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Relevance of Hepatitis B Virus genotypes of HBV/HIV coinfecting Patients from Sudan

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Disclosures



- D.Glebe received a research grant from GILEAD

Overview



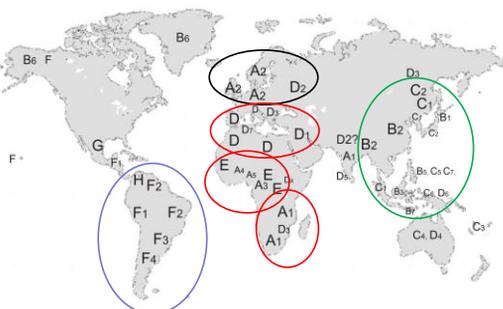
- Global distribution of HBV genotypes and subgenotypes
- Impact of HBV genotypes on disease progression and therapy (in Africa)
- Funding of African research
- HBV genotypes in Africa (Khartoum/Sudan)
- HBV and HBV/HIV coinfection in Khartoum/Sudan

Hepatitis B virus



- HBV has been classified phylogenetically into 9 genotypes A, B, C, D, E, F, G, H, I
- Potential 10th genotype "J" (single isolate)
- Genotypes must show nucleotide divergence of greater than 7.5 %
- Subgenotypes have at least more than 4 % genomic divergence
- Over 35 Subgenotypes in A-D, F, H and I, but not in E and G
- (Sub)-genotypes show distinct geographical distributions

Global distribution of HBV genotypes



Schäfer, Glebe, Gerlich. In: Doerr/Gerlich: Medizinische Virologie. 2010

Clinical differences of HBV sub/genotypes (selection)



- HBV genotypes A1, C, B2-B4, F1 show higher risk of serious complications during chronic HepB, like cirrhosis and HCC, compared to A2, B1, B5
- South Africans infected with A1 have 4.5 higher risk for HCC development (6.5 years earlier) compared to other genotypes
- Similar results from A1 infected persons in Southern India.
- Genotype F is often seen during sexual transmission with vaccine-breakthrough (anti-HBs lower than 100 IU/L) and severe acute and chronic hepatitis B.
- Genotypes A and B respond better to interferon-based therapy, compared to genotype C or D

For review see: Kramvis, A, Intervirology 2014; 57:141-150

HBV genotypes summary



Table 1. Comparison of Clinical, Virological and Geographical Distribution Differences among HBV Genotypes

	HBV genotype		
	A2, D3	A1, E, D7	B, C
Immune tolerant/HBeAg+ phase	Often absent	Short	Long 2-3 decades
HBeAg seroconversion	Early	Very early	Delayed
Geographic distribution	Western Europe	Africa	Asia
Endemicity	Low	Intermediate to high	High

Adapted from: Walsh and Locarnini, YMJ 2013

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Route of transmission	Sexual or percutaneous	Horizontal	Perinatal
Age of infection	Adult or adolescent	Early childhood	At birth or infant
Family history	Often none	HBeAg+ mother or HBeAg+ relatives	HBeAg+ mother or relatives
Chronicity following infection	Low (1-5%)	High (30-50%)	Very high (>90%)

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Chronicity following infection	Low (1-5%)	High (30-50%)	Very high (>90%)
Response to IFN-based therapy	Very good (A>>D)	Unknown	Good (B-C)
Risk of end-stage liver disease	Low	Intermediate	High
Risk of HCC	Low	High	High
Age at risk of HCC	Older persons	Young males	Middle age
Mortality from HBV	Low	Intermediate	High

HBV, hepatitis B virus; IFN, interferon; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen.

Adapted from: Walsh and Locarnini, YMJ 2013

The African perspective



- Africa is the 2nd largest continent
- Covers 20% of world's land area
- Currently 54 countries
- Population: 1.1 billion (2013)
- 15% of total world's human population
- Has the youngest population of all continents
- 50% of Africans are younger than 20 years

Adapted from: Walsh and Locarnini, YMJ 2013

Hepatitis B - from an African perspective



- Of 240 Mio chronic hepatitis B patients worldwide, **65 Mio. reside in Africa.**
- Improvement of preventive, diagnostic and therapeutic intervention is urgently needed, esp. for indigenous population

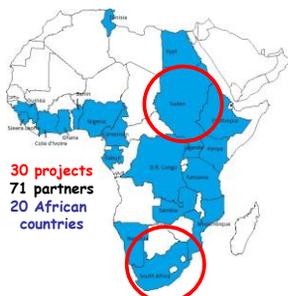
Improving Research in African countries



- DFGs "Africa initiative" to study "neglected infectious diseases" in Africa
- Consolidation of mutually beneficial equal partnerships between German and African researchers.
- Provide support and funding for the academic and professional careers of young African researchers in their home countries in order to contribute to building research capacities in Africa.
- strengthen research networks within Africa

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Improving Research in African countries



DFG Deutsche Forschungsgemeinschaft
German Research Foundation

- The **main goal** of the initiative is to allow for African scientists to work on elucidating fundamental biological principles of **neglected tropical diseases** relevant for their countries, (including indigenous population).
- So far, 30 projects are being funded with 71 partners in 20 African countries
- Hepatitis B is a neglected infectious disease in Africa**
- Project for cooperation of labs from South-Africa, Sudan and Germany started in 2009**

