Friday 27th February 2015

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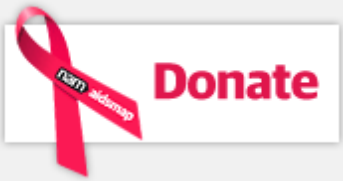

Two interferon-free regimens have high hepatitis C cure rates for people with HIV

David Wyles and Susanna Naggie presenting at CROI 2015. Photo by Liz Highleyman, hivandhepatitis.com.

A pair of two-drug, 12-week regimens containing neither interferon nor ribavirin cured hepatitis C for more than 95% of people with HIV and hepatitis C co-infection, according to two studies presented to CROI this week.

The first regimen was sofosbuvir plus ledipasvir (*Harvoni* coformulation), produced by Gilead. The second was sofosbuvir *(Sovaldi)* plus daclatasvir (*Daklinza*), with the latter drug produced by Bristol-Myers Squibb. Ledipasvir and daclatasvir are both NS5A inhibitors.

In both studies, the response rates in people with HIV and hepatitis C co-infection were as high as those for people with hepatitis C mono-infection in other trials. This supports recent hepatitis C treatment guidelines recommending that HIV-positive and HIV-negative people should be treated in the same way for hepatitis C.

For sofosbuvir plus ledipasvir (*Harvoni),* 335 people with co-infection took part in the open-label, non-randomised study. The trial had broad inclusion criteria and included more difficult-to-treat groups such as prior non-responders and people with liver cirrhosis than many other studies. Almost all had genotype 1, more than half were treatment-experienced and three-quarters had unfavourable IL28B gene variants. All were taking HIV treatment and most had an undetectable viral load.

Participants took a once-daily tablet for twelve weeks, with an additional twelve weeks follow-up to assess sustained virological response (SVR12), or continued undetectable hepatitis C. The overall SVR12 rate was 96%, similar to that in people with mono-infection. Having taken treatment before, having liver cirrhosis or NS5A resistance variants made little difference to the cure rate.

However, SVR12 rates were slightly lower in participants who were black. This had not been observed in mono-infection studies. One possible explanation, which will be explored, is an influence of genetics on drug response when both ledipasvir and antiretrovirals are used.

For sofosbuvir *(Sovaldi)* plus daclatasvir (*Daklinza*), 151 previously untreated individuals with co-infection were randomised to either eight or twelve weeks of the regimen, while 52 treatment-experienced individuals all took it for twelve weeks. Almost all participants were taking HIV treatment and had an undetectable viral load.

While two-thirds had hepatitis C genotype 1a, people with genotypes 2 to 6 were included – an advantage of daclatasvir is that it is active against multiple genotypes whereas ledipasvir is primarily active against genotype 1.

Participants randomised to take the once-daily tablets for eight weeks had poorer results (SVR12 76%), but the twelve-week course worked well – an SVR12 of 96% in people who had never taken treatment before and 98% in treatment-experienced individuals. Rates were similar across genotypes.

Both regimens studied were generally safe and well-tolerated.

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PEPFAR-funded abstinence work had no impact

