

Evidence for U=U: PARTNER studies & the prevention access campaign



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Simon Collins (i-Base.info)

NHIVNA conference, Brighton 2018

I'd like to thank the organisers for the chance to speak about U=U.

It is really helpful to have this pre-conference workshop focus on U=U – especially as nurses play such a key role in providing information for us.

Interests to declare

No financial conflict of interest

I am community rep on PARTNER steering committee
and i-Base are signed on to U=U campaign.

Timeline and evidence

1998 vs 2008 vs 2018

- Difficult to think pre-2016
- But at BHIVA 2018, most/some doctors do not tell all/some patients...

I find it difficult to remember clearly how difficult HIV was before U=U.

Not just the evidence, but the community campaign has overturned fear against HIV – for many people.

This has taken time – even with current evidence, some people are uncertain.

BHIVA statement (2017)

Prof Chloe Orkin, BHIVA chair



There should be no doubt that a person with sustained, undetectable levels of HIV in their blood **CANNOT** transmit HIV to their sexual partners. ”

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Personal views

- Current views – 100%? (or close)
- Translate to personal life
- Which year convinced you?
2018, 2017, 2016, 2014, 2008?

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It would help to have a show of hands for rough views in the audience.

Could we have a show of hands for who thinks HIV is not transmitted with undetectable viral load?

Or a close to 100% as matters?

Also, to see how many people are not convinced – perhaps worried about the 1 in a million chance?

Also, for people who are convinced, roughly when did this happen.

Was this in the last 6 months – ie 2018 ?

In the last year?

The year before – 2016 when full partner results were published and U=U was launched ?

What about 2014 when PARTNER results were first presented?

Or going back to 2008 with the Swiss Statement?

Timeline

- 1998 ART stops mother to baby transmission [1]
- 1998 US guidelines - early ART [2]
- 2000 Rakai Study (Observational) [3]
- 2008 Swiss Statement: zero risk (Evidence review) [4]
- 2011 HPTN 052: 1 vs 27 (Randomised: low risk) [5]
- 2014 PARTNER: zero/44,000 (Observational) [6]
- 2016 PARTNER published – zero/58,000 [6]
- 2016 U=U campaign
- 2017 Opposites Attract [7]

- 1. Beckerman et al. IAS, 1988
- 2. DHHS, 1998;
- 3. Quinn et al, NEJM 2000;
- 4. Vernazza et al, 2008. 5. Cohen et al NEJM 2011;
- 6. Rodgers et al. CROI 2014 and JAMA 2016;
- 7. Grulich A et al. IAS 2017.

So the timeline could go back 20 years.

Different types of evidence

- Observational data – large cohorts when randomised studies are not possible
- Randomised clinical trials (RCTs)
- Systematic review – comparing studies
- Case reports – small studies
- Expert opinion

The dramatic change had been to emphasise broad confidence in safety rather than any residual concern about risk.

There are also different types of evidence

Even though RCTs are often referred to as gold standard for evidence – often these are neither possible nor ethical.

All types of research has advantages and disadvantages – depending on the study question.

Opinion vs evidence

- Expert opinion - NOT evidence

There is currently no evidence that HIV transmission occurs when viral load is undetectable.

Challenge since 2008 is whether HIV transmission can occur – so far not been proven.

In absence of evidence, having an opinion against U=U is either out-of-date or just prejudice.

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References



HTB article:

“The evidence for U=U
(Undetectable = Untransmittable):
why negligible risk is zero risk”

www.i-base.info/htb/32308

Or just Google: “U=U”

A more detailed review – with additional studies – is online.

This is the URL – or just google U=U

1998

Beckerman et al,
IAS conference
1998, Abs 459.

Small observational
study treating HIV
positive pregnant
women with triple
therapy ART for their
own best care.

“Despite adherence problems
... the use of combination
ART ... during pregnancy
results not only in improved
maternal health, but also in
rates of transmission
that approach zero”

In 1998, the US obstetrician Karen Beckerman reported zero transmissions during pregnancy.

Vertical transmission – from the mother to her baby – is a far higher risk than any other exposure. Hundreds of times more risky than sex.

Dr Beckerman treated HIV positive women for their best health.

