Sexually transmitted diseases, co-infections and theirconsequences in Dermatology

Ph.D.thesis

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Introduction

Data on sexually transmitted infections (STI) is very heterogeneous all over the world. The incidence of major bacterial and viral STIs is estimated to be 125 million infections worldwide and their incidence is continuously increasing. Transmission of STIs is mainly sexually (genito-genital, oro-genital, genito-anal, oro-anal) causing their social significance, stigmatising and discriminating effect. The long term consequences and complications are important medical, epidemiological, economical, social and demographic factors.

Acquiring STIs is connected statistically to *high risk behaviour*. Although people in risk groups can be infected with higher possibility than normal population, the belonging to risk groups does not exclude or prove presence of venereological disease.

The most important risk factors are promiscuity, constant or group sexual intercourse, neglect of condom use, homosexuality (MSM, men who had sex with men), male gender and young adulthood. The fact that positive venereological history is one of the risk groups may emphasise that STIs are behavioural disorders.

International tendencies are sexual partner *pseudoanonymity* (avatar use) and *convenient forgetfulness of the names,* characteristically for the most promiscuous people, constituting another risk group. Social meeting points and common interests can also be risk factors: night clubs, sex clubs, baths or saunas, frequenting parks, public toilets may cause explosive spread of infections. Internet has all theses former properties: people with similar interests and sexual orientation can make contacts fast and purposefully, mostly hiding behind avatars.

Sexually transmitted diseases increase susceptibility to HIV infection: increasing the infectivity of HIV-positive individual's and non-infected people's tendency for becoming infected with HIV. *Treponema pallidum* increases the probability of HIV transmission increasing viral shedding and viral load in the blood and genital excretions of coinfected patients, along with a parallel induction of lymphocyte and T-cell apoptosis and a decrease in the CD4 T-cell count, while HIV probably influences the spread of other STIs, including syphilis. Therefore syphilis-HIV co-infection is another new risk group.

Subcutaneous injection of liquid paraffin or vaselinum album for penile enlargement is still practiced today in Hungary by non-medically trained persons by injecting 65C warm liquid paraffin between the skin and the fascia profunda where it remains relatively confined and flexible, enlarging the diameter of the penis. Paraffinoma patients may form a new group of high risk population, because of (i) the inadequate hygiene during operation, (ii) uninhibited sexual behaviour and loss of anxiety, (iii) lack of barrier function at site of paraffinoma resulting in the statistically increased risk of STIs.

The successful fight against any infectious disease, like venereal diseases, depends on the recognition and adequate treatment of the sources of infection. Contact tracing in Hungary is still based on the disciplines of *Károlyi*: (i) „tracing the unknown sources of infection due to occasional contacts concerning the largest incubation time",(ii)„repeated visits may give the opportunity to counsel, instruct and educate patients concerning venereal diseases". The risk group created by internet use was utilised in the United States of America where methods of XXIth century's contact tracing – online tracing and referral- has already become a process.

Aims

1. Data of syphilis and HIV-syphilis co-infections were examined concerning epidemiology, effectiveness of contact tracing to analyse classical and modern risk groups for STI acquisition to estimate whether the abolition of the *National Institute of Dermatology and Venerology* caused changes in theses parameters which demand further provisions. Effectiveness of contact tracing was analysed to estimate the need for new counselling methods.
2. Diagnostical challenges, clinical characteristics, complications and therapy effectiveness were analysed in HIV-syphilis co-infections to estimate the interaction of the two diseases.
3. Syphilitic infections during pregnancy and their outcome were analysed to estimate the suitability of prenatal screenings and the characteristics of congenital syphilis.
4. Patients' clinical data with clinical signs of paraffinoma were analysed to estimate their belonging to risk groups concerning STIs acquisition.

