ISSN 1472-4863

hiv treatment bulletin

htb: volume 18 number 9/10

september–october 2017

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Published by HIV i-Base

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HIV TREATMENT BULLETIN

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

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

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

EDITORIAL

This issue of HTB starts with two evidence reviews.

The first is an analysis of the data used in a recent Cochrane review of HIV drugs used during pregnancy. The BMJ, in addition to publishing the review, also produced worrying 'rapid recommendations' that challenged current guidelines, including those from WHO and BHIVA.

The i-Base article from Polly Clayden shows how easily the Cochrane methodology can produce misleading results. Far from being trustworthy, the BMJ initiative has more likely led to harm and concern. The BMJ were also quickly challenged both by key researchers and BHIVA (whose response we also publish later in this issue).

A second i-Base review provides an overview of 20 years of accumulating evidence to support the statement that ART effectively prevents HIV sexual transmission. But while many prominent doctors, scientists and healthworkers, including the US CDC, now endorse the Untedectable = Untransmittable (U=U) statement, reviewing the compelling the evidence is just as essential for those who are less convinced.

This issue of HTB also includes further conference reports on ART and PrEP from IAS 2017 in Paris and on advances in cure research from a related meeting on HIV and cancer.

And PrEP features in other articles, including the regional differences in the UK for accessing PrEP: yes, no and maybe depending on whether you live.

Plus journal reviews on OI prophlaxis and HIV and kidney disease and links to an impressive issue of the US community publication RITA focussed on HIV and drug adherence and a UK review of DFIDs international HIV funding.

And we cover the most exciting news for global HIV: a new pricing agreement that will enable treatment in low- and middle-income countries with new dolutegravir-based fixed dose combinations at an annual cost per person of around US $75.

Supplements with this issue

Two new patient guides are highlighted as supplements to the issue of HTB.

http://i-base.info/uk-guide-to-prep-2017

UK guide to PrEP (September 2017)

The third edition of this guide coincides with the upcoming IMPACT trial that is due to start this month.

This 24-page A5 booklet includes new information about PrEP and women, and PrEP and trans and non binary people. Also about access to PrEP in the UK.

PrEP in Scotland (September 2017)

New PrEP guide produced for people who are accessing PrEP in Scotland.

Please order these guides from Julian Heng:

julian.heng@ggc.scot.nhs.uk

i-Base 2017 appeal: we need your help....

This year, the i-Base 2017 appeal was launched to respond to larger changes in our funding.

Your regular support can make a big difference.

We could reach our £100,000 target if:

- 500 people support i-Base with £9.00 a month and...
- 1000 people support with £4.50 a month.

Please become one of our subscribers that help.

- i-Base continues to provide all services free, including free community publications for all UK clinics.
- The i-Base website gets more than 400,000 users every month. And last year the i-Base Q&A service answered almost 6,000 individual questions from HIV positive people.
- HIV services are being dramatically cut across the UK, and much of the voluntary sector is vulnerable, including i-Base.

http://i-base.info/donate

If you would like to help i-Base in other ways, or would like more information about this i-Base appeal, please contact Suzanne Thompson or Simon Collins at HIV i-Base on 020 8616 2210.

Thank you for your help.

EVIDENCE REVIEW

Experts disagree with controversial BMJ support for older HIV drugs in pregnancy

Polly Clayden, HIV i-Base

Two expert groups have announced that they do not support BMJ Rapid Recommendations favouring a zidovudine and lamivudine-based ART regimen over one that includes tenofovir and emtricitabine in HIV positive pregnant women.

On 21 September 2017, BMJ Open published a controversial analysis and accompanying clinical practice guideline on ART in HIV positive women concluding with low certainty evidence that: "tenofovir/emtricitabine is likely to increase stillbirth/early neonatal death and early premature delivery compared with zidovudine/lamivudine". [1, 2]

The guideline was informed by a systematic review, but the conclusion relies on the results of the PROMISE study. [3] The authors of the review, Siemieniuk et al, note: "The evidence for a likely increase of early premature delivery and neonatal mortality with tenofovir and emtricitabine comes mostly from a single study".

Although several large observational studies do not support this recommendation, nor do previous systematic reviews [4–7], Siemieniuk et al did not consider this evidence to be of sufficiently high quality to inform their recommendations.

The PROMISE investigators swiftly submitted a response to the BMJ disagreeing with the Siemieniuk interpretation of their data, stating: "We are the primary authors of the PROMISE study cited as the evidence for the recommendation in this paper; we disagree with the final conclusion based on our data." [8]

The BHIVA pregnancy guideline writing group also published a response on the BHIVA website in which they write: 'We do not support the BMJ recommendations "ART in pregnant women living with HIV: a clinical practice guideline". [9]

PROMISE study

PROMISE compared zidovudine/single-dose nevirapine (AZT-alone) to lopinavir/ritonavir (LPV/r)-based ART either with AZT/lamivudine (AZT-ART) or tenofovir disoproxil fumarate/emtricitabine (TDF-ART) for the prevention of vertical transmission in women with CD4 cell count >350 cells/mm^3.

The study was enrolled during two periods. The comparisons with TDF-ART were made in women who were randomised between the three study arms, in the second period of the study.

During the first year and a half of enrolment (when 65% of participants enrolled) only hepatitis B (HBV)-coinfected women were randomised to TDF-ART vs AZT-ART vs AZT-alone.

Only after a protocol modification, in the second year and a half of enrolment (when 35% of participants enrolled), were all participants randomised to all three arms, irrespective of HBV. As a result, PROMISE only compared TDF-ART with AZT-ART or AZT-alone in the second period of the study.

This comparison found a lower rate of very preterm delivery (<34 weeks) in the AZT-ART arm vs the TDF-ART arm (2.6% vs 6.00%,

p=0.04), leading to a difference in early infant mortality (<14 days), in the respective arms (0.6% vs 4.4%, p=0.001). Over 40% of very preterm deliveries and 47% of early infant deaths occurred in the second period of enrolment.

Notably there was no significant difference between the TDF-ART and AZT-alone arms in very preterm delivery (6.0% vs 3.2%, p=0.10) or early infant mortality (4.4% vs 3.2%, p=0.43). There was also an imbalance in neonatal deaths in the AZT-ART arm: 88% (15/17) of which occurred during the first period of the trial and the remaining 12% during the three-arm comparison. So, it might be that the AZT-arm had artificially low rates of both events and not that the TDF-ART arm had increased the risk.

PROMISE did not combine analysis of stillbirth and early infant mortality and there were no differences in rates of stillbirth and spontaneous abortion in the AZT-alone, AZT-ART and TDF-ART arms.

It is also important that the ART regimens used in PROMISE were LPV/r-based and the investigators noted that there are inconsistent findings on the association of PI-based ART and preterm delivery.

As well as this, LPV/r was given with a dose increase during the third trimester to 600/150 mg twice daily (standard dose is 400/100 mg twice daily) in PROMISE to overcome decreased plasma levels in late pregnancy. A potential explanation for the differences seen might be a pharmacokinetic interaction between LPV/r and TDF resulting in increased plasma and intracellular levels of tenofovir.

The investigators emphasised that because the study only included PI-based ART, data could not be generalised to TDF-based ART in regimens with other classes of ARVs such as the efavirenz (EFV)-based ART regimen currently recommended in pregnancy by the WHO.

PROMISE investigators response

In their response, published in BMJ Open on 19 September, the PROMISE investigators stress that they did not analyse stillbirth with early neonatal death in their study. [8] They note that: "Contrary to the authors' statement, the pathophysiology of stillbirth and early neonatal death are not necessarily the same and hence the PROMISE team did not feel it was appropriate to combine these endpoints". They add that the rates of spontaneous abortion and stillbirth were not significantly different between the three arms.

In the BMJ review, Siemieniuk et al combined data on stillbirth/early infant death from two hepatitis B mono-infection studies with very few events; neither included HIV positive pregnant women, which the PROMISE investigators also query.

And they explain that both AZT-ART and TDF-ART were associated with increased preterm delivery (<37 weeks) compared to AZT-alone and there was no significant difference in rate of preterm delivery between the AZT-ART and TDF-ART arms during the second period of the study.

It was only when they evaluated very preterm delivery (<34 weeks) that they observed a difference, with a higher rate in the TDF-ART compared to AZT-ART arm, p=0.04. But the rate of very preterm delivery in the TDF-ART was not significantly different than AZT-alone arm, p=0.10.

They suggest that both ART regimens might be associated with preterm delivery, with AZT-ART increasing this between 34–36 weeks and TDF-ART possibly increasing very preterm delivery <34 weeks. But the PROMISE investigators were not willing to draw a definitive conclusion from these data.

They also note that the AZT-ART arm appeared to have a very low rate of infant mortality during the second period of the study when it was compared to TDF-ART.

And they raise concerns about potential pharmacokinetic interactions between LPV/r and TDF.

Overall the PROMISE investigators felt it was inappropriate to use their study to make definitive conclusions on use of TDF-ART in pregnancy. They emphasise again that, as the study only included PI-based ART, it cannot be generalised to TDF-ART with third agents such as the widely used and recommended EFV-based regimen.

They note the recent study by Zash et al from Botswana, which compared birth outcomes, including preterm delivery and neonatal death, among HIV-positive women. [7] In this study, all other ART regimens (including AZT/3TC/LPV/r) were associated with higher risk of adverse outcome; increased risk of preterm birth, very preterm birth and neonatal death than EFV/TDF/FTC.

In conclusion, they write: "While the PROMISE team strongly supports further evaluation of the safety of ART regimens in pregnancy for the woman and her infant in order to find the optimal ART regimen, the PROMISE team does not agree that the PROMISE trial results support a recommendation against using a TDF-based ART regimen in pregnancy".

BHIVA

The BHIVA recommendation, published on 21 September 2017, is to continue or to start TDF or ABC with FTC or 3TC as an NRTI backbone in pregnancy. [9]

The statement also addresses the use of TDF/FTC as PrEP saying: "We do not think this data should influence use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential".

The BHIVA group notes that that UK guidelines do not recommend the use of LPV/r for the treatment of HIV in adults, including pregnant women, and certainly not at the higher dose used in the third trimester in PROMISE. They also explain that PROMISE looked at outcomes in women starting ART. Most women in UK will conceive on ART, most commonly with TDF/FTC backbone and PROMISE does not address that group.

As both arms received LPV/r the BMJ panel suggest that TDF/FTC is the cause of the difference. The BHIVA group also highlight data showing increased levels of both drugs when co-administered at standard doses.

