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

EATG workshop on TasP: 22 Sept 2020

Simon Collins i-Base.info





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## **HIV transmission**

Big changes in last few years: Treatment as Prevention (TasP) & PrEP

- Does U=U? Am I uninfectious?
- What does it mean to be undetectable? Your health now and in the future, your relationships, your Quality of life
- Evidence (vs stigma and fear)

## Does U=U? Am I uninfectious?

- Easy vs complex answers?
- Residual prejudice/concern etc?
- Limits of science?
- Legal issues: criminalisation and liability for health workers?
- Historical approach to condoms?
- Risk in life?
- Evidence: PARTNER and other studies

## TasP concept?

Whether something is true or not?

If true, it will be having this effect, whether or not people are aware of it.

This is the case for U=U. For years people have been infectious – only now is that effect appreciated.

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TasP: Treatment as prevention

#### U=U: undetectable = untransmittable

https://www.preventionaccess.org



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#### **TasP: 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.

## **Basic answers**

- Science can find out whether an idea is true, or provable: facts vs opinion, fake vs real.
- If results are true not just from luck then repeating the study with get the same results.
- Community involvement produces better science – better questions, engagement and enrolment – faster answers.
- Community activism can reduce delays in improving care.

## **Overview**

- This talk will look use different research that supports U=U.
- Two hours to explore this subject ask questions...
- Best way to learn please take notes.

## **Key timeline**

- 1998 US guidelines early ART<sup>[1]</sup>
- 1998 ART stops mother to baby transmission <sup>[2]</sup>
- 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: high risk) [6]
- 2016 PARTNER published zero/58,000<sup>[6]</sup>
- 2016 U=U with wide endorsements.
- 2019 PARTNER2 published in Lancet.<sup>[7]</sup>

1. DHHS, 1998; 2. Beckerman et al. 3. Quinn et al; 4. Vernazza et al; 5. Cohen et al; 6. Rodgers et al; 7. Rodgers et al.

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Three key concepts

Experimental vs observational.

Prospective vs retrospective.

Longitudinal vs cross-sectional.

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## 1998 – US guidelines

April 1998:

Principle 11. HIV-infected persons, even those whose viral loads are below detectable limits. Therefore, they should be considered infectious. Therefore, they should be counseled to avoid sexual and drug-use behaviors that are associated with either transmission or acquisition of HIV and other infectious pathogens. No data are available concerning the ability of HIV-infected persons who have antiretroviral therapy-induced suppression of HIV replication to undetectable levels (assessed by plasma HIV RNA assays) to transmit the infection to others.

#### Dec 1998:

Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection; Acute infection (p13). Rational for early treatment:

• to possibly reduce the risk of viral transmission;

Expert opinion: Both emphasise condoms etc



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CDC



April 24, 1998 / Vol. 47 / No. RR-5

Recommendations and Reports US DHHS guidelines (Dec 1998)

Expert opinion.

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

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## **1998 – TasP pregnancy**

Karen Beckerman et al. Oral 458, abs 12151.

IAS 1998 – World AIDS conference in Geneva.

Cohort of women in San Francisco who for their own best *health* continued to use PI-based triple therapy during pregnancy. Out of 71 pregnancies only one baby was Positive (adherence and late treatment).

1998: AZT monotherapy reduced transmission to 8%

new standard of care added C-section.

**Observational, retrospective, longitudinal (?)** 

## mother-to-baby transmission approaching 0%

g the risk of mother-to-baby transmission High success rates were reported using different use of AZT monotherapy, although substantially educing the risk of transmission (from 22% to 8%), would now be seen to endanger the mothers long-term health because of the increased risk of developing resistance. Karen Beckerman from Areas Perinatal AIDS

Center at San Francisco General Hospital (BAPAC) both at an oral presentation at the conference and at a session of the commun

the first trimester. This is to avoid an overlap of side effects and morning sickness

This resulted in a reduction of transmission at this nethods all stressing the importance of the treatment centre approaching 0% through the ealth as the key to any treatment. The use of viral load monitoring and latest information or combination therapy [12151] questioned the need for Car patients who were effectively Studies which showed the benefit of elected aesarean section all relied on only AZT monotherapy [23272, 23275, 23291, 23603] and may be out-of-

date for mothers with access to combination therapy In the light of the San Franciso



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## 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"

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## 2000 – Rakai cohort

Thomas Quinn et al. New Eng J Med (NEJM).