1998

US DHHS
guidelines
(Dec 1998)

Expert
opinion.

“Factors that would lead one to initiate early therapy include ... possibly decreasing the risk of viral transmission.”

In 1998, very conservative US guidelines also recognised that ART could reduce HIV risk.

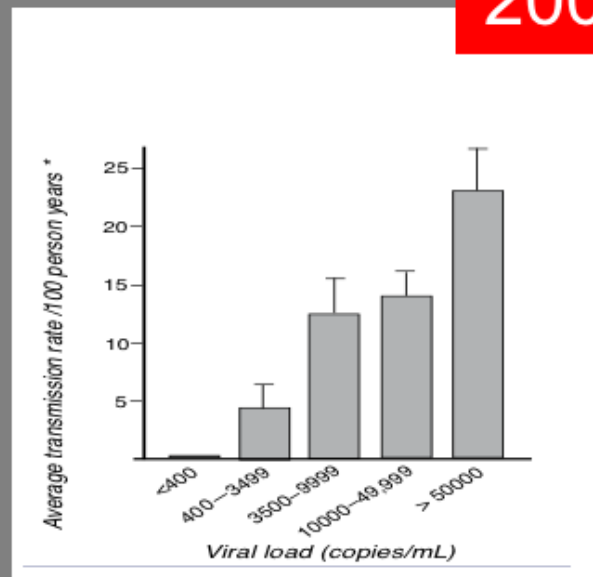
2000

Quinn et al, NEJM 2000

Rakai study:

~ 400 +ve/-ve couples
in Uganda for 30
months: no infections
when VL less than 1500
copies/mL.

Large observational study. Pre-
ART, low condom use, no STI
effect, new cases all
uncircumcised men.



Then in 2000, a study published in the NEJM reported n transmissions when VL was less than 1500 copies/mL

This was in heterosexual couple with little access to ART and low condom use.

The study found little impact of STIs but did see a strong signal about circumcision.

2008

Swiss Statement
(Vernazza et al,
2008)

Evidence review –
driven by criminalisation
in Switzerland.

Also: “We were telling
everyone to use
condoms when we had
no evidence they
needed to”.

“an HIV positive person on
effective HIV treatment (ART)
cannot transmit HIV through
sexual contact”

- on ART and adherent
- undetectable VL
- no STIs
- risk <1 in 100,000 (<0.001%)

The Swiss Statement was ground-breaking.

It used an evidence review to highlight that HIV transmission didn't occur at low viral load levels.

As a caution, there were several caveats: needing to be adherent on effective ART with no STIs.

Leading researchers were aware that HIV was undetectable in sexual fluids from sperm washing programme.

: “We were telling everyone to use condoms when we had no evidence they needed to”.

2011

HPTN 052

(Cohen et al,
2011)

Pilot from 2005,
enrolled 2007-
2010

96%
reduction

Randomised ~ 1700 +ve/-ve
couples to early ART vs waiting.

Study stopped early – ethics.

All linked infections in couples
waiting for ART (+ single case
with detectable VL).

Durable over 4 yrs (2017).

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In 2011, results from the randomised HPTN-052 study were so clear about the impact of ART in reducing transmission that the study was stopped early. All HIV positive partners were offered early ART.

This was reported as a 96% reduced risk from using ART.

Interestingly, a pilot phase started in 2005, with main study enrolling from 2007-2010.

The study expected 188 infections over six years, with rates of 8% vs 13% in the early vs late treatment groups.

All except one of the transmissions 27/28 linked transmissions – were not on ART.

The single case was very soon after starting ART when VL would still be high and detectable.

HPTN 052: reported 2011: (enrolled 2007-2010)

1700 couples: HIV+ CD4>350

Expected ~ 200
infections: 8% vs 13%

Randomised 1:1

ART

No ART

~ 6 years follow up

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N=1*



~ 4 years follow up

No ART



N=27

* Very early ART when VL was still detectable

Also interesting that in planning the study, the prediction was far from 0% risk

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Best evidence: PARTNER

2014
-2016

~ 900 HIV+/- couples
not using condoms.



Follow over time, collect info on risk.
After 58,000 times without condoms:
ZERO linked transmissions

Rodgers et al. CROI 2014 and IAS July 2016.