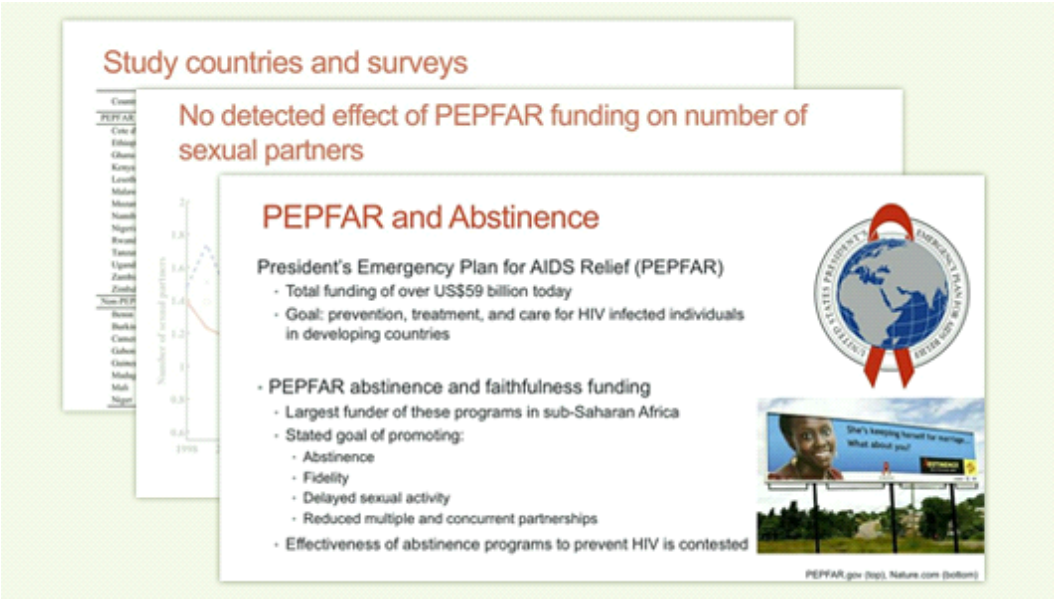

Image from the presentation by Nathan Lo, at CROI 2015.

Nearly US$1.3 billion spent on US-funded programmes to promote abstinence and faithfulness had no significant impact on behaviour in 14 countries in sub-Saharan Africa, a preliminary analysis of sexual behaviour data has shown.

The President's Emergency Plan for AIDS Relief (PEPFAR) was launched in 2004 with a Congressional requirement for a fixed proportion of PEPFAR prevention funds to be spent on programmes promoting abstinence from sexual relations, delaying sexual activity and faithfulness to one partner. Programmes supported by this funding stream also promoted partner reduction. But while there may be epidemiological grounds for thinking that delaying sexual debut and reducing sexual activity might reduce opportunities for acquiring HIV, especially in young women, there is limited evidence for interventions that are effective in achieving these objectives.

The researchers compared trends in sexual behaviour derived from national Demographic and Health Surveys in 14 PEPFAR focus countries and eight other African countries where PEPFAR funding was not determining the content of HIV prevention interventions.

While there was a trend for men to have fewer sexual partners in both sets of countries, the researchers could not identify any impact associated with PEPFAR funding. Higher levels of PEPFAR funding in specific countries didn't seem to be associated with differences in sexual behaviour either.

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New tenofovir formulation equally effective but safer

Paul Sax presenting at CROI 2015. Photo by Liz Highleyman, hivandhepatitis.com.

Tenofovir alafenamide (TAF), a new formulation that has lower concentrations in the blood but reaches higher levels in cells, is as effective as the currently available version, tenofovir disoproxil fumarate (TDF). Furthermore, it has less detrimental effects on the kidneys and bones compared with TDF.

Tenofovir disoproxil fumarate (*Viread*) is one of the most widely used antiretroviral drugs. It is a component of the *Truvada* coformulation and the single-tablet regimens *Atripla, Eviplera/Complera* and *Stribild.* TDF is highly potent and generally safe and well-tolerated, but can cause kidney and bone problems in some patients.

TAF is a new pro-drug that delivers the active agent, tenofovir diphosphate, more efficiently to cells infected with HIV. TAF produces adequate intracellular levels with lower doses, which means lower concentrations in the blood plasma and less drug exposure for the kidneys, bones and other organs and tissues.

Whereas cheaper, generic versions of tenofovir disoproxil fumarate will be available in many Western markets soon, TAF will be a new product exclusive to Gilead and protected by patent.

Data were presented comparing the *Stribild* coformulation (elvitegravir, cobicistat, emtricitabine and TDF) with an alternative coformulation replacing TDF with TAF. Around 1700 previously untreated people took part in the studies in Europe, North America, Latin America and Asia.

After 48 weeks, the two regimens had similar high efficacy, showing that the TAF coformulation is non-inferior. Rates of viral suppression were over 90% in both arms of the study, irrespective of age, sex, race, HIV-1 RNA and CD4 cell count. Fewer than 1% had evidence of primary resistance mutations in either arm.

Overall rates of side-effects and serious adverse events did not differ.

Kidney-related adverse events were examined in more detail. Compared with TDF, TAF had no discontinuations due to renal adverse events, significantly smaller decreases in eGFR and significantly less proteinuria, albuminuria and tubular proteinuria.

In relation to bone health, TAF has significantly less impact on spine bone mineral density (26% lost at least 3%, compared to 45% in the TDF group) and on hip bone mineral density (17% lost at least 3%, compared to 50% in the TDF group).

The coformulation studied here has been submitted to regulators in the USA and Europe for licensing.

Gilead is also developing a coformulation of TAF and emtricitabine, to replace *Truvada*. This may also be considered for use as pre-exposure prophylaxis (PrEP).