Methods

Diagnosis of syphilis and HIV was established based on the 2010 Dermatology Gudeline of *SemmelweisUniversityDepartment Dermatology, Venereology and Dermatooncology*. Diagnosis of paraffinoma was established based on the typical clinical picture and past history (subcutaneous foreign material injection). Retrospective past history was carried out examining the patients gender, age, sexual orientation, venerological past history, time and stage of the infection, clinical symptoms, gestation week, pregnancy outcome, HAART (highly active antiretroviral therapy) therapy, motivation of paraffinoma patients, quantity of paraffin and consequences of implantation.

Based on 1997CLIV. act26.§ (2) paragraph (c), contacts withinthe incubationperiodwere traced with all due care and respect to the index patients humanrights and anonymity.Tocontact sexual partners, two forms ofcommunication were used:*patients' self-referral* and *provider referral* (phone, or double closed envelope withno information about the indexperson,or thesuspected diagnosis).

A statistical analysis was performed with two sided *Student's t-tests* of unequal variation (IBM SPSS Statistics 20.0 software, IBM Corporation, Armonk, NY, USA). All data was expressed as the mean ± S.E.M. A 95% confidence interval was considered as statistically significant ($p<0.05$).

Treponema pallidum was demonstrated by dark field microscopy, or by serological tests (Immutrep RPR, Omega®; Immutrep VDRL, Omega®; Syphilis EIA, Bio-Rad®; Serodia TP-PA, MAST®; MastablotTp, MAST®).

Serum specimens were screened for HIV antibodies by the *National Epidemiology Center Microbiological Research Laboratory (Reference Laboratory for HIV),* and positive results were confirmed on second blood sample (Murex HIV Ag/Ab, Inno-Lia HIV I/II Score, Innogenetics®; Genscreen HIV-1/2 version 2, BioRad®; AID-anti-HIV 1+2 ELISA, Wantai®).

*Neisseria gonorrhoeae*culturing (VCAT3, BioMerieux®; PVX, BioMerieux®; API 20NE, BioMerieux®; MIC Strip Test, Liofilchem®), *Chlamydia trachomatis*determination (MicroTrak II Chlamydia EIA, Trinity Biotech USA®),

*Ureaplasmaurealyticum, Mycoplasma hominis*determination (Mycoplasma Duo kit, Bio-Rad®; SIR Mycoplasma kit, Bio-Rad®), *Trichomonasvaginalis*determination (native smear; CPLM, Chemium®), yeast culturing (chloramphenicol Saboraud agar, Biolab®; Chromagar, Csertex®; corn agar and Auxacolor, Bio-Rad®; ROSCO sensi-tab®), general bacteria culturing (COS, EOS, PVX, BioMerieux®).

Results

Results in syphilis mono-infected patients (*syphilis mono-infection – SM group*)

Between 01.01.2005- 01.01.2013., 27,148 screening tests for syphilis, and 44,289 screening tests for HIV were performed in the *Centre*. A total of 1,401 patients were diagnosed with syphilisinfection during this period. One thousand and two hundred and thirteen (1,213/1,401; 86.58%) syphilitic patients had only mono-infection *(SM group*). In 1,213 syphilis mono-infected patients: (i) male patients were at the age of 38.5±13.7 years and females were at the age of 33.6±13.02 years, (ii) male patients were significantly older than female patients at the time of the infection ($p<0.001$); (iii) 908/1,213 (74.85%) were male, and 305/1,213 (25.15%) female (male:female ratio 3:1); (iv) 681/1,213 (56.14%) occurred in MSM, 441/1,213 (36.36 %) in heterosexuals, and 91/1,213 (7.5%) in bisexuals; (v) 793/1,213 (65.37%) patients' past venerological history was positive: 382/1,213 (31.5%) had a former syphilis infection, 237/1,213 (19.53%) gonorrhoea infection, 174/1,213 (14.34%) syphilis and gonorrhoea co-infections.

