

Including CHIVA Parallel Sessions



Professor Andrew Leigh Brown

University of Edinburgh

9-10 October 2014, Queen Elizabeth II Conference Centre, London

BHIVA AUTUMN CONFERENCE 2014

Including CHIA Parallel Sessions



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COMPETING INTEREST OF FINANCIAL VALUE > £1,000:	
Speaker Name	Statement
Professor Andrew Leigh Brown	None
Date	October 2014

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Inferring HIV transmission dynamics from phylogenetics

Andrew Leigh Brown University of Edinburgh

Annual UK HIV Diagnoses

Estimates for 2012MSMAdjusted3,250MSMObserved2,964HETAdjusted2,880HETObserved2,581

Source: PHE



Transmission dynamics depend on the contact network

- Often reconstructed by interview data
 - Number, gender & identity of contacts in last year



Transmission dynamics depend on the contact network

- Often reconstructed by interview data
 - Number, gender & identity of contacts in last year
- HIV
 - Rapid evolution
 - Similar sequences reveal linked infections



Closely related viral sequences cluster in a phylogenetic tree



• 9 clusters visualised in this tree

The UK national epidemic - subtype B

- Subtype B still >80% MSM
- Data from UK HIV Drug Resistance Database
 - viral sequences from routine resistance assays
- 14,560 subtype B sequences, 1 per individual $\approx 2/3$ of diagnosed cases in MSM in 2007



Subtype B: 50% linked to \geq 1 other



Clusters of up to 100 individuals



Incorporating real time

- Based on "molecular clock"
 - viral mutations occur ~ constant rate
- Scale trees using calendar dates of samples
 - "BEAST" software (Drummond & Rambaut 2007)





Gives transmission rate within clusters

Time interval between transmissions

- 1 sequence from each patient
 - very dense sample
- Every split in tree (node) tracks a transmission



Subtype B transmission intervals can be short



Timing of all splits gives a network from the phylogeny

















A scale-free network?

brief communications

"Cumulative distribution of number of different sexual partners decays as a scalefree power law"

Liljeros et al 2001

In a scale free network, new links are preferentially attached to highly-connected nodes

The web of human sexual contacts

Promiscuous individuals are the vulnerable nodes to target in safe-sex campaigns.

naires. The response rate was 59%, which

Inlike clearly defined 'real-world' networks1, social networks tend to be subjective to some extent²³ because the perception of what constitutes a social link may differ between individuals. One unambiguous type of connection, however, is sexual contact, and here we analyse the sexual behaviour of a random sample of individuals⁴ to reveal the mathematical features of a sexual-contact network. We find that the cumulative distribution of the number of different sexual partners in one network, in which links may be short-lived, year decays as a scale-free power law that has a similar exponent for males and females. The scale-free nature of the web of human sexual contacts indicates that strategic safe-sex campaigns are likely to be the most efficient way to prevent the spread of sexually transmitted diseases. Many real-world networks1 typtfy the

small-world' phenomenon⁵, so called because of the surprisingly small average path lengths between nodes^{4,7} in the presence of a large degree of clustering²⁶ (Fig. 1). Small-world networks are classed as single-scale, broad-scale or scale-free. depending on their connectivity distribution, P(k), where k is the number of links connected to a node¹. Scale-free networks,

corresponds to 2,810 respondents. Two independent analyses of non-response error revealed that elderly people, particularly women, are under-represented in the sample; apart from this skew, the sample is representative in all demographic dimensions. Connections in the network of sexual contacts appear and disappear as sexual relations are initiated and terminated. To investigate the connectivity of this dynamic we first analysed the number, k, of sex partners over a relatively short time period the 12 months before the survey. Figure 2a shows the cumulative distribution, $\vec{P}(k)$, for female and male respondents. The data closely follow a straight line in a double-

logarithmic plot, which is consistent with a power-law dependence. Males report a larger number of sexual partners than females13, but both show the sam scaling properties.

These results contrast with the exponential or gaussian distributions - for which there is a well-defined scale - found for friendship networks⁴. Plausible explanations for the structure of the sexual-contact network described here include increased

Figure 1 if's a small world: social networks have small average path lengths between connections and show a large degree of clusterios. Pointing by Idehia Starley

partners, k_{ui} , in the respondent's life up to



What does this mean?

Does a new network member link <u>at random</u>?

Or to a member with <u>many</u> existing links?

Cluster size distribution reveals social mechanics of partner choice



Partner selection

- Partner selection **independent** of their no. of partners
 - Negative binomial

but if:

- **Preferential**: a new partner connects to one with many existing links
 - Yule/Waring





Preferential attachment in UK Subtype B

- Waring distribution is best fit
- Preferential attachment makes intervention difficult
 imperfect interventions ineffective if randomly given
- Most transmission interventions are not completely effective...

Preferential attachment means interventions are better if targeted

OPEN O ACCESS Freely available online

PLOS ONE

Using HIV Networks to Inform Real Time Prevention Interventions

Susan J. Little¹*, Sergei L. Kosakovsky Pond¹, Christy M. Anderson¹, Jason A. Young¹, Joel O. Wertheim¹, Sanjay R. Mehta¹, Susanne May², Davey M. Smith^{1,3}

Plos One 2014 Jun 5;9:e98443.

New heterosexual infections

New UK infections – 2012

MSM 3,250

.,880

The rest of the UK HIV epidemic

- 65% of UK HIV infections are heterosexual
 - most derived from sub-Saharan Africa
 - mostly not subtype B
- Most non-B is subtype C (~60%) & subtype A (12%)
- What has been happening in this epidemic?



Large non-B clusters are MSM/IDU



Cluster dynamics over time

- Clusters were picked in the 2007 HIV Rdb tree then reidentified in the 2010 tree
- Cluster growth was calculated as the number of new sequences per initial sequence (for each cluster)



Non-B cluster growth depends on risk group



N = 14,677

Conclusions

- High density sampling and phylogenetic analysis in time has allowed the description of the transmission dynamics for UK HIV
- for subtype B
 - 29% of clusters are large
 - 20% of their transmission intervals < 6 months</p>
 - fits Waring distribution with parameter ~ 3.0
 - preferential attachment
 - Means random interventions are not very effective
 - Leigh Brown AJ, Lycett SJ, Weinert L, Hughes GJ, Fearnhill E, Dunn DT, UK HIV Drug Resistance Collaboration (2011) J Infect Dis 204:1463-1469

Conclusions

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preferential attachment

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- for non-B HIV
 - far fewer very large clusters
 - largest clusters crossovers to MSM/IDU
 - MSM/IDU clusters growing fastest
 - epidemic not growing within UK heterosexuals



Edinburgh University

- Samantha Lycett
- Manon Ragonnet
- Gonzalo Yebra
- Emma Hodcroft

UK HIV Drug Resistance

Database

welcometrust

- Esther Fearnhill (MRC CTU)
- David Dunn (MRC CTU)
- Deenan Pillay