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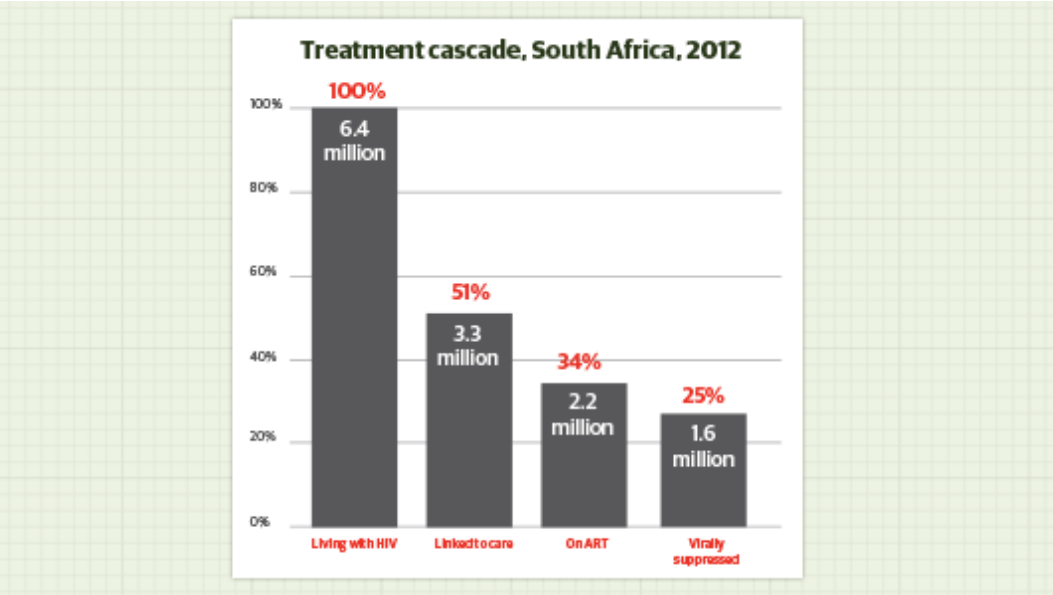
Treatment cascades in African countries



South Africa has the largest antiretroviral treatment programme in the world but an analysis of its treatment cascade shows that more focus is needed on improving engagement with care – especially in men and young people. This is necessary if the country is to maximise the preventive benefit of antiretroviral treatment.

Of the 2.5 million *men* living with HIV in South Africa, only 39% are linked to care, 27% are taking antiretroviral treatment and 19% are virally suppressed.

Of the 3.9 million women, 58% are linked to care, 38% are taking antiretroviral treatment and 28% are virally suppressed.

Young people aged 15-24 were much less likely to be on treatment and virally suppressed than older adults, despite similar rates of linkage to care.

David Maman presenting at CROI 2015. Photo by Liz Highleyman, hivandhepatitis.com.

A second study, based on data from three communities in Kenya, Malawi and South Africa, suggests that to maximise preventive benefits, efforts to expand treatment coverage need to focus on those with the highest viral load – mainly people who are already eligible for treatment under current guidelines.

Around 19,000 people took part in household surveys, with just over 4000 testing positive for HIV. The majority of those testing positive were eligible for treatment under national guidelines, although this varied from country to country due to different inclusion criteria (60% in Kenya, 69% in South Africa and 80% in Malawi).

The researchers focused on the viral loads of people not taking HIV treatment. Less than a quarter of untreated people with a CD4 count between 500 and 750 cells/mm^3 had a very high viral load (over 100,000 copies/ml), associated with a very high risk of onward transmission.

In contrast, over half the untreated individuals with a CD4 count below 350 cells/mm^3 had such a high viral load.

This suggests that to maximise *preventive benefits* of treatment, efforts to expand treatment coverage need to focus on people who are already eligible for treatment under current guidelines. This would have more impact than raising the CD4 cell count at which people begin treatment.

Nonetheless, a study presented the previous day at CROI showed that there are *individual health benefits* to beginning treatment with a CD4 cell count above 500 cells/mm^3 in resource-limited settings.