They cite the Zash et al study that included 11,932 HIV positive women, where preterm birth, very preterm birth, small and very small size for gestational age, stillbirth, and neonatal death were evaluated. In this large cohort, the risk for any adverse or severe adverse birth outcome was lowest among infants exposed to TDF/FTC/EFV, and the highest risk of adverse outcomes with observed in women receiving LPV/r-based regimes.

As well as the recommendation to continue or start TDF or ABC with FTC or 3TC as the NRTI backbone (Grading: 2C), BHIVA recommend that the third agent should be one of the following: EFV, raltegravir, rilpivirine, ritonavir-boosted darunavir or ritonavir-boosted atazanavir, as recommended in BHIVA adult treatment guidelines.

The BHIVA recommendation ... is to continue or to start TDF or ABC with FTC or 3TC as an NRTI backbone in pregnancy.

On PrEP they add: "the group does not think this data should influence decisions to use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential".

C O M M E N T

Both the PROMISE investigators and the BHIVA group responses clearly disagree with the BMJ panel. Both responses explain their reasons and are worth reading in full.

A few other things are notable in the Siemieniuk et al review.

Firstly, Siemieniuk et al emphasise the trustworthiness of their findings a couple of times: "Our approach contrasts with a prior effort that pooled randomised controlled trials (RCTs) with far less trustworthy observational studies" and "The BMJ Rapid Recommendation initiative attempts to provide timely, unconflicted and trustworthy recommendations for clinical situations where new evidence might change practice". It is not clear if they are implying that previous systematic reviews, the conclusions of the WHO and other guideline panels are then conflicted and untrustworthy.

Secondly, both the PROMISE and BHIVA responses acknowledge that observational data generally produce a lower grade of evidence compared with data from RCTs. But the PROMISE investigators rightly point out that it is improbable that there will be other RCTs and there have been a number of observational studies suggesting that TDF-ART is safe in combination with NNRTIs. But Siemieniuk et al conclude that TDF might not be safe based on one RCT with that is difficult to interpret as noted by the PROMISE investigators.

In their discussion of the Nachega et al systematic review (the "prior effort" above), Siemieniuk et al say that it "assumed equal credibility in randomised and observational studies" and "pooled RCTs and observational studies which, given the much higher certainty associated RCTs, we consider inadvisable and, indeed, inappropriate". [6] But Nachega et al explain in their methods that they assessed the quality of evidence using the GRADE approach which considers the difference between observational data and RCTs.

Thirdly, Siemieniuk et al also state that other studies have found "that TDF-based cART regimens are safe for women and their infants." But neither of the studies they mention – Nachega et al and Mofenson et al – draw an unqualified conclusion that TDF is safe. [5, 6] Both discuss PROMISE and the potential problems with interpretation. They respectively conclude: "TDF-based ART in pregnancy appears generally safe for women and their infants.

However, data remain limited and further studies are needed, particularly to assess neonatal mortality and infant growth/bone effects." And: "Although additional surveillance is important, given the available safety data, the benefits of PrEP use for prevention by pregnant/lactating women at high risk of HIV acquisition (and its accompanying increased risk of mother to child HIV transmission) appear to far outweigh the potential risks of foetal, infant and maternal TDF exposure."

Finally, the selection of studies in non-pregnant adults by Siemieniuk et al seems strange given the changes in maternal physiology that occur in pregnancy and the potential to alter absorption, distribution, and elimination (and in turn toxicity) of antiretrovirals.

Most problematic is the inclusion data from studies that included mostly men (using an endpoint of 26 weeks after enrolment to approximate the timeline of a woman starting ART in the second trimester).

It makes for curious reading of analyses of "maternal" clinical and laboratory adverse events when three out of four RCTs were conducted in non-pregnant adults.

Far from being trustworthy, the BMJ paper used inappropriate methodology to produce recommendations that would likely produce harm.

A similarly flawed Cochrane review was recently rapidly criticised for concluding that highly effective hepatitis C drugs had no proven benefit on reducing serious long-term outcomes. [10]

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EVIDENCE REVIEW

The evidence for U=U: why negligible risk is zero risk

Simon Collins, HIV i-Base

Over the last year, hundreds of HIV organisations, including the US Centre for Disease Control (CDC), have joined a new campaign to endorse the statement that HIV transmission does not occur when viral load is undetectable on ART.

And while the dramatic impact of ART on reducing HIV transmission has been known for a long time, saying ART stops this completely is new.

This change is especially important given that prejudice and discrimination against HIV positive people is still widespread. So while it is easy to simply answer "no" to the question of whether someone with an undetectable viral load is still infectious, it is more complicated to explain why.

This article summarises selected key studies from 20 years of accumulating evidence that should directly challenge the prejudice and fear of HIV that is still widespread.

U=U: Undetectable = Untransmittable (or Uninfectious)

Launched in 2016, the Undetectable = Untransmittable (U=U) campaign is based on the following statement: "A person living with HIV who has undetectable viral load does not transmit HIV to their partners". [1, 2]

The statement has been endorsed by more than 350 HIV organisations from 34 countries, including by leading scientific and medical organisations such as the International AIDS Society (IAS), UNAIDS, and the British HIV Association (BHIVA).

The support for the statement is also remarkable given that science is not able to prove a negative - ie that something will not happen.

Instead, people who claim that HIV is transmittable when viral load is undetectable, should be challenged to prove it.

20 years of accumulating evidence

The scientific approach to understanding the world usually involves three stages.

1. Observing something.
2. Deciding on one or more hypotheses that might explain it.
3. Testing any theory in a suitable experiment.

The strength of this approach is that a good study, by definition, should be repeatable. If the results are true and not by accident, other researchers should be able to repeat the study and get similar and consistent results each time.

The evidence supporting U=U includes different types of research spanning observational studies, randomised trials, systematic reviews and expert opinion. See Table 1.

Key stages in this timeline include:

- 1998: observations that triple therapy ART reduced transmission.
- 1998: expert opinion that risk would be reduced (including based on reviewing evidence related to the details of this protection).
- 2000 – 2005: prospective observational studies and related research (Rakai cohort and others).
- 2008: further expert opinion and evidence review (Swiss Statement).
- 2011: first evidence from a randomised clinical trial (HPTN 052).
- 2014 – 2017: further prospective observational studies (PARTNER and Opposites Attract) - the first studies to provide data about risks for gay men.
- 2016 – 2017: further expert opinion (U=U campaign).

Each of these studies is now explained in more detail.

Early evidence: mother-to-child and Ugandan heterosexual couples

A remarkable report in July 1998 provided some of the first clinical evidence for the impact of viral load on HIV transmission.

At the IAS conference held in Geneva, Dr Karen Beckerman reported on a small cohort of HIV positive women in San Francisco who had used triple therapy during pregnancy. Instead of the 30% mother-to-infant transmissions reported before ART, or the 10% seen with AZT monotherapy, triple therapy reduced transmissions to approaching zero. [3]

Although this study reported on vertical rather than sexual transmission it provided clinical results showing that an undetectable viral load stopped a much higher risk of transmission.

Then later that year, the December 1998 update to the US DHHS guidelines, included "possibly decreasing the risk of viral transmission" as an additional reason for starting early ART. [4]

These expert guidelines noted the lack of direct evidence supporting this statement and emphasised that condoms should still be used even with undetectable viral load – but this inclusion in the 100-page document from leading US doctors this was important.

One of the next key studies provided direct evidence linking viral load with risk of HIV sexual transmission. This was a prospective observational cohort study in 415 serodifferent heterosexual couples in Rakai, Uganda, where one partner was HIV positive and the other was HIV negative. The study, by Thomas Quinn and colleagues was published in the New England Journal of Medicine in 2000. [5]

After median follow-up of 22 months, the risk of HIV transmission was not only clearly linked to higher viral load. No transmissions were reported among the 51 couples where the HIV positive partner had viral load below 1500 copies/mL.

Several details of the Rakai study are important. It was before ART was available and condom use was low. It found that transmissions rates were similar for men and women and that other STIs didn't affect HIV risk. It also reported highly significant impact from

Table 1: Key selected evidence supporting U=U

Study	Study details	Results	Date	Reference
San Francisco cohort	Clinical results from small cohort of HIV positive women using triple ART during pregnancy.	Transmission from mother to baby was reduced to approaching zero.	1998	Beckerman K et al. [3]
DHHS guidelines	Expert opinion included in evidence-based guidelines.	Theoretical plausibility of reducing transmission risk was used as a factor for early ART.	1998	DHHS guidelines. [4]
Ugandan cohort (Rakai)	Prospective observational cohort in ~ 400 serodifferent couples.	Zero transmissions when viral load was less than 1500 copies/mL.	2000	Quinn TC et al. [5]
Spanish cohort	Prospective observational study in 393 heterosexual discordant couples enrolled from 1991 to 2003 where the negative partner became HIV positive.	Zero transmissions in couples where the HIV positive partner was on ART with undetectable viral load. Cautions emphasised good adherence and no STIs.	2005	Castella A et al. [6]
Swiss Statement	Expert opinion and evidence review of >25 smaller studies looking at impact of ART on risk factors for HIV transmission.	Concluded that transmission would not occur undetectable with viral load.	2008	Vernazza P et al. [7]
HPTN 052	1763 serodifferent heterosexual couples randomised to immediate or deferred ART. Although condom use was high the impact of ART was highly significant.	All infections occurred in people with detectable viral load: n=17 in the deferred ART group and one early infection in the ART group before VL was undetectable. Follow-up reported out to four years.	2011	Cohen M et al. [8, 9]
PARTNER	Prospective observational European study in ~900 serodifferent couples who were not using condoms.	Final results reported zero transmissions after more than 58,000 times couples had sex without condoms when viral load was undetectable <200 copies/mL.	2014 (interim). 2016 (final)	Rodgers A et al. [10, 11]
Opposites Attract	Prospective observational study in 358 serodifferent gay male couples in Australia, Thailand and Brazil.	Zero transmissions when viral load was undetectable <200 copies/mL.	2017	Grulich A et al. [12]
PARTNER2	Extension of PARTNER study to collect additional follow-up in gay male couples.	Study is fully recruited and still ongoing (2014–2017).	Expected 2018.	[13]

circumcision – all the men who became positive during the study were uncircumcised.

These results were 17 years ago.

Expert opinion and evidence review: the Swiss statement

From 2000 to 2008, many smaller studies reported reductions in other routes of transmission, or supplemented observational data with supportive research, such as reporting the impact of ART in genital fluids.