Results in HIV mono-infected patients (*HIV group*)

Between 01.01.2005- 01.01.2013., 44,289 screening tests for HIV were performed in the *Centre*. A total of 338 patients were diagnosed with HIV infection during this period (*HIV group*). The number of newly infected HIV patients grew between 2005 and 2008 (21-45/year, 214.28% increase), with the exception of year 2009 (33/year), and grew again between 2010 and 2012 (57-64/year). Currently there is a 304.76% increase concerning 2005 data. In 338 newly diagnosed HIV infected patients: (i) male patients were at the age of 35.1±9.8 years, females were at the age of 33.9±12.3 years; (ii) there was no statistical difference between male and female patients concerning age at the time of acquisition ($p=0.596$); (iii) 310/338 (91.71%) were male, 28/338 (8.29%) were female; (iv) 279/338 (82.54%) occurred in MSM, 28/338 (8.28%) in heterosexuals, and

31/338 (9.18%) in bisexuals; (v) 125/338 (36.98%) patients' past venerological history was positive: 82/338 (24.26%) syphilis mono-infection, 31/338 (9.17%) gonorrhoea mono-infection, 12/338 (3.55%) syphilis and gonorrhoea co-infections.

Results in HIV and syphilis co-infected patients (*HIVS group*)

Between 01.01.2005- 01.01.2013., HIV and syphilis co-infection were established in 188/1,401 (13.42%) patients (*HIVS group*): (a.) 111/1,401 (7.92%) had already contracted HIV infection, (b.) 77/1,401(5.5%)were simultaneously diagnosed with both infections. In our Centre the number of HIV infections diagnosed simultaneously with a syphilitic infection doubled between 2005-2008 (8-16/year, 200% increase), then it started to decrease and in 2013 only 3 new cases were diagnosed, which was a 62.5% decrease. In HIV seropositive patients with syphilis infection: (i) male patients were at the age of 36.1±9.8 year, the female patient was 39.5±0 years old, (ii) 187/188 (99.47%) men and 1/188 (0.53%) woman were detected, (iii) 172/188 (91.5%) were MSM, 3/188 (1.6%) were heterosexual and 13/188 (6.9%) were bisexual, (iv) while 77 patients acquired both diseases at the same time, we detected 111 syphilis cases in HIV seropositive patients: 67 within the first 5 years, 34 within 5-10 years, 10 of them after the 10^{th} year; (vi) in 115/188 (61.17%) cases the syphilis was a re-infection; (vii) 92/188 patients (48.93%) had required HAART at the time of syphilis infection or re-infection.

Results of syphilitic pregnant women and their newborns

Between 01.01.2006. and 01.06.2010. 53 syphilitic maternal infections were detected at our Centre. The diagnosis and treatment occurred at the right time- in the first trimester - in 21/53 cases (39.63%) due to the compulsory antenatal syphilis screening test. Other infections were verified in 17/53 cases (32.07%) in the second trimester, in 15/53 cases in the third trimester (28.3%), and in 4/53 cases at the time of delivery. The mothers average age was 27,13 years at the time of the diagnosis, they were all heterosexuals and HIV seronegative, and their venerological past history was in 5/53 cases positive for syphilis (9.43%).

The clinical symptoms of the secondary stage were observed in 4 cases (8th, 9th, 26th and 28th week of pregnancy), in 49 cases the infected mother was symptomless. Based on the result of serological tests 42 mothers were verified in early latent stage and 7 in late latent stage. Twelve out of the 15 mothers verified in the third trimester were newly

infected (II. stage: 2/53, 3.77%; early latent stage: 10/53, 18,87% - high titer of RPR, positive TPPA and TP ELISA, former negative serology), 3 mothers (3/53, 5.66%) were in late latent stage (specific test positivity and negative RPR).

Congenital syphilis was suspected in 12 newborns, but finally only 6 infections were verified. Three of the mothers underwent no syphilis screening during pregnancy (drug consumer: 2; screening test performed in the 3rd trimester: 1). Mothers were verified in early latent stage, on the 25.3th (16-32) week of pregnancy. The titer of RPR was in 4 cases above 1/64: 1 of these pregnancies ended up in *in utero* death (18th gestation week), 3 in early symptomatic congenital syphilis (diagnosed at delivery on the 32nd gestation week). We observed a further 2 *in utero* death: in these cases the titer of the mother was 1/8 (24th gestation week), and ¼ (16th gestation week). Based on the clinical symptoms and serological results the 3 *in utero* deaths were a consequence of an infection during pregnancy, the 3 early symptomatic congenital syphilis cases were a consequence of a pre-gestational syphilitic infection.