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The results showed lack of transmission from 58,000 times when condoms were not used.

PARTNER [1, 2, 3]

2014

- ~900 couples not using condoms (1/3 gay men).
- Detailed sexual questionnaires.
- Already not using condoms (for years)
- One third were gay male couples.
- Calculated absolute real risks.
- STI were common in gay men.
- Undetectable = less than 200 copies/mL
- Protected anonymity

1. Rodgers et al. CROI Feb 2014; 2. IAS July 2016; 3. JAMA accepted Feb 2016, published July 2016.

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As a response to Swiss statements – before HPTN-052 – the PARTNER study was planned.

HPTN -52 couldn't quantify risk.

There was no data for anal sex – gay or straight – and none for gay men.

Believed risk to be zero – but needed to set estimated ranges across all cases – called 95%CI

The was an observational study – just following couple who were already not using condoms.

PARTNER - UK sites

2010-
2018

UK sites

Birmingham: Birmingham Heartlands Hospital

Brighton: Lawson Unit, Royal Sussex Country Hospital

Bristol: Southmead Hospital

Cardiff: Cardiff Royal Infirmary

Coventry: Coventry and Warwickshire Hospital

Edinburgh: Western General Hospital

Leicester: Leicester Royal Infirmary

Manchester: North Manchester Hospital

London centres

Royal Free Hospital

St. Stephens Centre/Kobler clinic

Royal London Hospital

Homerton Hospital

North Middlesex Hospital

King's College Hospital

St. Thomas Hospital

Mortimer Market Centre

St. Mary's Hospital

This was an international study – with large involvement of UK research centres

PARTNER

2014

- Intensive involvement of nurses (Tina Braun, CHIP)
- Recruiting and retaining couples depended on close connections with researchers.
- Enrolment slower than predicted, but steady.
- Sometimes driven by one rather than both partners
- Often difficult if relationships were short-term
- High participant interest in outcome
- High community involvement throughout

PARTNER involved a lot of involvement from community nurses

Even though many couple were already not using condoms, engaging with the study involved time and commitment

The study produced posters, leaflets and newsletters to help recruitment and retaining participants



The PARTNER 2 Study:
a study for sero-different
gay couples



If you would like
to consider joining the
study, please mention
this to one of the
clinic staff participating
in PARTNER.

Understanding the risk of
HIV transmission when the
HIV+ partner is on therapy

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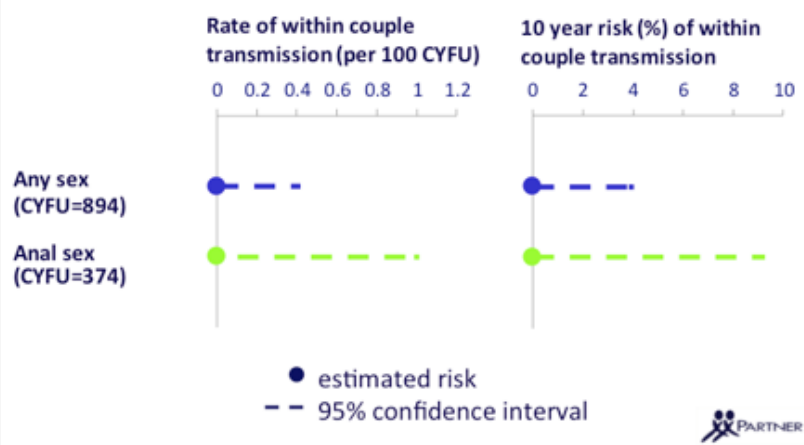
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This was a community supported and driven study

Leaflets and posters were produced in about ten languages

Real people were included.