For example, in 2005, a Spanish cohort reported on almost 400 heterosexual serodifferent couples where the negative partner became HIV positive during the period 1991 to 2003. The results were presented for three time periods – pre-ART (1991–1993), early-ART (1996–1998) and late-ART (1999–2003) – and reported no transmissions when the positive partner was on ART. [6]

Cautions for these results were that other risks reduced over time, such as condoms being more widely used and people having less sex as they grew older, but zero transmissions was still significant.

In 2008, Pietro Vernazza and colleagues published the first high profile evidence review that concluded that ART stopped transmission. [7]

This paper, published in French but quickly translated into English, was a response to the laws in Switzerland that criminalised an HIV positive person if they had sex with a negative partner, even if condoms were used or if a couple wanted to conceive with full consent. This paper reviewed more than 25 studies and concluded that transmission did not occur. The estimated risk as a very rare event was less than 1 in 100,000 (0.00001%) – and therefore effectively zero.

Important considerations for the Swiss Statement included that the HIV positive person should be adherent on effective ART (not missing doses), have an undetectable viral load, and not have sexual infections that might increase viral load.

The Swiss statement was not only widely publicised but it was also widely cricitised, generating a very high profile. As such, it set a challenge to other doctors and researchers to report any cases that disproved the statement. Given the competitive nature of academic research, it is notable that after almost ten years no cases have been published that refute the Swiss statement.

Randomised data: HPTN 052

Scientists grade evidence based on the design of studies to be able to prove a link between and intervention and outcome. For many questions, the best quality of evidence comes from a randomised clinical trial. The process of randomly assigning participants to two or more groups where only the intervention is different, is the best way to rule out the results having been due to chance.

Because there is always the potential for other factors to affect outcomes, randomised studies are usually credited as the gold standard for evidence.

In 2011, US researchers, led by Myron Cohen and colleagues at the HIV Prevention Treatment Network (HPTN) reported early results from the HPTN 052 study. [8]

HPTN 052 recruited more than 1700 serodifferent couples (mainly in southern Africa, Latin America and South-East Asia. These were almost entirely heterosexual couples, and the HIV positive partners were randomised to either start ART immediately or wait until their CD4 count dropped to 350 cells/mm^3 (the then threshold in WHO guidelines for starting treatment).

All couples were supported with condoms and information on reducing the risk of HIV transmission, but it soon became clear that HIV transmissions were almost exclusively occurring in the group waiting for ART. Of the 39 transmissions, 28 were linked to HIV positive partner. Of these, 27/28 were in group waiting for ART. The single transmission in the immediate ART group occurred within weeks of starting treatment, when viral load would have still been high and certainly detectable.

This provided a very high level of evidence that ART was directly linked to protection against sexual transmission and as a result the HPTN 052 study was stopped early so that all HIV positive participants could receive immediate ART. Longer follow-up of HPTN continued for at least another four years and confirmed these early results. [9]

HPTN 052 produced evidence to enable HIV positive people to access ART earlier in order to protect their partners – called Treatment as Prevention (TasP). But limitations of the study meant that it could only report relative differences between the two study groups, rather than quantify any actual risk (even if the risk was theoretical).

Again, this was a heterosexual study, anal sex was rarely reported and condom use was relatively high. This meant that while ART could be proved to reduce infection, the study couldn't estimate how low this risk became, or the likely risk for different types of sex.

Large observational cohorts: PARTNER study and Opposites Attract

In 1999, several years before the results from HPTN 052, a group of European researchers led by Jens Lundgren from the Centre of Excellence for Health, Immunity and Infections (CHIP) launched the prospective observational PARTNER study. [10, 11]

The PARTNER study was important for enrolling serodifferent couples where the HIV positive partner was on ART and where the couples were already not always using condoms (often for many years).

Importantly, approximately one-third of the almost 900 couples were gay men and the study included detailed questionnaires on sexual activity to estimate risk based on actual exposure.

As with all studies, information about reducing HIV transmission, including free condoms, were included for all participants. All couples were then followed over time, trying to see whether transmissions occurred.

In a planned early analysis, presented at a conference in February 2014, PARTNER reported zero linked (within-partner) transmissions after more than 44,000 times when condoms hadn't been used and viral load was undetectable (defined as less than 200 copies/mL). [10]

PARTNER also provided reassurance for previous theoretical concerns from viral load blips or other STIs. No transmissions were seen in the 91 couples where the positive partner reported an STI (approximately one-third of gay couples had open relationships). The final results, presented and published in July 2016, reported zero transmissions after 58,000 times without condoms. [11]

The PARTNER results made headlines globally, but a less well-known aspect of this study was that the ground-breaking results took nearly two years to be published. This is likely linked to the implications the results would have on HIV prevention campaigns that were based on always using a condom, even when the limitation of condom-only prevention were clear from continued high rates of HIV transmission.

Because an important outcome of the PARTNER study is to quantify the theoretical range of risk (the upper limit of the 95% confidence interval), the PARTNER 2 study continued to collect results in gay couples to provide an equal balance of evidence compared to heterosexual data. [12]

Finally, at the IAS conference held in Paris in 2017, results from the Opposites Attract study in 358 gay male couples from Australia, Thailand and Brazil, also reported zero linked transmissions after almost 17,000 when condoms were not used. [13]

Again, STIs were not uncommon (present in around 1,000 of these occasions) and didn't result in HIV transmission.

Zero to negligible: what is in a word?

HIV transmission, even without a condom and without ART, is generally an uncommon event.

For example, the average upper range of estimated per-exposure risk ranges from 0.014 for receptive anal sex (14 in 1000) to from 0.001 for receptive or insertive vaginal sex (1 in 1000) and the lower ranges are many fold lower. [14]

However, during the first 2 to 4 weeks after infection, when viral load can be millions of copies/mL and people still believe they are HIV negative, risk will be higher. This led to many health campaigns pointing out that someone who believes they are HIV negative based on their last HIV test is associated with a much higher relative risk than any HIV positive person with undetectable viral load on ART.

Nevertheless, the semantic difference between zero risk and negligible risk, even when this theoretical risk is increasingly tiny (as with the Swiss Statement), prevented some people saying that the risk was effectively zero.

The most significant change over the last year, driven by the U=U campaign, has been for leading HIV scientists to now assert that a negligible theoretical risk is effectively zero.

Reversing the challenge: to now prove whether transmission is possible

Under ideal circumstances, large prospective studies that were designed to find cases of transmission when viral load was undetectable have not been able to do so.

So the evidence gap in 2017 is now the lack of any proof showing that HIV transmission is possible when viral load is undetectable.

This reverses the scientific challenge from proving safety to proving risk. Purely theoretical risks are no longer a good enough level of evidence to sustain stigma and discrimination and certainly not criminalisation.

Instead, there is no evidence to show that HIV transmission occurs when viral load is undetectable. People who want to assert the theory that HIV transmission might be possible, now have to provide some level of proof.

Conclusion

A comprehensive body of evidence now supports the U=U statement. This ranges from early clinical and theoretical studies, through small observational studies, randomised trials and the large prospective cohorts.

In addition, no cases of HIV transmission have been reported, over nine years since the Swiss Statement set this challenge. This includes data for gay men, for couples that have anal sex, over periods when low-level viral blips are likely and even when STIs are present.

In reality, even if the actual risk is zero, it is not healthy to think about anything in life as being risk-free. Even if at some point in the future an unlucky and rare case of transmission is reported with undetectable viral load, the U=U campaign is still right for closing the gap between zero and the real-life meaning of negligible in real terms.

The article is based on a talk given to the Positive People's Forum held in Glasgow on 1 July 2017. [15] Simon Collins is on the Steering Committee for the PARTNER studies.

C O M M E N T

The US CDC endorsement in September 2017 is especially important. [16]

Currently, the HIV criminalisation laws in many US states are outdated and severe. As a result, hundreds of HIV positive people have been imprisoned for many years for non-disclosure and often in the absence of actual transmission.

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CONFERENCE REPORTS

IAS 2017: ANTIRETROVIRALS

9th IAS Conference on HIV Science

23-26 July 2017, Paris

Introduction

The 9th IAS Conference on HIV Science (IAS 2017) was held from 23–26 July 2017.

As with all IAS conferences, many of the key presentations are available online after the meeting.

All abstracts are also posted online, with full versions of the posters and presentations often also available from the conference website.

http://www.ias2017.org

Webcasts are published to three different webpages:

The main IAS 2017 youtube channel includes most oral abstract presentations and some plenary sessions.

IAS 2017 on youtube.com

Live broadcasts for opening and closing ceremonies, and some press conferences are at this link on the conference website. Currently the link to the closing ceremonies with rapporteur summaries and the community speech is not available.

http://www.ias2017.org/Get-Involved/IAS-2017-Live

Press conferences and other webcasts are online on a different IAS youtube channel.

IAS 2017 press conference webcasts.

https://tinyurl.com/y8966f5e

Articles in this issue are:

- Dual therapy with dolutegravir plus lamivudine as first-line ART
- Dual therapy with darunavir/r plus lamivudine as first-line ART
- Once-daily raltegravir: 96-week results from the ONCEMRK study
- New IPERGAY analysis shows on-demand PrEP dosing works with less frequent sex
- On-demand dosing for PrEP is highly effective in French expanded access programme
- Psychological impact of PrEP: beyond efficacy and cost-effectiveness
- Early ART and testing HIV negative with rapid HIV tests

Dual therapy with dolutegravir plus lamivudine as first-line ART

Simon Collins, HIV i-Base

Results from a US pilot study using dolutegravir plus lamivudine dual therapy in treatment-naive participants reported good early efficacy including with high baseline viral load.

ACTG A5353 was a single-arm, open-label, phase 2 pilot study in 120 participants with viral load < 500,000 copies/mL. Exclusion criteria included active hepatitis B infection or major drug-associated mutations in RT, PI or integrase.

Baseline characteristics included median age 30 (IQR: 24 to 41) years; 87% male; 40% black, 28% white, 27% Hispanic. Median CD4 count and viral load were 387 (288 to 596) cells/mm^3 and 4.61 (3.94, 5.05) log copies/mL.

At week 24, the primary endpoint of viral load <50 copies/mL was reported for 108/120 participants (90%CI: 83% to 95%). Response rates were similar when stratified by baseline viral load being above/below 100,000 copies/mL, even though baseline characteristics of the >100,000 group (n=37) by definition had higher viral load and lower CD4 counts associated with more advanced HIV infection.

