monitor HIV disease progression (including CD4 count and CD4/CD8 ratio) and a large suite of T cell markers that are perturbed by HIV infection (including activation, exhaustion and immunosenescence markers). Focusing primarily on untreated HIV infection, the researchers find that the CD4/CD8 ratio is the best predictor of the combined pathological changes to the T cell immune system that occur in HIV-positive people compared to uninfected controls. The paper concludes: "these findings are of particular interest to future therapy or cure studies, in which simple measurements are required to monitor ongoing pathological events of the T cell repertoire in HIV-infected subjects."

Source

TAG Basic Science Blog. The Relevance of the CD4/CD8 Ratio in the Antiretroviral Therapy Era. (05 February 2014).

http://tagbasicscienceproject.typepad.com

References

1. Serrano-Villar S et al. The CD4/CD8 ratio in HIV-infected subjects is independently associated with T-cell activation despite long-term viral suppression. Journal of Infection 66(1):;57-66 (January 2013). http://www.journalofinfection.com/article/S0163-4453(12)00281-2/abstract
2. Serrano-Villar S et al. The CD4/CD8 ratio as a marker T-cell activation, senescence and activation/exhaustion in treated HIV-infected children and young adults. AIDS 27(9);1513-1516. (1 June 2013). doi: 10.1097/QAD.0b013e32835faa72. http://journals.lww.com/aidsonline/Abstract/2013/06010/The_CD4_CD8_ratio_as_a_marker_T_cell_activation,.18.aspx
3. Serrano-Villar S et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. HIV Med. 2014 Jan;15(1):40-9. doi: 10.1111/hiv.12081. Epub 2013 Sep 6. http://onlinelibrary.wiley.com/doi/10.1111/hiv.12081/abstract
4. Serrano-Villar S et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. PLoS ONE 9(1): e85798. doi:10.1371/journal.pone.0085798. (30 January 2014). http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0085798
5. Sereti I et al. Decreases in colonic and systemic inflammation in chronic HIV infection after IL-7 administration. PLoS Pathogens, 30 January 2014. doi: 10.1371/journal.ppat.1003890. http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1003890
6. TAG et al. Letter to Sangamo on its development for zinc finger functional cure. (12 Jauary 2102). http://www.treatmentactiongroup.org/cure/2012/sangamo-letter-zinc-finger-functional-cure-development
7. Buggert M et al. Multiparametric bioinformatics distinguish the CD4/CD8 ratio as a suitable laboratory predictor of combined T cell pathogenesis in HIV infection. The Journal of Immunology. 03 February 2014. doi: 10.4049/jimmunol.1302596. http://www.jimmunol.org/content/early/2014/01/31/jimmunol.1302596.abstract

First human trial of AAV as a delivery vehicle for HIV neutralising antibodies gets underway

Richard Jefferys, TAG

Over the past few years there has been growing interest in the use of adeno-associated virus (AAV) as a vehicle for generating anti-HIV neutralizing antibodies in humans.

The approach is different from traditional vaccination, in that AAV is used essentially as a gene therapy: the AAV vector is designed to take up residence in cells and then act as a factory for churning out broadly neutralising antibodies against HIV (genes that encode these antibodies are inserted into the vector).

This novel idea may be able to circumvent the challenging problem

of inducing the production of broadly neutralising antibodies with traditional vaccines, and could potentially offer significant protection against HIV acquisition.

As covered previously on the blog, there are two main research groups working on AAV-based HIV prevention. [1]

The laboratory of David Baltimore has named their approach vectored immunoprophylaxis (VIP) and published a study in Nature Medicine demonstrating protection against vaginal HIV transmission in a humanised mouse model. [2] The study was supported by the National Institute of Allergy and Infectious Diseases, who issued a press release drawing attention to the findings). [3]

Meanwhile Philip Johnson and colleagues at the Children's Hospital of Philadelphia are collaborating with the International AIDS Vaccine Initiative (IAVI) on a phase-1 clinical trial of an AAV vector encoding the HIV neutralising antibody PG9, and, according to clinicaltrials.gov, the trial started recruiting participants last month. [4]

This is a major milestone for the research, as there were many challenges associated with obtaining regulatory approval for a human trial and Johnson and IAVI have been working toward this goal for many years. The estimated date for completion of the study is January 2016.