Rakai study:

~ 400 +ve/–ve couples in Uganda for 30 months.

Limited ART (little)

No infections when VL less than 400 c/mL.

Large observational, prospective, longitudinal (?)



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## 2000 - 2008

Numerous smaller studies.

Some reporting no transmissions in cohorts – often linked to pregnancies on ART.

Some looking at supportive evidence – for example at drug levels and viral load in genital tract.

Swiss Statement (Pietro Vernazza et al, 2008)

Literature review and expert opinion – driven by criminalisation in Switzerland. Risk "similar to kissing" "an HIV positive person on effective HIV treatment (ART) cannot transmit HIV through sexual contact"

So long as:

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

#### Randomised studies = "Gold standard evidence"



## HPTN 052 (NEJM 2011)

"Prevention of HIV-1 Infection with Early Antiretroviral Therapy"

- n=1763 couples, nine countries, 54% Africa.
- CD4 <350 550 early ART vs <350.
- Advice to use condoms.
- Expected 188 transmission ~8% vs 13%:
  ~40% reduction.

## HPTN 052 (NEJM 2011)

"By the end of the trial, we anticipated a total of 188 transmission incidences, with cumulative incidence rates of 8.3% in the early-therapy group and 13.2% in the delayedtherapy group, for a total duration of 6.5 years, with an accrual period of 1.5 years and a 5% annual loss to follow-up"

Cohen et al, NEJM 2011.

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HPTN 052 (Myron Cohen et al, NEJM 2011)

https://www.nejm.org/ doi/full/10.1056/ NEJMoa1105243 Randomised ~ 1700 +ve/-ve couples to early ART vs waiting

• 39 infections, 28 linked, all in couples waiting for ART (+ single case with detectable VL)

- study stopped early
- protection over 4 yrs
- high condom use...

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# **PARTNER study**



- set up in 2009 by European researchers to get a dataset to look at Swiss Statement.
- Community-driven research included community reps.
- Set up to calculated absolute real risks (not relative risks).





Community-driven research - included community reps and (some) models.

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



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- >800 couples not using condoms.
- 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



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## **PARTNER study**

i-boze	HIV i-Base
	Published k

Published by Simon Collins (?) • 12 July 2016 • @

PARTNER study published in JAMA - will improve quality of life for millions and provides dataset to challenge criminilisation laws.

...

Boost Again



40,712 people reached

Decent estivity



Final results published in JAMA to coincide with IAS conference in Durban in July 2016..

# 40,000 i-Base FB hits in one week.

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## **PARTNER2** study

- Extended follow-up and enrolment for gay couples.
- Needed equality of data to match that for straight couples.
- Results at IAS 2018 and in the Lancet in 2019.





## **PARTNER2** study



Results from the PARTNER studies involved calculating a theoretical range for the results (even with zero transmissions). This is called the 95% confidence interval (95%CI). This statistical detail is often reported wrongly.

PARTNER 2 generated more data for gay men supporting zero risk than PARTNER 1 did for heterosexual couples.

# Rate of HIV transmission by sexual behaviour of the negative partner



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## PARTNER2 – May 2019

Rodger A et al. Lancet 2019. + press release.

https:// www.thelancet.com/ journals/lancet/ article/ PIIS0140-6736(19)3 0418-0/fulltext

#### HTB

PARTNER 2 study published in the Lancet: global news coverage that ART stops HIV transmission I Edit

3 May 2019. Related: HIV prevention and transmission.

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On 2 May 2019, the final results from the PARTNER study, including the full results in gay men, were published as an open access article in the Lancet. [1]

Although these data were widely reported when they were presented at the IAS



conference in Amsterdam last year [2], the high profile of the Lancet, which also included an accompanying editorial commentary and its own press release, meant that this research was picked up by mainstream news media.