However, there were more virological failures in the high viral load group: n=3 (8%) vs n=2 (2%). In contrast, failure due to missing data was less common for the high viral load group: n=1 (3%) vs n=6 (7%), though numbers are small.

Three participants met protocol-defined viral failure linked to low adherence (confirmed by low drug levels), one of whom developed R263R/K (integrase) and M184V (RT).

Reference

Taiwo BO et al. ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/mL. IAS 2017, Paris. Oral abstract TULBPEB21.

http://programme.ias2017.org/Abstract/Abstract/5634

http://programme.ias2017.org//PAGMaterial/eposters/5634.pdf (PDF)

Dual therapy with darunavir/r plus lamivudine as first-line ART

Simon Collins, HIV i-Base

Dual therapy using boosted darunavir plus lamivudine for first-line ART was compared to standard triple therapy (with added tenofovir DF) in a randomised open-label phase 4 study.

The ANDES study enrolled 145 treatment-naive participants at sites in Argentina. Interim viral efficacy results at 24-week results using <400 copies/mL cut-off (presented as a late-breaking oral abstract at IAS 2017) were used to determine whether the study enrolled an additional 190 participants are enrolled with primary endpoint of viral suppression <50 copies/mL at week-48.

Baseline characteristics included median age 30 (IQR: 25 to 39) years, 91% male. Median baseline CD4 and viral load were 383 (IQR: 286 to 562) cells/mm^3 and 4.5 (4.0-5.0) log copies/mL respectively, with 24% having viral load >100,000 copies/mL.

At week-24, viral suppression <400 copies/mL was reports for 95% vs 97% participants in the dual vs triple therapy groups (difference: –2.5%; 95% CI: –7.9 to 2.9). Median CD4 increases were also similar: +206 vs +204 cell/mm^3, respectively.

Although there were more discontinuations in the dual therapy arm (4 vs 1), the only case of virological failure was in the triple-therapy arm.

Side effects were broadly similar, but GI side effects were more common in the triple therapy group (6% vs 12%).

The second phase of this study in now enrolling to provide 48-week final data.

Reference

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Once-daily raltegravir: 96-week results from the ONCEMRK study

Simon Collins, HIV i-Base

Longer follow-up results from the phase 3 registrational ONCEMRK study were presented at IAS 2017 as a later breaking poster. [1]

This was a double-blind, placebo-controlled non-inferiority study in 797 treatment naive participants randomised (2:1) to either the once-daily formulation (2 x 600 mg once-daily) or the original version (400 mg twice-daily). TDF/FTC were used as background NRTIs in both groups.

Baseline characteristics and demographics have been described before but this was a largely male (85%), white (60%) study with mean (SD) age 36 (+/–10.5) years. Mean CD4 and viral load were 415 cells/mm^3 and 4.6 log copies/mL respectively, with 28% having viral load >100,000 copies/mL.

At 96 weeks, viral load was <40 copies/mL in 81% vs 80% of participants (difference: +1.4; 95%CI: –4.4 to +7.3), continuing to show non-inferiority. This compared to the primary endpoint virological response rates of 88% in each arm at week 48 (difference: +0·5%; 95% CI: –4·2 to 5·2).

Response rates at 96 weeks for those with baseline viral load >100,000 copies/mL, were 85% vs 83% (difference: +1.8; 95%CI: –8.2 to +13.6).

Although discontinuation rates were similar in each group (n=64 vs 39) most were due to participant withdrawal or lost to follow-up. Viral non-response was reported in 6 vs 3 participants and discontinuation due to side effects in 7 vs 6 participants.

Resistance to raltegravir was infrequent, occurring in 4/531 (0.8%) and 2/266 (0.8%) in the QD and BID groups, respectively. CD4 responses at week 96 were similar (approximately +260 cells/mm^3 in each arm) as were tolerability and side effects.

COMMENT

Based on 48-week results from ONCEMRK, the once-daily formulation of raltegravir was approved in May 2017. [2] It was launched in the UK on 28 September 2017. [3]

The 48-week results from ONCEMRK were also recently published online. [4]

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IAS 2017: HIV PREVENTION

New IPERGAY analysis shows on-demand PrEP dosing works with less-frequent sex

Simon Collins, HIV i-Base

A new subgroup analysis from the French/ Canadian ANRS IPERGAY study provided new results from people using IPERGAY dosing for infrequent sex.

Dosing in IPERGAY involved taking four pills for someone having sex once: a double-dose 24 to 2 hours before sex and two single doses 24 and 48 hours after the first dose.

This infrequent sex subgroup is important as majority of participants in IPERGAY were having sex every week (median 10 times a month), generating a dataset for the overall study from taking four doses of PrEP a week (median 15 pills a month).

Frequent IPERGAY dosing has different pharmacokinetics to single use of four doses, given both drugs in PrEP have long half-lives, especially tenofovir in rectal tissue.

Guillemette Antoni presented results from a new analysis of participants who were only using on-demand dosing for less frequent sex, defined as routinely using PrEP for sex over a three month period, but taking <15 pills a month. This was taken as a good marker for true on-demand dosing. Individual participants varied in PrEP use during the study and only contributed appropriate follow up time for this analysis. Combined analysis of antigen/antibody, RNA and Fiebig stage results were used to accurately attribute likely dates of infection within the three-month window for reported PrEP use.

There was approximately 134 patient years of follow up (PYFU) from 269 participants, equally divided between the active vs placebo arms. This subgroup reported having sex a median of 5 (IQR: 2 to 10) times a month, using a median of 9.5 (IQR: 6 to 13) pills a month.

All six infections occurred in the placebo arm. This produced incidence rates of 9.3 /100 PY (95%CI: 3.4 to 20.1) vs 0.0 (0.0 to 5.4) and a significant relative reduction rate of 100% (95%CI: 39 to 100), p=0.13. Similar results were found when the analysis was restricted to periods when participants reported not using condoms.

COMMENT

These results are important. Even though the study numbers are low in terms of follow up time, the randomised design and significant differences between arms show this that IPERGAY dosing is significantly effective compared to no PrEP.

The degree of protection would need longer follow-up, even though this is unlikely to be available.

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http://programme.ias2017.org/Abstract/Abstract/3629 (abstract)

https://www.youtube.com/watch?v=vvKApONuutE (webcast, second presentation)

On-demand dosing for PrEP is highly effective in French expanded access programme

Simon Collins, HIV i-Base

Results from the expanded access PrEP programme in France, provided continued efficacy of on-demand or daily dosing for PrEP.

This poster, presented by Eric Cua, included data on 2,805 people enrolled from January to December 2016 in an early access programme that covered more than 130 clinics nationally.

This was a high-risk group with 30% having had two or more STIs during the previous year. Approximately 11% had used PEP and 20% used recreational drugs. Median age of participants was 36 years (IQR: 30 to 44) and most (97.4%) were gay men. On-demand dosing was used by 59% of participants.

During 1100 patient years (PY) of follow up, there were four new HIV infections (rate 0.36/100 PY; CI95%: 0.07 to 7.20). Of these, 2/4 were acute HIV seroconversions without drug resistance that occurred before inclusion in programme. One case presented with HIV seroconversion at month 1 visit with a 500 copies/mL and a M184I mutation. The final case presented with seroconversion (with no resistance) two months after PrEP had been stopped (participant decision).

The study notes the high efficacy shown by these data in a real life setting, with the importance of early and continued monitoring given the risk of starting PrEP after recent infection or risk.

Full results from this study were published in the September 2017 edition of Lancet HIV. [2]

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Psychological impact of PrEP: beyond efficacy and cost-effectiveness

Simon Collins, HIV i-Base

The impact of PrEP on quality of life in reducing HIV-related anxiety and more dynamic and fulfilled sex lives is potentially as important as hard endpoints for reduced HIV infections.

Mitzy Gafos presented experiences from using PrEP as part of the UK PROUD study, based on semi-structured interviews with 41 participants.

In addition to reporting behavioural changes, the results gave insight into psychological impact of PrEP.

Many of these imply significant changes in outlooks and approach to life:

"PrEP has replaced fear as the central focus of relationships".

"The feeling of relief of 25 years of weight, of stress... where every sexual interaction is a wave of risk".

"Worry obviously ruins the sexual experience ... removing that worry... probably improved my life over the past 2 years'.

"For the first time in my life since I started taking it I actually have had sex as I like it – without having this horrible feeling of 'my god' after".

"I was selecting negative [partners]… I am more looking at the person now ... not if they're positive".

"There is more intimacy not using the condoms and the tablets can prevent me from getting HIV".

"It gives you the peace of mind the added control of minimising that risk".

"It's been very good for my mental health (ADHD) because I've not had to associate sex with danger so much which is good".

"If I wasn't taking it, sooner or later the inevitable is going to happen".

"The whole experience has really made me quite liberated".

"I haven't changed the way I think because I am taking this pill. Having these pills doesn't give me an excuse to be more crazy than I already am".

"There is no marked difference, I was having a huge amount of condomless sex before".

C O M M E N T

Overall, these quotes provide insight into the qualitative impact that PrEP can have.

When PrEP had no direct impact on behaviour, this was often because the level of risk was already so high. However, PrEP as a medical intervention was clearly warranted.

Reference

Gafos M et al. Experiences and perceptions of PrEP among gay and other men who sex with men (MSM) using PrEP in the PROUD study in England. IAS 2017, 23–26 July 2017, Paris. Oral abstract TUAC0105.

http://programme.ias2017.org/Abstract/Abstract/4164

Early ART and testing HIV negative with rapid HIV tests

Simon Collins, HIV i-Base

A timely poster reported that very early initiation of ART, followed by several years of viral suppression, can have a relatively common outcome of testing HIV negative.

The negative results from the waning HIV antibody responses are rarely reported when ART is started later in infection. Importantly, the results only highlight a limitation for the test sensitivity and not that HIV has been cleared.

This study was presented as a poster by Karl Stefic from an analysis of 44 participants in the French ANRS primary HIV infection (PHI) PRIMO cohort who started ART during PHI and who had undetectable viral load for at least the following three years.

Frozen serum samples were tested using the CE-certified self-test Autotest VIH, two point-of-care tests (INSTI HIV1/2 Rapid Antibody Test and VIKIA HIV1/2), and a 4th generation ELISA (ARCHITECT HIV Ag/Ab Combo).

