Transmission of the NS5A resistant variant M28V among acute HIV/HCV co-infected MSM

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Background

- The World Health Organization (WHO) declared to eliminate hepatitis C virus (HCV) as a global health treat by 2030
- This goal can be feasible by expanding direct-acting antivirals (DAAs)
- Virological failure can occur and is linked to the presence of resistance associated substitutions (RAS)
- Transmission of RAS can hamper elimination efforts
- Unrestricted DAA therapy has halved HCV incidence among men-who-have-sex-with-men (MSM), whom are the main HCV transmitters [1]

1) A.Boerekamps et al Clin Infect Dis 2018

Aim

To investigate the transmission dynamic of HCV and its specific RAS among MSM before and after the widespread use of DAAs

Methods

- 87 plasma samples from recently acquired HCV among mostly HIV co-infected MSM were used
- Patients were included in one of the ten Dutch and one Belgium HIV treatment center between 2013-2014 [1] and 2016-2018 [2]
- RAS were defined based on the EASL guidelines
- Maximum likelihood analysis (GTR+G4+I) was performed on a concatenated NS5A+NS5B alignment [3]
- Clusters were defined as a bootstrap support value of >90% and a genetic distance threshold <3%

1) SJ.Hullegie et al. J Hepatol 2016 (DAHHS 1 study)
2) A.Boerekamps et al. 2019, Lancet GE (DAHHS 2 study)
3) S.Popping et al. Clin Infect Dis 2020

Results

- Six clusters containing 82 out of 87 (94%) recently acquired HCV infections were identified (Fig. 1)
- Four clusters included ≥ 10 MSM
- Clusters remained present and of a similar size after the widespread use of DAA therapy (Table 1)
- The largest cluster (cluster III) 96% of recently acquired HCV infections harbored the NS5A M28V RAS at baseline (Fig. 2)
- Patients in this cluster had several other RAS including H58P, E62A, and Y93H

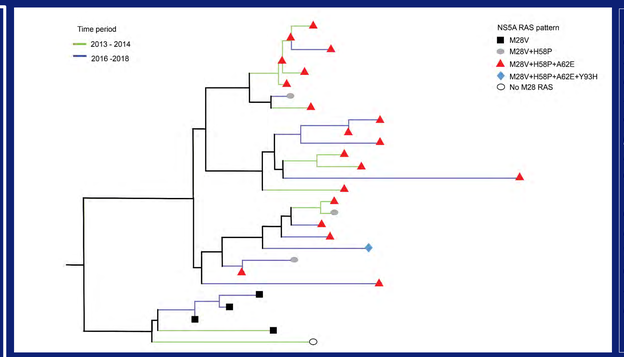

Figure 2: Phylogenetic analysis of a concatenated NS5A and NS5B alignment showed a clusters including 28 MSM (HIV-infected (n=27) and HIV-uninfected (n=1). 96% of individuals in this cluster harboured an NS5A M28V containing variant. All patients in this cluster treated with an NS5A-inhibitor (GZR/ELB for 8 weeks) obtained a sustained virological response. The sequences depicted with green are collected prior to the massive DAA therapy uptake in 2015, the sequences depicted with blue in the years thereafter. The cluster had a bootstrap value and Shimodaira Hasegawaa like approximate likelihood ratio >90 and a genetic distance <3%

Phylogenetic cluster/pair	I	II	III	IV	V	VI	VII	VIII	IX
Included 2013-2014	2	9	13	1	7	5	1	1	1
Included 2016-2018	1	2	15	2	11	5	4	1	1
Total number of MSM from our cohort	3	11	28	3	18	10	5	2	2

Table 1: An overview of the clusters and transmission pairs obtained with maximum likelihood phylogenetic reconstruction. The samples are divided in the ones included between 2013-2014 prior to the widespread use of the direct-acting antivirals in 2015 and 2016-2018.

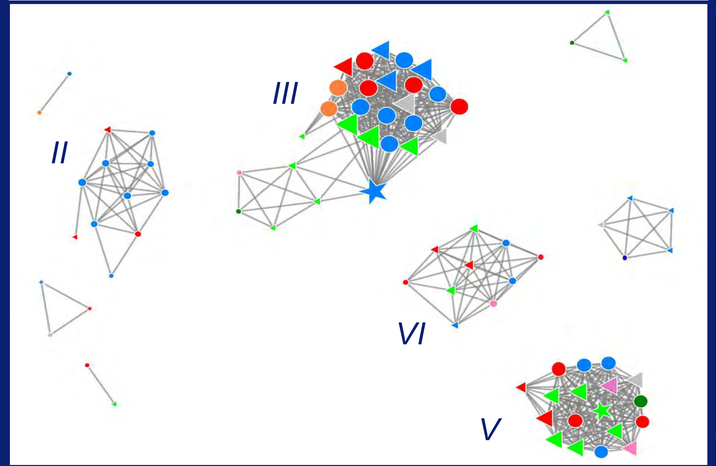

Figure 1: An overview of the clusters and transmission pairs with a genetic distance threshold <3%. The circles represent HCV infections included prior to the widespread use of DAA therapy (all in HIV-positive MSM). The triangles represent HCV infections among HIV-positive and star among HIV-negative MSM after DAA introduction. The size of the nodes represent the degree of neighbours. The colours represent the centres where patients were diagnosed with HCV (dark blue= Haarlem, dark green = The Hague, grey = Arnhem, light blue = Amsterdam, light green = Antwerp (Belgium), pink = Maastricht, orange = Utrecht, red = Rotterdam).

Figure 2 has been published as "S.Popping et al. **Transmission of NS5A resistance associated substitutions among MSM recently infected with hepatitis C virus genotype 1a"** Clin. Infect. Dis 2020

Conclusions

- Large clusters were detected in the years before and after DAA introduction suggesting ongoing transmission regardless of prevention measurements
- The highly clustered epidemic is suitable for targeted prevention measurements
- A stable transmission of the M28V RAS was detected, which can lower cure rates to 3D therapy
- Ongoing resistance surveillance is recommended to timely detect the transmission of other RAS

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