Results of contact tracing in syphilis infection

Between 01.01.2005. and 01.01.2008. 749 syphilitic infections were diagnosed at our Centre. With the help of the regional contact tracing venerological network we identified 1434 sexual contacts of which 52 were unidentifiable because of *pseudoanonymity*, or false personal data. The real number of unidentifiable, anonymous or pseudoanonymous contacts can hardly be estimated. Three hundred and six named and identified sexual contacts were syphilis infected (2005: 73, 2006:59, 2007:72, 2008:102), and treated adequately. Preventive treatment was given– based on epidemiologicaly evidence, despite the lack of clinical symptoms and serological negativity – to 1.076 persons (2005:66, 2006:350, 2007:313, 2008:347).

Between 01.01.2006. and 01.06.2010. 53 syphilis infected gravidas named 50 sexual contacts, 48 of them were the father of the unborn child. Twenty of them were syphilis infected and treated adequately, 28 were given preventive treatment. Only 3 pregnant women named casual partners – 1 received preventive treatment and 2 remained anonymous.

The effect of HIV on syphilis infection

In syphilis mono-infected patients 525/1,213 (43.3%) had clinical symptoms (skin or mucosal involvement): 235/1,213 (19.4%) patients were diagnosed with primary stage, 290/1,213 (23.9%)with secondary stage. In 676/1,213 (55.73%) patients the syphilis infection was diagnosed as a result of a serological check-up: 579/1,213 (47.73%) of them in early latent stage, and 97/1,213 (7.99%) in late latent stage. Asymptomatic neurosyphilis was diagnosed in 8/1,213 (0.66%) patients based on seroresistance, but no symptomatic neurosyphilis was diagnosed. Early congenital syphilis was detected and treated in 4 (0.32%) new-borns.

In HIV seropositive patients 71/188 (37.76%) had clinical symptoms for syphilis: 12/188 (6.38%) were diagnosed with primary stage (in 2 of them deep, ulcerating, multiple and painful primary affections were found), 59/144 (31.38%)with secondary stage (in 4 of them persistent primary lesions were also found). In 106/188 HIV seropositive patients (56.38%) early latent syphilis infection was diagnosed as a result of a routine serological check-up, late latent infection was established in 4/188 (2.13%) patients (in 2012 we detected 1 cardiovascular complication). Early symptomatic neurosyphilis (meningitis, uveitis) was detected in the early secondary stage in 5 out of 96 not HAART treated patients (5/188; 2.65%), and asymptomatic neurosyphilis in 2 out of 92 HAART treated patients (2/188; 1,06%). No congenital syphilis was detected.

The treatment result was checked in the 1st month after the treatment, and every 3rd month afterwards. A 2-step titer decrease of non-specific RPR test was accepted as a successful result. In *SM group* 8/1,213 patients (0,66%) were seroresistant. Further examinations proved asymptomatic neurosyphilis. In *HIVS group* successful treatment was established in 152/188 (80.85%) patients, no seroresistance was detected, but 36/188 (19.15%) patients arbitrarily discontinued the penicillin therapy, and were believed to have continued it abroad.

Age, gender distribution and venerological past history analysis

The age of male patients at the time of different STI acquisition was statistically different: syphilis mono-infected were significantly older than (i) HIV mono-infected ($p<0.001$) and (ii) HIV and syphilis co-infected patients ($p<0.001$). There were no

statistical difference between HIV mono-infected and co-infected male patients (p=0.266), and among any female groups.