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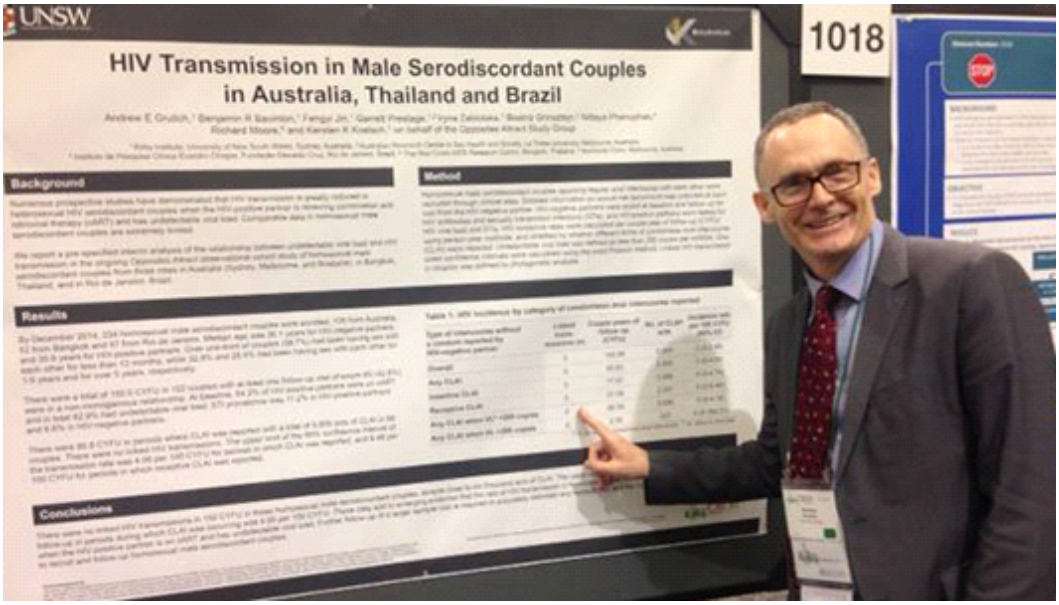
No HIV transmission in gay couples study



Andrew Grulich at CROI 2015. Image by The Kirby Institute (http://kirby.unsw.edu.au).

An early analysis of an Australian-based study of gay male couples of opposite HIV status (serodiscordant couples) has so far seen no transmissions from the HIV-positive partner within the couple. These observational data from the Opposites Attract study concur with the interim analysis of the larger PARTNER study that was released at CROI one year ago. PARTNER reported no episodes of transmission during 16,400 episodes of anal sex (including condom-protected episodes) in gay men.

Recruitment to the new study began in late 2013 in three Australian cities (Sydney, Melbourne and Brisbane), and now also includes Bangkok in Thailand and Rio de Janeiro in Brazil. Most of the HIV-positive partners are on treatment and have an undetectable viral load.

During the study's first year, 152 couples provided data. A total of 5905 episodes of anal sex were reported. No transmissions between couples (linked transmissions) have so far been seen in the study.

Because of the relatively small numbers enrolled so far, there is some uncertainty to these findings. Although there have been zero transmissions, this does not necessarily mean a zero chance of transmission. The researchers have calculated that in this population, the highest-likely figure for the chance of transmission during condomless anal sex with an HIV-positive partner (regardless of viral load) is 4%. The highest-likely figure when the HIV-negative partner was receptive (bottom) is 7%.

But as with PARTNER, these estimates are likely to get closer to zero as the researchers collect more data.

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Circumcision is reducing HIV incidence in Uganda

The roll out of medical male circumcision in the rural Rakai district of Uganda is having a substantial impact on new HIV infections in men. The data come from one of the sites which conducted a randomised controlled trial of circumcision and show that circumcision can make a

difference outside of a trial setting.

The proportion of non-Muslim men who were circumcised increased from 9% in 2007 at the time of the randomised trial to 26% in 2011. After adjustment for other factors that could impact HIV transmission (such as greater use of antiretroviral therapy), every 10% increase in circumcision coverage was associated with a 12% reduction in HIV incidence in men.

But so far, HIV incidence in women has not declined.

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Survey: HIV dialogue

Do you work in health care **in Europe**, or are you living with HIV, or both? Please help us to understand communication between healthcare professionals and people living with HIV in Europe.

We're running two anonymous online surveys, one for people living with HIV and one for healthcare professionals. Both surveys are available in English, French, Italian, Portuguese, Russian and Spanish.

The surveys are investigating what happens in HIV care appointments; such as the type of topics patients and healthcare professionals prioritise.

If one of the surveys applies to you, we would really appreciate your help.

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Take part in the online survey for healthcare professionals in Europe

Take part in the online survey for people living with HIV in Europe

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