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Background Acyclovir (ACV) is the first-line treatment for symptomatic primary and recurrent genital herpes in South Africa. Resistance to ACV is mainly due to mutations in the HSV-2 viral *UL23* gene that codes for thymidine kinase (TK), resulting in an inability for the drug to inhibit viral replication. The objectives of this study were to obtain genotypic data on the frequency of HSV-2 TK resistance mutations and natural polymorphism as well as to assess the prevalence of ACV-resistant HSV-2 among participants in the genital ulcer aetiological studies conducted between 2007 and 2011.
Methods We amplified and fully sequenced the *UL23* gene of 254 HSV-2 positive specimens obtained from participants in genital ulcer aetiological studies conducted between 2007 and 2011 in Gauteng Province, South Africa. Additionally, intratypic differences between the HSV-2 were determined based on the number of reiterated sequences located in the non-coding regions of the *US1* and *US12* genes of HSV-2.
Results We identified 63 single and/or double nucleotide mutations in the *UL23* genes analysed, that resulted in 30 silent mutations and 32 amino acid changes. 41% of these amino acid changes were due to natural polymorphism. In addition, we identified 19 unknown amino acid changes in 30 samples that have not been described before. All unknown mutations detected were outside the TK resistance "hotspots", which are renowned sites for ACV resistance mutations to occur. No frameshift mutations or mutations causing stop codons were identified in the *UL23* genes of the samples analysed.
Conclusions No evidence was found of known ACV resistance mutations in HSV-2 following the addition of ACV as first-line therapy for genital ulceration in South Africa. Genotyping of HSV-2, based on the length of reiterated sequences in the *US1* and *US12* genes of HSV-2, revealed a high degree of HSV-2 heterogeneity in this population.

P1.015 ON THE MECHANISMS OF DRUG RESISTANCE IN HIV-1 RT

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Human Immunodeficiency Virus Reverse Transcriptase (HIV-1RT), catalysing synthesis of proviral cDNA has been widely exploited as a most suitable target for attack by anti-AIDS chemotherapeutics. The antiHIV-1RT molecules involve dideoxy analogues of dNTP (nucleoside reverse transcriptase inhibitors, NRTIs), which inhibit it competitively by terminating DNA chain extension. The other group of HIV-1 RT inhibitors involves non-nucleoside reverse transcriptase inhibitors (NNRTIs), which bind preferably in the hydrophobic pocket or elsewhere at enzyme surface, inhibit it non-competitively. The AIDS therapy prescribes different combinations of various anti-HIV drugs mainly the antiHIV-1RTs and antiproteases (in highly active antiretroviral therapy; HAART), which significantly reduces HIV count to undetectable level. Unfortunately, due to drug selection pressure drug resistant variants of HIV-1 emerge and preclude chemotherapy of this pandemic. This paper is an endeavour to illustrate possible mechanisms involved in anti-HIV drugs resistance. Apart from attributes of numerous mutations reported in three key enzymes of HIV (RT, protease and integrase) in making antiHIV drugs, one plausible mechanism of nucleoside analogue resistance involves ATP/GTP-based excision to unblock chain-terminated primers; thereby allowing viral replication to continue. Such unblocking has also been reported *in vitro* in presence of excess of pyrophosphate concentration; a reaction known as pyrophosphorolysis. In addition to viral mutants isolated from the AIDS patients, we have shown some artificial mutants of K154, which exhibited antiHIV-1 drugs resistance property and the mechanism involved reduction in binding of the drugs to RT because of conformational change. Our recent report on mechanism of resistance of HIV-1RT against rilpivirin due to E138K mutation proposes a new aspect in this context. However, an extensive study exploring some new targets and drug resistance mechanisms is needed for design and development of novel and potential anti-viral agents to combat this challenge

P1.016 MOLECULAR ANALYSIS OF ANTIMICROBIAL RESISTANT NEISSERIA GONORRHOEA ISOLATES FROM DELHI, INDIA: A FUNCTIONAL GENOMICS APPROACH

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Background In India, knowledge regarding N. gonorrhoeae antimicrobial resistance profiling is limited, and data concerning genetic characteristics of N. gonorrhoeae is also lacking. Herein, we investigated the genetic resistance determinants for various antimicrobials used against N. gonorrhoeae isolated in Delhi, India. Various studies have shown that this resistance towards antimicrobials could be either plasmid or chromosomal mediated involving mutations in various genes.
Methods Molecular basis of plasmid and chromosomal mediated antimicrobial resistance was analysed by amplifying and sequencing the most target genes, pen A and por B, of N. gonorrhoeae. Attempts have been made to in-silico model the structure of mutant PenA to understand how mutations in these genes affect the drug binding. A PCR assay was also carried out to analyse the penicillinase producing N. gonorrhoeae (PPNG).
Results Out of the 40 clinical isolates of N. gonorrhoeae studied which were resistant to various antimicrobials, twenty eight isolates showed high resistance to penicillin (3–32μg/ml). These resistant isolates were PPNG positive (70%; 28/40) and predominantly harboured the African type of PPNG plasmid. Only two isolates carried the Asian type of plasmid. Mutations were also observed in penA and porB genes which correlate their effects on drug resistance. Through in silico modelling studies, we were able to even show that a single point mutation at G452S in penA gene changed the susceptibility of N. gonorrhoeae towards penicillin and tetracycline.
Conclusions This study clearly shows a cumulative effect of increasing mutations with subsequent increase in resistance towards various antimicrobials. Presence of both African and Asian type of penicillinase producing plasmid gives an indication of extensive travel of patients affected with Gonorrhea. Our in silico modelling studies of mutant proteins provide new insights to access increasing antimicrobial resistance among Neisseria gonorrhoeae.

P1.017 UNIQUE ACTIVITY OF SITAFLOXACIN, ONE OF NEWER FLUOROQUINOLONES, AGAINST CIPROFLOXACIN-RESISTANT N. GONORRHOEAE

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Background Fluoroquinolone-resistance in Neisseria gonorrhoeae is spreading in the world and almost 80% of N. gonorrhoeae strains are resistant to fluoroquinolones in Japan. It is known that the resistance to fluoroquinolones is closely related to genetic mutations of quinolone-resistance determining regions (QRDR) on gyrase genes such as gyrA or parC. In 2009, the first national surveillance of antimicrobial susceptibilities of N. gonorrhoeae was performed in Japan. In this surveillance, we found that sitafloxacin, one of newer

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