Rate of HIV transmission according to sexual behaviour reported by the negative partner

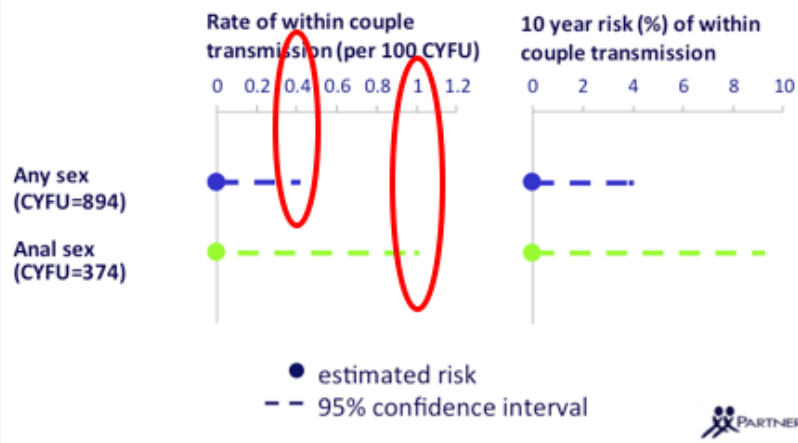


Rodgers et al.
CROI Feb
2014

The technical aspect of the study focussed on upper limit of 95%CI interval.

This was not based on a real risk – just not being able to rule out the real risk could be in this range.

Rate of HIV transmission according to sexual behaviour reported by the negative partner



Rodgers et al.
CROI Feb
2014

The red ovals show the different amount of data for vaginal vs anal sex

PARNTER wasn't proving zero risk, but qualifying range of potential risk (that couldn't be ruled out).

PARTNER timeline

2016

- 2009 Protocol, funding and planning - Rate 0.5/100 CYFU
- 2010 Sep – first enrolled participants
- 2014 Feb - Preliminary results at CROI
- 2014 March – Launch of PARTNER 2
- 2014 May – Final data collection
- 2014-15 Paper rejected by several journals, JAMA accept but take 18 months to publish with repeated analyses.
- 2016 Apr – JAMA accept – then delay to IAS (July)
- 2018 – PARTNER 2 results

PARTNER took five years to generate first good evidence and another two years to be published – linked to publicity for zero risk

Zero HIV transmissions in the PARTNER study

ZERO

i-Base: >35,000 facebook views in first week

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The graphic is the important summary – irrespective of time on ART, type of sex, ejaculation or not, STIs etc – zero transmissions

This post – with a related Q&A page – generated the biggest social media response for any i-Base article.

The Q&A was translated into Spanish and Russian within a week.

2016

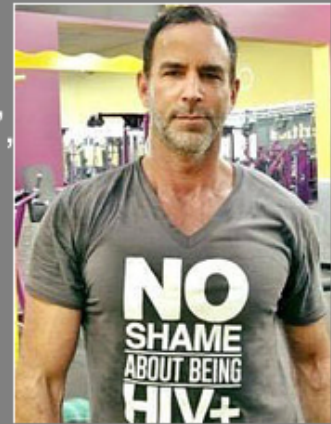
Prevention Access Campaign

Launched in July 2016 by Bruce Richman and other researchers and activists.

Driven by problems with “96% reduced risk”, use of “reduced”, “negligible” but not 0.

Pressure for scientist to shift focus from minimal (if any) risk.

Mainstream campaign – IAS, BHIVA, US CDC: EFFECTIVELY ZERO = ZERO



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NHIVNA conference, Brighton 2018

At the same IAS conference, the Prevention Access Campaign launched the consensus statement – supported by PARTNER researchers

Driven by public information focusing on risk rather than safety – including problems with 96% figure.

The community activity in publicising protection from ART pressured scientists to talk about the results in realistic language.

Rather than continue to emphasise increasingly marginal risks (that might not even exist).

*Karim,
prof de danse*

ACT UP
DUBLIN

**PEOPLE WITH HIV ON EFFECTIVE
TREATMENT DO NOT SEXUALLY
TRANSMIT HIV**
UNDETECTABLE = UNTRANSMITTABLE

*Les séropositifs sous traitement
ont beaucoup de choses
à nous transmettre.
Mais pas le virus du sida.*

AIDES
aides.org

www.preventionaccess.org

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Since 2016, many organisations have publically supported U=U – initially community groups

International AIDS Society

A graphic for the U=U campaign. It features a teal background with a geometric pattern. On the left, the text 'U=U' is written in large white letters. Below it, the text 'UNDETECTABLE = UNTRANSMITTABLE' is written in smaller white letters, with an equals sign between the two words. On the right, a white box contains the text 'A PERSON LIVING WITH HIV WHO HAS AN UNDETECTABLE VIRAL LOAD DOES NOT TRANSMIT THE VIRUS TO THEIR PARTNERS.' in teal. In the top right corner of the graphic is the IAS logo, which consists of the letters 'I', 'A', and 'S' in a grid, with a red ribbon symbol below the 'S'.