Participants were mostly male (82%), median age was 40 years. At diagnosis, median CD4 cell count was 372 cells/mm^3 and plasma viral load and cell-associated HIV-DNA were 5.3 and 3.6 log$_{10}$ copies/million PBMCs, respectively.

ART was started a median of 43 days (range 20-115) after estimated date of infection. This corresponded to Fiebig stage II (5%), III (2%), IV (36%), V (21%) or VI (36%).

After a median of 84 months (range 36-204) on ART, HIV-specific serological responses were non-reactive for 30% of self-tests, 9% for INSTI and 7% for VIKIA. All participants remained positive with 4th generation ELISA (median index=48; range: 1.9 to 491) but 7/44 had an index value < 10.0.

Cell associated HIV-DNA at time of self-test was not associated with non-reactivity. Of note HIV-DNA remained detectable for 9/13 patients (69%) with negative self-test. Under ART, western blot were indeterminate for 4/13 patients with non-reactive self-tests (31%) compared to 2/31 patients with reactive self-tests (6%).

The poster also noted that awareness of this possibility might be important for people using HIV self-testing in the future.

Reference

Karl Stefic K et al. Non-reactive HIV-1 self-tests after sustained viral suppression following early antiretroviral therapy. IAS 2017, 23–26 July 2017, Paris. Poster abstract MOPOB0253.

http://programme.ias2017.org/Abstract/Abstract/1246 (abstract and poster)

CONFERENCE REPORTS

Report from the IAS HIV cure and cancer forum 2017

Richard Jefferys, TAG

The IAS HIV Cure & Cancer Forum was held at the renowned cancer research center Institut Curie in Paris from 22–23 July this year.

A report from the meeting, authored by Genevieve E. Martin, José Alcami, Jean-Phillipe Spano and Anna Laura Ross, has just been published in the open access Journal of Virus Eradication. [1]

Many of the slide presentations are posted to the Forum website. [2]

Some of the intersections between the two disciplines were described in a presentation by Olivier Lambotte at last year's IAS Towards an HIV Cure Symposium in Durban, South Africa, and the 2017 event expanded on the theme. [3]

Similarities include the need to identify and target relatively rare, hard-to-access cells for elimination - a task which requires gaining an understanding of the reasons why natural immune responses are ineffective. Also, the development of strategies to bolster immunity against the cells of interest (whether cancerous or latently infected by HIV).

As the meeting report notes, many approaches being pursued as cancer therapeutics are also being studied in the context of HIV cure research, including immune checkpoint inhibitors, cytokine therapies, genetically modified chimeric antigen receptor (CAR) T cells and other gene therapies.

The coverage of the presentations offered in the report is fairly comprehensive, but there are some additional pieces of information that may be of interest. There was a presentation by Francoise Villinger from the University of Louisiana at Lafayette describing the use of radiolabelled anti-virus antibodies to image the locations of SIV expression in the bodies of macaques, [4] and a clinical trial is due to open soon in Australia that will explore a similar approach in humans using a radiolabelled version of the broadly neutralising antibody 3BNC117. [5]

Larry Corey from the Fred Hutchinson Cancer Research Center gave an excellent talk on the potential of CAR T cells, [6] describing both the positive results in cancer (a CAR T cell therapy for acute lymphoblastic leukaemia became the first to be approved by the FDA not long afterward [7]) and some of the issues that have arisen with adverse events. In the context of HIV cure research, Corey highlighted a number of factors he considers likely to be important, including:

- The provision of HIV-specific CD4 T cell help to CAR CD8 T cells using CD4 T cells that have been modified to resist HIV infection.
- Targeting of CAR T cells to HIV reservoir sites such as lymph node B cell follicles (some experiments addressing this issue using CD8 T cells modified to express the trafficking receptor CXCR5 have already been conducted in SIV-infected macaques).
- Equipping CAR T cells with receptors that allow them to recognise and kill HIV-infected cells quickly after the virus is reactivated (a recently published study from the research group of Brad Jones suggests that the HIV Nef protein may be a particularly important target for this purpose).
- Ensuring CAR T cells can persist at the sites where they are needed.
- Avoiding the adverse events that have been observed in some cancer studies, most notably cytokine release syndrome and neural toxicity.

Corey focused on the potential of directing CAR T cells to HIV antigens, but a recent cancer trial may also raise the possibility of targeting cellular receptors that are preferentially expressed by latently infected CD4 cells. In a paper published in the Journal of Clinical Investigation, researchers describe promising results obtained with CAR T cells engineered to recognise CD30, a receptor expressed by non-Hodgkin's lymphomas. [8]

Ongoing work by the laboratory of Timothy Heinrich (as yet unpublished, but briefly described in a summary for the supporting NIH grant) has identified CD30 as a possible marker for CD4 cells containing latent HIV. [9]

While Heinrich's group is initially looking at brentuximab vedotin, an FDA-approved antibody-drug conjugate that targets CD30 but has some notable toxicities, CAR T cells could offer an alternative means to the same end.

One presentation that is not covered in the meeting report was delivered by Marina Cavazzana from Hôpital Necker in Paris. [10]

Cavazzana is working on a novel approach to promoting immune reconstitution by accelerating production of naïve T cells from the thymus. At one time, this was an area of intense interest in HIV research, and a number of candidate therapies were evaluated (keratinocyte growth factor is among the examples) but results proved disappointing and there has been little activity related to the thymus in recent years. Persistent deficits in naïve T cell levels are still a concern however, particularly for individuals who experience suboptimal CD4 T cell recovery on antiretroviral therapy (immunologic non-responders or INRs), so a candidate treatment could still have relevance.

Cavazzana's strategy involves the use of a laboratory culture method to generate T cell precursors from stem cells, mimicking the early steps of maturation that would normally occur in the thymus. In experiments where these lab-generated T cell precursors were infused into immunodeficient mice, reconstitution of mature naïve T cells was significantly accelerated. Phase I/II clinical trials involving adults receiving stem cell transplants for cancers and children with primary immunodeficiencies are due to begin in January 2018. Cavazzana noted that there is also the potential to modify the T cell precursors with gene therapy prior to infusion.

A lively roundtable discussion on clinical trial design and participation is summarised in the meeting report (see box 1 in the report), but a video of the presentation by Michael Louella from the University of Washington AIDS Clinical Trials Unit is also available on the defeatHIV Youtube channel. [11, 12]

Panel participant Thomas Uldrick from the National Cancer Institute drew attention to an important initiative involving the U.S Food & Drug Administration, American Society of Clinical Oncology and Friends of Cancer Research that is attempting to expand eligibility criteria for trials of novel anticancer agents to include HIV-positive people. [13] Uldrick pointed out that the median time from phase 1 to an HIV-specific study for novel anticancer agents (6.3 years)

is only a few months shorter than the average time from phase 1 to FDA approval, a problem that urgently needs to be addressed given that the prognosis for people with HIV is so much improved due to ART. Uldrick encouraged attendees to spread the word about the initiative.

In addition to the new report, the IAS blog also published a commentary on the meeting by Geneviève Almouzni, Director of the Institut Curie Research Center and CNRS Research Director, timed to coincide with World Cancer Research Day. [14]

Source

Jefferys R, TAG Basic Science blog (29 September 2017)
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TREATMENT ACCESS

Generic dolutegravir-based FDCs at US $75 a year for low- and middle-income countries

Polly Clayden, HIV i-Base

A new pricing agreement has been announced that will speed up access to generic, dolutegravir-based fixed dose combinations (FDCs).

This will enable use to treat HIV in low- and middle-income countries (LMICs) at an annual cost per person of around US $75. [1]

This announcement was made on 21 September 2017 at UNGA by the governments of South Africa and Kenya with UNAIDS, the Clinton Health Access Initiative (CHAI), the Bill & Melinda Gates Foundation, Unitaid, DFID, PEPFAR, USAID, and the Global Fund, in collaboration with Mylan Laboratories Limited and Aurobindo Pharma.

The new products combine tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) and were developed by Mylan and Aurobindo under licensing agreements from ViiV Healthcare, the originator of DTG. Both generic manufacturers received tentative approval from the US FDA for TLD in August of this year. [2]

The agreements, which set ceiling prices for TLD, apply to public sector purchasers and will offer substantial reductions compared with the price of efavirenz-based FDCs (around US $100 per person per year) [3]. This could lead to savings of up to US $900 million over the next six years in South Africa. Across the 92 countries covered under ViiV's dolutegravir licensing agreement, six-year savings have been estimated at US $1 billion.

COMMENT

2017 is proving to be a banner year for ART optimisation.

Further price reductions are anticipated in the not too distant future, with the arrival of new FDCs that will replace tenofovir disoproxil fumarate with the much lower dose tenofovir alafenamide (TAF).

Meanwhile several studies are underway to fill the evidence gaps associated with these regimens so they can be universally recommended in LMICs – including for pregnant women and people coinfected with TB.

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UK donates well to the Global Fund, but slashed bilateral aid for HIV

Global Fund Observer

The UK's generosity to multilateral institutions, and to the Global Fund in particular, has come at the expense of the country's bilateral aid, according to STOPAIDS, a network of UK agencies working on HIV. [1]

STOPAIDS has released a new publication, a stocktake review of the work of the Department for International Development(DFID) on HIV, in which it says that although the UK increased its contribution to the Global Fund in the last replenishment, and has maintained its level of contribution to UNAIDS and UNITAID, the country has implemented significant cuts to its bilateral programmes focusing on HIV.

STOPAIDS said that DFID's overall funding for HIV declined 22% between 2012 and 2015 (from £416 million to £324 million). DFID's bilateral funding for HIV-specific programs declined from a peak of £221 million in 2009 to £23 million in 2015.

"Cuts to country offices have cancelled out DFID's increased contribution to the Global Fund," STOPAIDS said. Funding for civil society has been particularly hard hit, it added, declining from £30 million in 2011 to just £8 million in 2015.

The network said that despite a legacy of UK government financial leadership within the HIV response, civil society and the U.K. Parliament have raised concerns that DFID's commitment to HIV is fading.

"DFID has closed the majority of its bilateral programmes specifically focussed on HIV and no longer has a position or strategy on HIV," STOPAIDS stated. The UK's presence at high-level international forums where HIV is discussed has also declined in recent years, it added. Multilateral funding is making up an increasing share of DFID's overall funding for the global HIV response. In 2012 multilateral spending accounted for 25% of total funding, but by 2015 the proportion of multilateral spending had increased to 57%.

All three multilaterals – the Global Fund, UNAIDS and UNITAID – performed well in the UK's Multilateral Development Review in 2016. "The UK recognised the Global Fund as achieving exceptional results and UNITAID was found to be a very good match with UK development objectives," STOPAIDS said.