## U=U campaign: 2016

Founded 2016 by US activist Bruce Richman with researchers including Pietro Vernazza, Jens Lundgren, Myron Cohen etc.

Now an international campaign linking over 1000 NGOs in more than 100 countries.



## U=U campaign: 2016 –

#### **International AIDS Society**



#### 

A PERSON LIVING WI WHO HAS AN UNDET VIRAL LOAD DOES N TRANSMIT THE VIRUS PARTNERS.

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

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## **U=U campaign: 2016 –**

V



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



www.preventionaccess.org/ undetectable



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## TasP – other questions

Partner study also provided real world data that covered many other cautions.

- Viral blips 50 200 c/mL.
- Adherence, STIs (30% gay couples).
- Viral load in genital tract.

These would have occurred throughout PARTNER but there were still ZERO cases.

## Language

Importance of clear and confident language.

Need to routinely use "zero" – not "almost zero".

BHIVA April 2019: A survey of UK doctors still used: extremely low (8%), next to zero (21%), virtually impossible (10%) or negligible (11%).

BHIVA issued new statement on using direct language.

## Conclusion

- Zero transmissions without condoms when VL undetectable in all studies.
- No published case reports since Swiss Statement in 2008.
- PARTNER data includes random blips and also STIs. Includes VL <200 c/mL.
- Caution: VL cut-off is 1000 c/mL in many lowincome countries (WHO guidelines) – but maybe Rakai cohort (Quinn et al, 2000) support this higher threshold for undetectable.

## Question

Q: Why do some doctors not actively tell all their patients about U=U?

A: Because we still let them!

As activists, we should be working in every country to make sure U=U is widely known. We need to challenge doctors who try to ignore the scientific evidence that supports U=U, including publicly.

## Source

The evidence for U=U.

#### https://i-base.info/ htb/32308

#### HTB

The evidence for U=U (Undetectable = Untransmittable): why negligible risk is zero risk I Edit

1 October 2017. Related: Special reports, HIV prevention and transmission.

Note: See postscript for results from the PARTNER2 study that provided further evidence for U=U in gay men. Table updated May 2019.

- Article translated into German.
- i-Base U=U resources



Undetectable viral load = Untransmittable HIV

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Over the last year, hundreds of HIV

organisations, including the US Center for Disease Control (CDC), have supported 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

#### Thanks

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# Additional slides

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#### HIV negative partners: Characteristics

	MSM couples (n=282)	Heterosexual couples (n=445)	
		M -ve (n=245)	W -ve (n=240)
At study entry			
Age, median (IQR)	40 (32-47)	45 (37-50)	40 (34-46)
Yrs CL sex, median (IQR)	1.5 (0.5-3.5)	2.7 (0.6-6.9)	3.5 (0.7-10.6)
During follow up			
Years in the study, median (IQR)	1.1 (0.7-1.9)	1.5 (1.0-2.0)	1.5 (0.9-2.0)
Diagnosed with STI, %	16%	5%	6%
CL sex with other partners, %	34%	3%	4%
CL sex acts/year, median (IQR)	43 (18-79)	37 (14-77)	38 (14-71)
Estimated total number CL sex acts	16,400	14,000	14,000



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#### HIV positive partners: Characteristics

	MSM couples	Heterosexual couples (n=445)				
	(n=282)	W +ve (n=245)	M +ve (n=240)			
At study entry						
Age, median (IQR)	42 (36-47)	40 (34-46)	45 (40-49)			
Years on ART, median (IQR)	5 (2-11)	7 (3-14)	10 (4-15)			
Self-reported adherence >=90%, %	97%	94%	94%			
Self report undetectable VL, %	94%	86%	85%			
CD4>350 cells/mm <sup>3</sup> , %	90%	88%	84%			
During follow-up						
Having missed ART for more than 4	2%	7%	4%			
consecutive days, %						
Diagnosed with STI, %	16%	4%	5%			

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