Male gender dominance was evident in all examined groups (*SM group*: 908/1213, 74.85%; *HIV group*: 310/338, 91.71%; *HIVS group*: 187/188, 99.47%). MSM orientation was dominant in all groups, however the lowest percentage was observed in cases of syphilis mono-infection patients (*SM group*: 56.14%, *HIV group*: 82.54%, *HIVS group*: 91.5%). Past venerological history was positive in a high percentage of the examined groups: highest in syphilis mono-infections (*SM group:* 793/1,213; 65.37%, *HIV group*:125/338, 36.98%; *HIVS group*:115/188, 61.17%). Seeding syphilis infected pregnant women from *SM group* past history was positive also in 9.43% (5/53).

Results of paraffinoma patients

Between 01.01.2008- 01.05.2012.71 paraffinoma patients were diagnosed and screened for STI at our STD Centre (2008: 9, 2009: 9, 2010: 23, 2011: 17, 2012:13). Diagnosis was established based on clinical picture and past history of the patients (foreign material subcutaneous injection).

The mean age of patients at the time of the operation was 30.1 years (18- 59-y-o). All patients were heterosexually orientated. Past venerological history was positive in 2/71 patients (2.89%) for syphilis, they denied having had any other STIs. Their motivation was in 69/71 cases (97.18%) the enlargement of the penis. The amount of the injected material was usually between 5-10 ml (average 22ml), in 2 extreme cases 50ml.

The appearance of the first symptoms were known by 62/71 patients (87.32%). Based on their data the complications forced them mainly with a 2.23 month delay to attend proper medical care (1 week – 1.5 years). Early complications were detected immediately after the intervention 13/71 patients (18.31%): spontaneous pain or pain by erection, inflammation. Delayed complications occurred by 57/71 patients (80.28%), 2.83 years after the intervention (6 month–8 years): pain, erectile dysfunction, ulceration and necrosis. Patient's medical histories supplied information on possible triggers as local trauma, and in one case herpes progenitalis, or primary syphilitic ulceration.

Serological screening tests were performed and in 4/71 patients (5.63%) syphilitic infection was diagnosed (2 latent recent syphilis, 1 late latent syphilis, 1 I.stagesyphlis), in a further 2/71 cases the known syphilitic past history was confirmed (1.81%). No HIV infection was diagnosed. Microbiological screening tests were not performed from the urethra in 13/71 patients (18.31%) because of lack of permission. In the remaining cases microbiological screening tests confirmed 3/58 (5.17%) *Ureaplasmaurealyticum*, 4/58 (6.89%) *Streptococcus agalactiae*, 3/58 (5.17%) *Haemophilusinfluensae* and 2/58 (3.45%) *Candidaalbicans* infection. No *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma hominis* and *Trichomonasvaginalis* infections were detected.

Conclusions

Primary prevention is the most important device for venereologists, which can prevent STIs and their long term incurable complications detected by associated professions. The tools of prevention are recognition and education of risk group members, contact tracing, early diagnosis and prompt treatment of co-infections.

Classical and modern risk groups

Concerning our results we can assume that young MSM males with positive venerological history (syphilis and/or gonorrhoea) belong to risk groups acquiring STI. HIV mono-infected and HIV-syphilis co-infected male patients were significantly younger than syphilis mono-infected patients, and younger than the other observed groups' patients. The dominance of male gender and MSM orientation is obvious – mainly in *HIVS group* patients. The relatively high female proportion and bi-/heterosexual orientation in *SM and HIV groups* may cause the infections of female heterosexuals with vertical transmission as a consequence, predicting a new risk group.

Positive venerological past history can be considered as at-risk behaviour. Our data in all groups – even in the pregnant women's group - demonstrates that the infected individuals did not change their high-risk sexual behaviour and re-acquired STIs. The fact that *HIVS group* number is increasing suggests that despite their regular counselling HIV infected individuals form one of the newest risk groups. The effect of HAART decreased AIDS-related mortality – increasing number of syphilitic infections due lack of condom use – was well observed in our patients also.

Young, poorly educated patients who underwent subcutaneous paraffin injection procedure form the newest risk group for acquiring STIs.