At the Global Fund's Fifth Replenishment Conference in September 2016, the UK pledged £1.1 billion, an increase of 37% over its previous contribution. According to STOPAIDS, at the conference the UK referred to the Global Fund as "one of the world's most effective aid institutions." The UK also recently recommitted to maintain funding for UNAIDS at £15 million per year "in a challenging context when many other donors are pulling back," STOPAIDS stated.

Source

GFO. While it has given generously to the Global Fund, the UK has slashed its bilateral aid for HIV, NGO says. GFO 320 (20 September 2017).

http://www.aidspan.org/node/4342

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Dozens of countries left out of new PEPFAR strategy, threatening the global AIDS response

Health GAP

Secretary of State Rex Tillerson yesterday unveiled the President's Emergency Plan for AIDS Relief (PEPFAR) "Strategy for Accelerating HIV/AIDS Epidemic Control (2017-2020)" at the United Nations General Assembly. The plan includes a greater push toward epidemic control in 13 target countries, but takes the foot off the gas for more than 37 countries PEPFAR does not designate as 'priority,' leaving behind millions of people living with HIV due to a lack of resources and a waning commitment to evidence-based strategies.

Health GAP Executive Director Asia Russell said: "The strategy announced today is the kind of global AIDS response policymakers craft when they have one hand tied behind their backs. An ambitious strategy wouldn't limit efforts toward epidemic control in just 13 of PEPFAR's more than 50 countries, but would aggressively map out a plan for ending AIDS as an epidemic in all countries, including those with the highest burden and greatest need such as Mozambique, South Sudan, the Democratic Republic of Congo and other parts of West Africa

"This strategy makes the right moves in too few places, at the expense of saving lives everywhere else," said Russell. "PEPFAR leadership should sound the alarm about the risks of committing too few resources to the global AIDS response and the dangers of using scarce resources for anything other than evidence-based strategies."

The plan announced today is remarkable in that:

- It does not include support for rapid treatment scale-up in all PEPFAR countries, including high-burden countries like Mozambique and impoverished countries like South Sudan.
- It fails to name the costs of not scaling-up efforts in all PEPFAR countries, which will include preventable deaths, new infections, and a more expensive future global AIDS response.
- It does not include an aggressive strategy for reaching key populations, including LGBT people, sex workers, or women and girls.
- It does not highlight the dangerous impact of expanding the Global Gag Rule to PEPFAR.
- It does not call on Congress to increase funding for the global AIDS response.
- It does not include a human rights component.
- It calls for increasing engagement with faith-based organisations, which have historically rejected evidence-based strategies.

During his campaign, President Trump responded to a question about whether he would commit to doubling the number of people receiving treatment through PEPFAR to 230 million by 2020, saying: "The answer is yes. I believe strongly in that and we are going to lead the way." Trump reiterated his support for PEPFAR during the United Nations General Assembly today, but has proposed $1 billion in cuts to the U.S. global AIDS response, including PEPFAR. While Congress has so far rejected those cuts, it has also failed to

increase funding for life-saving global HIV treatment and prevention. Dr. Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, said in a recent speech that additional resources will be necessary to achieve epidemic control targets.

Congress must add $700 million for PEPFAR during the upcoming budget reconciliation process in order to fund a truly ambitious and effective strategy for achieving epidemic control in all PEPFAR countries and not just a chosen few," concluded Russell.

Source:

Health CAP press release. Dozens of countries left out of new PEPFAR strategy, threatening the global AIDS response. (20 September 2017).

http://www.healthgap.org/dozens_of_pepfar_countries_left_out

ANTIRETROVIRALS

Gilead uses voucher to speed FDA review of bictegravir

Simon Collins, HIV i-Base

On 10 August 2017, Gilead announced that the FDA of the bictegravir fixed-dose combination (FDC) would be processed using a priority review voucher.

These vouchers are bought and sold by companies and enable a faster review process.

In this case, the decision on the single tablet combination of the new integrase inhibitor, coformulated with tenofovir alafenamide (TAF) and emtricitabine (FTC) will be made by 12 February 2018.

The application was filed in the US in June 2017 and is also filed with the EMA in Europe.

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PREGNANCY & PMTCT

BHIVA challenges BMJ recommendations on ART during pregnancy: tenofovir still strongly recommended

BHIVA statement

On 21 September, the British HIV Association (BHIVA) took the unusual step of issuing a statement (reproduced below) to publicly challenge a recent paper from the British Medical Journal (BMJ). The statement challenged the linked BMJ recommendations, especially over choice of ART during pregnancy.

The controversial BMJ study, published two weeks earlier, used a Cochrane analysis for serious outcomes related to NRTI component of ART, and concluded that zidovudine should be used in preference to tenofovir DF (TDF) or abacavir.

The methodological problems with the BMJ paper are covered in an i-Base review earlier in this issue of HIV Treatment Bulletin.

Response from BHIVA pregnancy guidelines group

- BHIVA does not support recommendations of "ART in pregnant women living with HIV: a clinical practice guideline" (BMJ, 11/9/17).
- Other systematic reviews and numerous observational studies show TDF to be safe in HIV in pregnancy.
- BHIVA does agree any decision regarding ARVs should always be discussed in full with every woman.
- BHIVA's recommendation remains to continue or to start TDF or abacavir with emtricitabine or lamivudine as a nucleoside backbone.
- We do not think this data should influence use TDF/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential.

This BMJ systematic review has "strongly recommended" that pregnant women living with HIV should not be treated with the combination TDF/emtricitabine/lopinavir/ritonavir due to higher rates of early neonatal death reported in the PROMISE, randomised clinical trial (2).

The PROMISE trial compared the efficacy of zidovudine/single-dose nevirapine with combination protease inhibitor-based (lopinavir-ritonavir) ART using zidovudine/lamivudine or tenofovir/emtricitabine backbone to prevent mother-to-child transmission in women with CD4 cell count >350 cells/mm^3.

BHIVA does not recommend the use of lopinavir/ritonavir for the treatment of HIV in adults, including in pregnant women, and certainly not at the 50% higher dose used in the 3rd trimester in the PROMISE trial. In addition PROMISE investigated outcomes in women initiating therapy. Most women in UK will conceive on ART, most commonly with TDF/FTC backbone and this study does not address that cohort.

The systematic review also made a "weak recommendation" that zidovudine/lamivudine should be used preferentially over TDF/emtricitabine as the nucleoside backbone in pregnant women because of the lower number of stillbirths and early neonatal deaths in this arm of the PROMISE study. As both arms received lopinavir/ritonavir the BMJ panel postulates that TDF/emtricitabine is the cause of the difference. Despite the BMJ panel's assertion that pharmacokinetic interactions between tenofovir and lopinavir/ritonavir are not relevant there are data reporting increased levels of both drugs in the host when co-administered at standard doses.

Three previous systematic reviews(3–5) reported no increase of birth adverse events or safety events (and no increased risk of congenital anomalies) in infants exposed to tenofovir compared to non-TDF-containing regimens in HIV-exposed infants, although data remain limited and studies evaluating neonatal mortality, infant anthropometry and bone growth are required. WHO used these systematic reviews to inform their guidelines on HIV and pregnancy, which include the use of TDF-containing regimens.

In addition to these systematic reviews, there are numerous observational studies showing TDF/emtricitabine to be safe in pregnancy. For example, Zash et al (6) published a birth surveillance study of 47,027 pregnant women in Botswana, including 11,932 women with HIV, where preterm birth, very preterm birth, small and very small size for gestational age, stillbirth, and neonatal death were evaluated. In this very large cohort, the risk for any adverse or severe adverse birth outcome was lowest among infants exposed to a combined regimen of TDF, emtricitabine and efavirenz but all TDF/emtricitabine-based regimens were found to be safer than those with zidovudine/lamivudine as a backbone and the highest risk of adverse outcomes with observed in those women receiving lopinavir-based regimes.

The writing group agree that any decision regarding ARVs should always be discussed in full with every woman. Currently, our recommendation remains to continue or to start tenofovir or abacavir with emtricitabine or lamivudine as the nucleoside backbone (Grading: 2C). The third agent should be one of the following: efavirenz, raltegravir, rilpivirine, ritonavir-boosted darunavir or ritonavir-boosted atazanavir, as per national BHIVA Adult treatment guidelines7. In addition the group does not think this data should influence decisions to use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential.

The BHIVA guidelines on the management of HIV in pregnancy will be published for consultation later this year.

Source: BHIVA. British HIV Association (BHIVA) response to BMJ article 'Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline'(1) published 11 September 2017. (21 September 2017).
http://www.bhiva.org/BHIVA-response-to-BMJ-article.aspx

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www.bhiva.org/guidelines

GUIDELINES

UK PrEP guidelines online for comment

Simon Collins, HIV i-Base

The first UK guidelines on the use of PrEP have been produced by BHIVA/BASHH and are now online for comment.

The deadline for responses is Friday 29 September 2017.

The evidence-based document has been produced to provide guidance on best clinical practice in the provision, monitoring and support on PrEP in the UK.

Sections include:

- Evidence for efficacy and safety in different populations.
- Risk assessment before PrEP.
- Prescribing.
- Monitoring.
- Dosing options.
- Buying generic PrEP.
- Cost effectiveness.

The guidelines are aimed at clinical professionals who are directly involved in HIV prevention, and at community advocates and organisations responsible for supporting HIV prevention strategies in those at risk of HIV acquisition.

Please download and comment via the BHIVA website.

http://www.bhiva.org/PrEP-guidelines-consultation.aspx

US HIV pain management guidelines (IDSA)

Simon Collins, HIV i-Base

The Infectious Diseases Society of American (IDSA) has published new online guidelines for pain management of HIV positive people.

The open-access document reviews the types of chronic non-cancer pain commonly seen among persons living with HIV together with the evidence base for treatment.

This includes for specific populations including people with substance use and mental health disorders.

The 30-page guidelines cover screening, management, pharmacological and other options, with almost 300 references.

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HIV TRANSMISSION AND PREVENTION

NHS access to PrEP in the UK: country update

Simon Collins, HIV i-Base

Currently in the UK, access to PrEP depends on which country you live in.

PrEP Scotland

For people living in Scotland, PrEP is available free on the NHS.

This summer, NHS Scotland agreed to fund PrEP for people at risk and recently announced that from November this will be with generic PrEP.