U=U

UNDETECTABLE
=
UNTRANSMITTABLE

A PERSON LIVING WITH HIV
WHO HAS AN UNDETECTABLE
VIRAL LOAD DOES NOT
TRANSMIT THE VIRUS TO THEIR
PARTNERS.

The International AIDS Society is proud to endorse the U=U consensus statement of the Prevention Access Campaign.

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Then scientist with a higher profile – this is IAS, but large organisations also joined or issued similar statements in 2017:

BHIVA, UNAIDS, US CDC, US NIH, NYC public health etc

Balance now shifted to consensus view to officially support U=U

 **nycHealthy** 
@nycHealthy

If your viral load is undetectable, it means you can't pass HIV to others. Treatment = Prevention! on.nyc.gov/staysure #PlaySure #TasP



HIV treatments can make the virus undetectable, meaning it cannot be passed on

#TestWeekScot

www.preventionaccess.org

2016

U=U Statement

Since 2016 more than 670 organisations signed the U=U statement.

From more than 60 countries

Statement update in Jan 2018:
EFFECTIVELY ZERO = ZERO

Challenge: is transmission is possible?



This campaign has provided a new way to challenge discrimination.

It has become an international focus that is easy to translate.



www.preventionaccess.org



Se o preconceito é uma doença, a informação é a cura.

I = I

Indetectável = Intransmissível

Cientistas declaram: pessoas que vivem com HIV, estão em tratamento regular e têm carga viral **indetectável há mais de 6 meses não transmitem o vírus sexualmente.**

Para maiores informações acesse o site: giv.org.br

www.preventionaccess.org

K = K

**KHÔNG PHÁT HIỆN
=
KHÔNG LÂY TRUYỀN**

"Bằng chứng khoa học là rõ ràng. Một người có tải lượng virus không phát hiện được trong máu của họ không có nguy cơ lây nhiễm cho bạn tình của họ."

- Bản tuyên bố của NAM
aidsmap (Tháng Hai năm 2017)

www.preventionaccess.org

2018

London
version:



Ain't no viral load...
Ain't no risk of HIV

PARTNER 2 timeline

2018

2014 March – launch PARTNER 2

~900 gay couples only

- March 2014 to May 2018
- Provide similar level of confidence for gay men
Even though actual risk is believed to be zero

2018 May – Final data collection

2018 – PARTNER 2 results at IAS 2018

Personal views

- How important is PARTNER 2?
- Any changed views during today
- Increased confidence to talking about U=U?

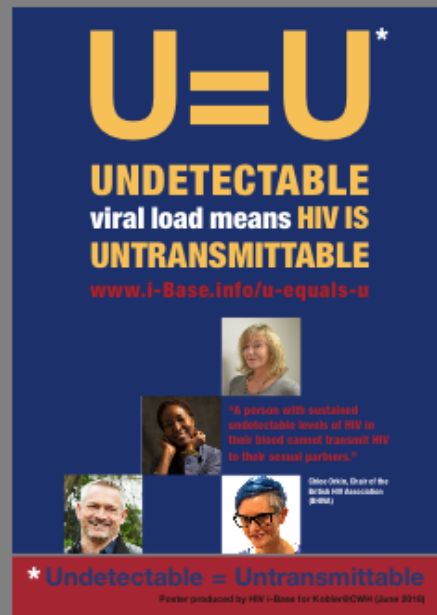
Conclusions

- Zero transmissions without condoms when VL undetectable in all studies.
- No published cases in ten years.
- U=U based on of upper range of acceptable risk
- Still not talked about by all health workers to all HIV positive patients
- PARTNER 2 results due July 2018.

Thanks:

Tina Bruun, PARTNER
Roy Trelvelion, i-Base
Michelle Ross, cliniQ
Angelina Namiba, Salamander Trust
Garry Brough, UK-CAB
Prof Chloe Orkin, BHIVA
PARTNER study

Questions?



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Here are a recent poster form i-Base for use in NHS clinics