Source

TAG Basic Science Blog. First human trial of AAV as a delivery vehicle for HIV neutralising antibodies gets underway. (11 February 2014).

http://tagbasicscienceproject.typepad.com

References

1. TAG Basic Science Blog. David Baltimore and vectored immunoprophylaxis. (18 January 2013).
2. Balazs AB et al, Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission, Nature Medicine (2014) doi:10.1038/nm.3471. Published online 09 February 2014.
3. US NIH press release. NIH-funded researchers use antibody treatment to protect humanized mice from HIV. (11 February 2014). http://www.niaid.nih.gov/news/newsreleases/2014/Pages/HIV-Humanized-Mice.aspx
4. ClinicalTrials.gov. A phase 1, randomized, blinded, dose-escalation study of rAAV1-PG9DP recombinant AAV vector coding for PG9 antibody in healthy male adults. http://clinicaltrials.gov/ct2/show/NCT01937455

ON THE WEB

Conferences

CROI 2014 - online resources and reports

Community video interviews from CROI 2104 (IFARI)

Currently there 36 videos from Fred Schaich excellent video interviews, produced for the community organisation IFARI.

The format pairs an experienced activist to interview one or more leading researchers on key themes and studies presented at the conference, with a non-technical discussion about the implications in practice.

http://www.youtube.com/user/AccessHIV

All videos are linked from this page:

http://www.youtube.com/user/AccessHIV/videos?view=0&sort=dd&shelf_id=1

The videos are more difficult to navigate on the IFARI site but can be viewed from this page and then select 'newer posts".

http://accesshiv.org/2014/page/9/

CROI 2014 - BHIVA feedback meetings

Each year, immediately after CROI, BHIVA organises several meetings to report key research from CROI, arranged in four themes.

- Antiretroviral treatment strategies and new drugs
- Complications of HIV disease or treatment
- HIV/hepatitis C co-infection
- HIV transmission, prevention and testing

The slide-sets from the Edinburgh workshop are now online.

http://www.bhiva.org/BestofCROI2014.aspx

Online articles

400 vs 600 mg efavirenz study published in the Lancet

The Lancet, Early Online Publication, 10 February 2014 doi:10.1016/S0140-6736(13)62187-XCite

Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2813%2962187-X/abstract

FUTURE MEETINGS

Conference listing 2014/15

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

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

15th International Workshop on Clinical Pharmacology of HIV Therapy and Hepatitis Therapy

19-21 May 2014, Washington DC

http://www.virology-education.com

International Workshop on Antiviral Drug Resistance

3-7June 2014, Berlin, Germany

http://www.informedhorizons.com/resistance2014

10th HIV and Hepatitis Coinfection Workshop

12 - 13 June 2014, Paris, France

http://www.virology-education.com

6th International Workshop on HIV Paediatrics

18-19 July 2014, Melbourne

http://www.virology-education.com

20th IAS World AIDS Conference

20-25 July 2014, Melbourne, Australia

http://www.aids2014.org

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

http://www.hiv11.com

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

23 - 26 February 2015, Seattle

http://www.croi2014.org

HIV i-BASE

HIV i-Base is an HIV positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.

http://www.i-base.info

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

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

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV
- HIV testing and risks of sexual transmission

The site also includes a web-based Q&A section for people to ask questions about treatment.

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

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

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

i-base
0808 800 6013

HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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

STANDING ORDER DONATION **THANK YOU FOR YOUR SUPPORT**

Title: _____ First Name _____ Surname _____

Address _____

_____

_____ Postcode _____

Email _____ @ _____

Telephone (s) _____ _____ _____

Please pay HIV I-Base £ _____ each month until further notice

Please debit my account number _____

Name of account (holder) _____ Bank sort code _____/_____/_____

Starting on _____/_____/_____ (DD/MM/YY)

Signature _____ Date _____/_____/_____ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

_____

_____

Please complete the above and return to: HIV i-Base, 57 Great Suffolk Street, London SE1 0BB

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
Sort Code: 60-12-14. Account Number: 28007042)

ONE-OFF DONATION

I do not wish to make a regular donation at this time but enclose a one-off cheque in the sum of £ _____ .

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrpahy Book £ _____.

GIVE AS YOU EARN

If your employer operates a Give-As-You-Earn scheme please consider giving to i-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

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

REFUNDS FROM THE TAX MAN

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

However you chose to donate to i-Base,
we would like to thank you very much for your support.

REG IN ENGLAND WALES WITH LIMITED LIABILITY REG NO 3962064 CHARITY REG 1081905

HIV i-Base

www.i-base.info

Southern African HIV Clinicians Society

www.sahivsoc.org

HIV i-Base, 4th Floor, 57 Great Suffolk Street, London, SE1 0BB.

T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489