Access is mainly through sexual health clinics with details on a new website.

www.prep.scot

PrEP Wales

For people living in Wales, PrEP is also available free.

Access is provided free at sexual health clinics by NHS Wales, with minimal entry criteria, other than risk of HIV.

Although the announcement over access in Wales has referred to the PrEP programme being part of a study, this does not require active enrolment by participants. Instead, it refers to using anonymised data about PrEP use over the next three years to decide on future programmes.

www.friskywales.org/wales-prep-project.html

PrEP England

For at least the next year, access to PrEP on the NHS in England will only be available by joining the PrEP IMPACT Trial.

This study plans to enrol 10,000 participants from about 200 sexual health clinics across England, with some places ring-fenced for women, trans and non-binary people and for African people. This is designed to have greater involvement of people from other risk groups to gay men.

Although the IMPACT study was due to start in September, the first sites (in London, Brighton, Manchester, Liverpool and Sheffield) are now expected to start by the end of October.

Although IMPACT is planned as a three year study, interim results might answer the study questions earlier than initially planned.

www.prepimpacttrial.org.uk

For further information on the trial, please email:

enquiries@prepimpacttrial.org.uk

PrEP Northern Ireland

There is currently no NHS access to PrEP in Northern Ireland.

Generic PrEP in France and Scotland challenges access across the UK

Simon Collins, HIV i-Base

In early September 2017, two interesting developments were reported in relation to generic tenofovir disoproxil/ emtricitabine in the UK.

Firstly, the French HIV community organisation AIDES, reported that the French courts had not supported extending the patent for tenofovir disoproxil fumerate (TDF)/emtricitabine(FTC), coformulated as Truvada and manufactured by Gilead.

Although a generic formulation of TDF/FTC has been available in France since July 2017, this was challenged by Gilead. In addition to the challenge not being upheld, Gilead had to pay costs to the generic manufacturer Mylan. Thirty tablets of TDF/FTC is currently priced at approximately 180 euros for the generic compared to 406 euros for Truvada.

Secondly, on Friday 8 September, HIV Scotland announced that NHS Scotland would be using generic formulations for both ART and PrEP. [2, 3]

The tender for use as HIV treatment will use tenofovir disoproxil phosphate/FTC, manufactured by Zentiva, while the tender for use as HIV treatment will be with tenofovir disoproxil succinate/FTC, manufactured by Dr Reddy's.

Although no details were published on the prices, the new contracts will start from 1 November 2017 and will replace use of the current patent formulation TDF/FTC manufactured by Gilead.

This is important because in September 2016, the European Medicines Agency (EMA) approved three generic formulations of TDF/FTC that use a different base salt for tenofovir. [4]

However, in January 2017, when the patent for TDF/FTC was challenged in the courts in England and Wales, a decision on the patent was referred to the European Court, making the timeline for access to more affordable versions uncertain. [5]

The precedents shown in France and Scotland, challenge NHS England to proactively move to generic formulations, if the price differences continue to be so high. This would also challenge the decision by NHS England to defer providing PrEP until after results of the upcoming IMPACT study. [6, 7]

Of note, the IMPACT trial is also using generic PrEP.

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PrEP use in adolescent gay and bisexual men at high risk of HIV: US study shows need for easier access and easier PrEP

Simon Collins, HIV i-Base

The increasing efficacy of PrEP in contributing to reduced HIV incidence often highlights the limited access in populations at high risk of HIV who were not included in original studies.

Results from an adolescent PrEP study in six US cities are therefore as important for highlighting the need for PrEP as they are for reporting acceptability and efficacy. The results from the ATN 113 study, published on 5 September 2017 in JAMA Paediatrics, showed that PrEP reduced HIV infections in this high-risk group, but also showed many challenges. [1]

This was a phase 2 PrEP implementation study in young men aged 15 to 17 at high risk of HIV and willing to take PrEP, with primary endpoints of safety and acceptability. [3]

At the time the study was run, approximately 22% of new HIV diagnoses in the US were in people aged 13 to 24 years old, 80% of which were gay men or other men who have sex with men (MSM).

The first challenge was engaging appropriate participants for this study. Out of more than 2800 young people approached for pre-screening from August 2013 to September 2014, 260 were eligible and 78 were enrolled. Mean age was 16.5 years. Ethnicity included 29% black, 21% Hispanic, 14% white and 36% mixed race or other. Most self-identified as gay (58%) or bisexual (28%), 88% lived with their families but 15% had been forced to leave their primary home because of their sexuality; 86% were still at school. Other demographics including relatively high use of alcohol and marijuana (only a third never used either).

Baseline risk for enrollment was defined as any of the following within the previous six months: condomless sex with a male partner, more than three partners, exchange sex or an STI. PrEP was included as part of a combination prevention package, with monthly visits for the first three months and quarterly visits through to week 48, with compensation per visit of $50 to $75. Participant questionnaires included acceptability and adherence related to PrEP and behaviour risk. Adherence was also evaluated by drug level testing at study visits.

Of the 78 participants enrolled, 72 (92%) started oral daily PrEP (TDF/FTC) and only 46 (64%) completed 48 weeks follow up, with most of the other participants (n=19) lost to follow up.

Most participants had detectable drugs levels at some point during the

study. Although about half of participants had drug levels equivalent to taking four or more doses a week needed for protection for the first 3 months of the study, this level of adherence halved again for the remainder of the study. Tenofovir diphosphate levels consistent with >/= 4 doses a week were found in 42 (54%), 37 (47%), 38 (49%), 22 (28%) 13 (17%) and 17 (22%) participants, at weeks 4, 8, 12, 24, 36 and 48, respectively.

Common reasons for low adherence were being away from home (32%), being too busy (28%), forgetting (26%) and changing routines (18%). Lower adherence was also significantly associated with a worry that PrEP would be associated with being HIV positive (p=0.03).

Over 48 weeks of PrEP there were three new HIV infections (at weeks 32, 36 and 38): an annual rate of 6.4 (95% CI: 1.3-18.7) per 100 person-years. One of these cases had not shown detectable TDF drug levels for several months and two cases had levels associated with taking less than two doses a week at the likely time of infection.

Although tolerability was reported as good, with no PrEP discontinuations due to side effects or laboratory abnormalities, there was a small but significant decline in total body bone mineral density z-score in the 43 participants with week 48 DEXA results (0.7%; IQR, –0.3 to 0.0; p <0.001), although changes in hip and spine did not change significantly. These changes were not related to TDF-DP levels.

There were 23 sexually transmitted infections diagnosed in 12 participants, showing that this population was certainly at risk, but rates were similar to the baseline figure of 19 prevalent STIs in 14 participants. Although more STIs were diagnosed during the first six months of the study this was not statistically significant.

COMMENT

These results were first presented last year at AIDS 2016 conference in Durban. [3]

A related adolescent PrEP study (ATN 110) in a high risk group of slightly older gay men (aged 18 to 22) reported similar high level of need, with related challenges of recruitment and retention, but also a significant loss in BMD on PrEP (which returned to baseline after PrEP was stopped). [4]

The details of the ATN PrEP studies are important for showing not just the need for PrEP in young people at risk of HIV, but the need for PrEP that is easier to take.

Although the risk of HIV is likely to outweigh the risk of BMD reductions from short-term use of TDF/FTC, these results also highlight the need for PrEP that would not have this concern in young people.

A randomised placebo-controlled study of vitamin D3 injections (50,000 IU every three months) in 16-24 adolescents and young adults on ART reported significant increases in lumber spine BMS of 1.15 % (-0.75, 2.74) independent of baseline vitamin D status. All participants received oral multivitamins, but this wasn't sufficinet to produce significant BMD changes with the placebo injections. [5]

An accompanying editorial by Renata Arrington-Sanders, an adolescent HIV specialist, notes that these exciting results will help young men at risk for HIV to access and use TDF/FTC in their daily lives. Also, the likely support from an "interdisciplinary, multiteam, community approach that recognises the complexity of adolescent needs to support their daily work of HIV prevention". [6]

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SIDE EFFECTS & COMPLICATIONS

Enhanced OI prophylaxis reduces mortality when starting ART late

Polly Clayden, HIV i-Base

Enhanced antimicrobial prophylaxis combined with ART reduced rates of death at both 24 and 48 weeks in HIV positive adults and children with advanced HIV in the REALITY trial. [1]

In sub-Sharan Africa, 20–25% of people with HIV still present for care with 100 CD4 cells/mm3 of less. Among this group, approximately 10% die within the first three months of starting ART, and severe bacterial infections (including tuberculosis and cryptococcus) are often the cause.

The REALITY trial, conducted in Uganda, Zimbabwe, Malawi and Kenya, looked at three strategies to potentially reduce the risk of death: enhanced antimicrobial prophylaxis, adding raltegravir to standard ART, and food supplementation.

It was a factorial open-label trial enrolling adults and children five years of age or older who had not received previous ART and were starting with CD4 count less than 100 cells/mm3.

The primary outcome was death from any cause at 24 weeks. Secondary outcomes included death from any cause at 48 weeks, serious adverse events, grade 4 adverse events, and adverse events leading to modification of ART or other trial drugs; as well as changes in CD4 count or weight, incidence of bacterial infections, adherence and acceptability.

The investigators reported the effect of the enhanced prophylaxis in the 20 July 2017 edition of NEJM in a paper authored by Hakim et al. The evaluation found no evidence of benefits from other factorial randomisations to adding raltegravir or supplementary food (p>0.7).

All participants started ART with two NRTIs and one NNRTI. They were then randomised (1:1 ratio) to start enhanced prophylaxis or standard prophylaxis.

Enhanced prophylaxis included: a single dose (400 mg) of albendazole, five days of azithromycin (500 mg once daily), 12 weeks of fluconazole (100 mg once daily), and 12 weeks of a fixed dose combination of trimethoprim–sulfamethoxazole (160 and 800 mg respectively), isoniazid (300 mg), and pyridoxine (25 mg) as a scored once-daily tablet (total, three tablets per day for 1 to 5 days, then two pills per day for 12 weeks).

Children younger than 13 years of age, received half doses of all drugs except for albendazole. Standard prophylaxis was trimethoprim–sulfamethoxazole alone.

Participants in the enhanced prophylaxis group discontinued fluconazole after 12 weeks and continued trimethoprim–sulfamethoxazole or the fixed dose combination. Those in the standard prophylaxis group continued trimethoprim–sulfamethoxazole or switched to the fixed-dose combination.

Use of isoniazid–pyridoxine after 12 weeks was according to national guidelines.