Congenital syphilis

Prevention, early detection and proper treatment of syphilitic pregnancies are the only effective methods to reduce the incidence of congenital syphilis, but present-day Hungarian practice is not able to fulfil them perfectly. Syphilis screening tests (specific and non-specific diluted tests) are recommended in every trimester and at the delivery, together with HIV screening test and the screening of the male partner. This practise is already used in the *Sex Health Unit of Józsefváros* during prenatal care.
Since not belonging to a risk group can't exclude the presence of an STI, these patients must be screened without discrimination.

Contact tracing in the 21st century

Contact tracing based on 1997CLIV. act26.§ (2) paragraph (c) is unsuccessful in practical terms because of *pseudo-anonymity* and convenient forgetfulness of the nameof sexual partners. Due to this, despite the thoughtful and sympathetic counselling, syphilis infected partners were identified and treated in only 2:1 ratio, which was even worse in infected pregnant women.

The lack of index patients' compliance requires changes of the present practice of contact tracing. The use of internet – as a first line communication tool – is essential in the 21st century's prevention and contact tracing. It is essential to inform risk groups and target the whole of society with modern online STI enlightening programs and furthermore to establish online venerological network for contact tracing with secure privacy.

Constant education of nurses and venerological assistants is crucial for the adequate treatment and counselling, to be able to make changes in high risk behaviour of STI patients. This was initiated in 2011 by the *Semmelweis University Department of Dermatology Venereology and Dermatooncology* as *Venerological Assistant Training* e-learning and e-book (*A venerológiai betegellátásszakdolgozóispecifikumai – e-learning: http://sote.etan.hu*).

As primary prevention the Department's *STI Task Force* developed the first online enlightenment homepage in 2012 (www.biztonsagosszex.hu), which targeted mainly the teenagers' age-group, but the risk groups also. While observing the users anonymity there was the possibility for quick medical consultation to enable approaching risk groups and preparing the opportunity for online follow up and contact tracing.

HIV-syphilis co-infection

HIV and syphilis infections are particularly significant because each disease may facilitate the acquisition and transmission of the other, which in turn may affect the prognosis and the clinical course of the original illness. HIV infected patients become more infectious and may transmit the original viral infection together with *Treponema pallidum*.

The clinical picture, prognosis, diagnostic and therapy of syphilis in HIV infected individuals – especially by non-HAART treated ones- may be specifically problematic. The similar way of acquisition and the increasing incidence of HIV infection is going to cause the increase of syphilis-HIV co-infection in the future.

Long follow-up including regular physical check-ups and routine syphilis serology testing is only suitable for the early diagnosis and proper treatment of syphilis co-infection which can prevent complications. Furthermore counselling may promote safe sex and prevent further STI acquisition and spread of HIV.

Conclusion

Presently, despite the wide spectrum of the antibiotic arsenal, sexually transmitted diseases particularly syphilis renaissance is observable. The number of HIV infected people is constantly increasing, the vigilance of society and infected individuals is decreasing, improved life quality and decreasing mortality due to HAART therapy and lack of condom use predict further spread of HIV and co-infections –mainly syphilis infections.

We have to pay attention to classical risk groups and possible new risk groups as paraffin enlargement of the penis and the possible threat by bisexual orientated infected people building a bridge between the high risk population and the low risk heterosexual female population and consequent vertical transmission.

Nowadays epidemiological situation venerological principles developed in the fifties aren't suitable anymore. The use of the classical methods for tracing infected contacts are practically useless in everyday practice because of fast spreading endemics due to the internet respecting no geographical distances, lack of consequences and sanctions. The first attempts for making online contact making and the constant information of venerological staff training were initiated but further changes are needed. New methodological standards of contact tracing, long term follow up, and regular screenings have to be processed, as does the use of modern tools helping to interrupt the chain of infection - online counselling- and stop further spreading of STIs, which is only possible with the help and close cooperation of associated professions (gynaecology, urology, infectology, microbiology, neurology, cardiology, ophthalmology, otolaryngology, psychiatry).

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List of publications

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