The trial included 1805 participants: 1733 adults and 72 children or adolescents (906 enhanced prophylaxis and 899 standard prophylaxis). They were followed for 48 weeks. Overall loss to follow-up was 3.1% (56 participants, 24 in the enhanced and 32 in the standard prophylaxis groups).

Participants were a median age of 36 years; 72 (4.0%) were children and adolescents 5–17 years of age. Median CD4 count was 37 cells/mm3, and 1300 of 1763 (73.7%) had a viral load of at least 100,000 copies/mL. But almost half (47.3%) were asymptomatic or mildly symptomatic (WHO stage 1–2).

At 24 weeks, there were 80 vs 108 (8.9 vs 12.2%) deaths in the enhanced vs standard prophylaxis groups: HR 0.73 (95% CI 0.55 to 0.98), p=0.03). By 48 weeks, there were 98 vs 127 (11.0 vs 14.4%) deaths, respectively: HR 0.76 (95% CI 0.58 to 0.99), p=0.04.

Participants in the enhanced prophylaxis group had significantly lower rates of a new diagnosis of tuberculosis (7.1 vs 10.2%), p=0.02; cryptococcal infection (1 vs 2.6%), p=0.01; candidiasis (1.1 vs 2.6), p=0.02), and new hospitalisation (17 vs 20.7%), p=0.03.

There was also a significantly lower rate of likely IRIS events (as judged by the end-point committee) with enhanced prophylaxis (7.4 vs 12.00%), p=0.001.

But there was no significant difference in the rate of severe bacterial infection between groups (42 vs 33), p=0.32). There were slightly lower rates of serious adverse events and grade 4 adverse events in the enhanced-prophylaxis group, but these were not significant (p=0.08 and p=0.09, respectively).

Rates of viral suppression and adherence to ART were similar in the two groups.

The authors noted that among HIV positive adults and older children with advanced HIV who started ART, the relative rate of death was 27% lower in those who received enhanced prophylaxis than those who received standard prophylaxis. This benefit was maintained through 48 weeks: 24% lower. The number-needed-to-treat to prevent one death was 29.

The cost of enhanced prophylaxis ranged from US $8 to $34 across the trial countries. But drug costs varied by a factor of 10, once again highlighting the importance of ensuring access to medicines at the lowest prices across all countries.

The authors concluded that enhanced prophylaxis is relatively inexpensive, and would be fairly easy to implement at primary health centres, since it only requires screening for clinical symptoms and CD4 testing to identify asymptomatic people with advanced HIV.

Reference

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Increased frequency and progression of kidney disease in HIV positive people

Gareth Hardy, HIV i-Base

A recent review in JID reported higher rates of renal complications in HIV positive people that was not explained by traditional risk factors.

Chronic kidney disease (CKD) is known to be more prevalent in people with HIV infection, but it is not certain if this is due to HIV infection, ART or traditional CKD risk factors, like hypertension, smoking or diabetes. Exposure to certain ARVs, such as tenofovir or atazanavir is known to cause renal dysfunction.

Furthermore, elevated markers of chronic inflammation that result from HIV infection, are also associated with renal dysfunction. A team of researchers at the Amsterdam Institute for Global Health Development in the Netherlands, investigated the relationship between these factors and the prevalence of CKD by comparing markers of renal impairment in middle-aged HIV positive men with those of HIV negative men, alongside information about medical histories and socio-demographic categories. [1]

Comparisons of renal impairment, albuminuria and proximal renal tubular dysfunction were made between 596 HIV positive middle-aged men and 544 HIV negative men in the AGE IV Cohort Study. In addition, longitudinal follow up was conducted to asses whether being on ART was associated with worsening renal impairment or albuminuria, and data was censored at the point of any change in ART regimen.

Renal impairment was determined as estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, while albuminuria was defined as albumin/creatinine ratio of ≥3 mg/mmol, and proximal renal tubular dysfunction was defined as a retinol-binding protein/creatinine ratio of >2.93 mcg/mmol and/or fractional phosphate excretion of >20% with plasma phosphate <0.8 mmol/L.

Mean age at baseline for the study was 52.7 years for HIV positive people and 52.1 years for HIV negative people. Out of the HIV positive people in the study, 95% were currently taking ART and 94.3% had undetectable viral loads (200 copies/mL plasma). Current tenofovir use was reported for 73.3% of HIV positive participants while prior use was reported for 12.3%. Median total cumulative exposure to tenofovir was 4.0 years (IQR: 2.1 to 6.5). Significantly higher proportions of the HIV positive participants were of African descent, had HCV infection, were smokers, had dyslipdemia, cardiovascular disease or elevated inflammatory markers, than the HIV negative participants.

Renal impairment was significantly more prevalence in HIV positive participants (4.7%) than HIV negative participants (2%) (p = 0.01). Similar differences were found for albuminuria, observed in 24.4% of HIV positive participants and 5.6% of negative participants (p<0.001), as well as proximal renal tubular dysfunction observed in 40.1% HIV positive participants and 8.6% of HIV negative participants (p<0.001). Furthermore renal impairment was most prevalent in HIV positive people who had previously taken tenofovir (16.4%), in comparison to those who had either never taken it (4.7%) or were currently taking it (2.8%). The authors suggest the latter group have not had to discontinue taking tenofovir presumably as they have not experienced tenofovir toxicity. Albuminuria and proximal renal tubular dysfunction were not different between tenofovir usage groups.

After adjusting for age, sex, being of African descent, smoking, HCV infection, hypertension, diabetes and dyslipidemia, HIV infection remained independently associated with renal impairment (adjusted odds ratio [OR] 2.1; 95% confidence interval [95%CI] 1.0 to 4.4, p=0.05), albuminuria (OR 5.8; CI 3.7 to 9.0. p<0.001), and proximal renal tubular dysfunction (OR 7.1, CI 4.9 to 10.2. p<0.001).

Traditional CKD risk factors and older age were also both independently associated with all three markers of impaired renal function. Proximal renal tubular dysfunction was associated with a post HIV diagnosis low nadir body weight (OR 0.59; 95%CI 0.50 to 0.70. p <0.001), exposure to a protease inhibitor (OR 1.54; 95%CI 1.00 to 2.30, p=0.03) and cumulative exposure to tenofovir (OR 1.54; 95%CI 1.00 to 2.30, p=0.03).

Longitudinal analysis was performed with 377 of the HIV positive study participants who had 3.9 years of median follow up and 479 of the HIV negative participants who had 4.1 years of median follow up. Rapid eGFR decline occurred more frequently in HIV positive participants (5.8%) than HIV negative (2.3%, p=0.008).

The rate of decline in renal impairment was significantly greater for HIV positive people than HIV negative people, with an unadjusted eGFR slope of –1.36 (95%CI: –1.59 to –1.14) mL/min/1.73 m^2/year in HIV positive and –0.71 (95%CI :–0.90 to –0.51) mL/min/1.73 m^2/year in HIV negative participants. After adjusting for all other variables, HIV infection was independently associated with greater eGFR decline. Adjustment for diabetes, dyslipidemia, hypertension and baseline cardiovascular disease had little effect on the association between eGFR decline and HIV infection. Exposure to tenofovir was not independently associated with rate of eGFR decline (OR 1.6; 95%CI: 0.5 to 5.2; p = 0.41).

In summary, HIV positive people in this study were more likely than HIV negative people to have renal impairment, albuminuria and proximal renal tubular dysfunction, as well as more rapid eGFR decline during follow up.

The authors state that their data could not explain the association between HIV infection and the prevalence or progression of CKD by a higher prevalence of traditional CKD risk factors alone. Importantly the association of proximal renal tubular dysfunction was particularly prevalent in HIV positive people with current or historical exposure to tenofovir.

Reference

Katherine Kooij et al. Higher prevalence and faster progression of chronic kidney disease in HIV positive middle-aged individuals compared with HIV negative controls. JID 2017. 216(6);622–631. (15 September 2017).

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OTHER NEWS

DFID's work on HIV and AIDS: A stocktake review

STOPAIDS

When DFID indicated it would not undertake a review of its work, perhaps because of the lower priority given to HIV, a civil society review was produced by STOP AIDS.

The aim is to help DFID to effectively target its capacity and resources to have the most impact on the global HIV response. It aims to ensure that the UK does its part to realise the end of AIDS as a public health threat by 2030.

https://stopaids.org.uk/resources/a-stocktake-review-of-dfids-work-on-hiv-and-aids

https://stopaids.org.uk/wp/wp-content/uploads/2017/09/Stocktake-Review.pdf (PDF)

ON THE WEB

Community resources

HIV and adherence

Research Initiative Treatment Action! (RITA)

The latest issue of RITA looks at HIV adherence, including an interview with Seth Kalichman and several review articles (that provide simple and practical advice for doctors.

Available online:

http://centerforaids.org/pdfs/rita0917.pdf (PDF)

FUTURE MEETINGS

Conference listing 2017/18

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.

cliniQ's 4th international Trans Health Matters conference

17 October 2017, venue tbc, London

www.eventbrite.co.uk/e/cliniq-trans-health-matters-2017-tickets-34763486524

19th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

23–25 October 2017, Milan

www.intmedpress.com

16th European AIDS Conference

25–27 October 2017, Milan

www.eacsociety.org

BASHH gender and sexual minorities conference

3 November 2017, Birmingham

bashh.org/events/training-courses-and-meetings/gender-and-sexual-minorities-gsm-sig-biennial-conference-day

International Workshop on HIV Drug Resistance and Treatment Strategies (IWHDR)

6–8 November 2017, Johannesburg

www.HIVresistance2017.co.za

Hepatology Highlights for the Healthcare Specialist in collaboration with BVHG

15 November 2017, London

www.bhiva.org

BHIVA Autumn Conference

16-17 November 2017, London

/www.bhiva.org

International Workshop of HIV & Women

2-3 March 2018, Boston

www.virology-education.com

Conference on Retroviruses and Opportunistic Infections (CROI 2018)

4–7 March 2018, Boston

www.croiconference.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

- Introduction to ART (September 2016)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (February 2015)
- Guide to HIV, pregnancy & women's health (December 2015)

New pocket guides

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.

The first five pocket leaflets are: Introduction to ART, HIV and pregnancy, ART and quality of life, UK guide to PrEP and HCV/HIV coinfection.

We hope these are especially useful as low literacy resources.

The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

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http://i-base.info/order

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- **Guide to HIV, pregnancy and women's health** *(November 2015): 52-page A5 booklet*

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