Prevalence of hepatitis B in Sudan



DFG Deutsche Forschungsgemeinschaft
German Research Foundation

- HBV exposure rate: 47% - 78%
- HBsAg-prevalence: 7% - 18.7%
- The Regional committee for the WHO Eastern Mediterranean Region (EMR), to which Sudan belongs, urged member states to:
 - "*Improve the epidemiological surveillance systems, develop a hepatitis registry and implement serosurveys in order to produce reliable data to guide prevention and control measures and monitor impact of preventive strategies.*"

Prevalence of hepatitis B in Sudan



DFG Deutsche Forschungsgemeinschaft
German Research Foundation

- Build up of a molecular biology lab in Khartoum/Sudan (including equipment, personnel and consumables funded by DFG).
- Training of Sudanese PhD students and technicians was done in Johannesburg, South Africa (lab of Anna Kramvis).
- A cross-sectional, laboratory based study was conducted to molecular analyze chronic hepatitis B cases.
- We collected 100 sera from HBV-monoinfected patients from medical clinics at IbnSina Hospital, Soba University Hospital and Khartoum Teaching Hospital in Khartoum State between August 2008 and March 2009.

Prevalence of hepatitis B in Sudan



Yousif et al. BMC Infectious Diseases 2013, 13:328
<http://www.biomedcentral.com/1471-2334/13/328>

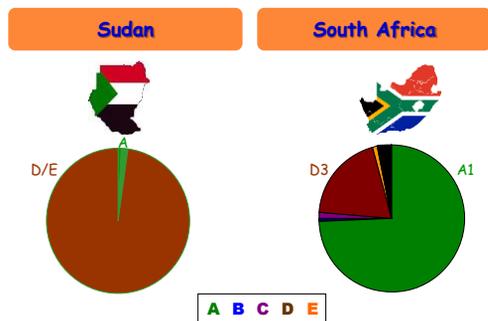


RESEARCH ARTICLE Open Access

Molecular characterization of hepatitis B virus in liver disease patients and asymptomatic carriers of the virus in Sudan

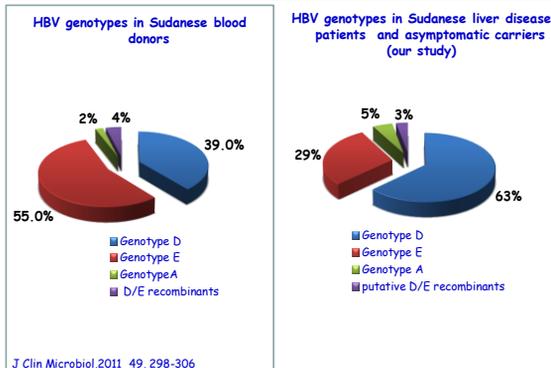
Mukhlid Yousif¹, Hatim Mudawi², Sahar Bakhiat³, Dieter Glebe⁴ and Anna Kramvis^{1*}

Distribution of HBV genotypes in Africa



Yousif et al., 2013

Genotypes of HBV-monoinfected patients in Sudan



Yousif et al., 2013

HBV/HIV coinfections in Africa



- HIV infection is a serious health problem in Africa.
- 34 Mio HIV-infected persons globally, 69% reside in Sub-Saharan Africa
- HBV/HIV co-infection causes rapid progression of liver disease, cirrhosis and HCC. HIV prevalence in Sudan is 0.52 % (2011)
- No study on HBV/HIV coinfection in Sudan has been done before.
- Cross-sectional study in Khartoum, Sudan with **358 (100%) treatment-naive HIV-positive adults.**
 - 62 % showed evidence of current or past HBV infection
 - 42 patients (11.7%) HBsAg positive
 - No difference of HBV exposure rate between HBV-mono or HBV/HIV coinfecting persons (similar to other Sub-Saharan countries).
 - Mode and timing of transmission of HBV in Africa is independent to HIV
 - HBV in childhood, long before exposure to HIV

Yousif et al., IJID 2014, in press; Mudawi et al., IJID 2014, in press

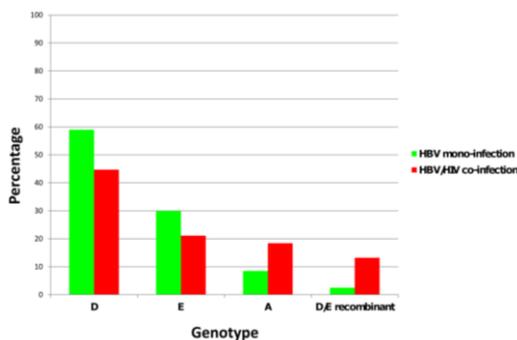
HBV/HIV coinfections in Africa



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 - 62 % showed evidence of current or past HBV infection
 - **96 patients (26.8%) were HBV-DNA positive, of those**
 - **42 patients (11.7%) HBsAg positive**

Yousif et al., IJID 2014, in press; Mudawi et al., IJID 2014, in press

HBV/HIV coinfections in Khartoum/Sudan



Yousif et al., IJID 2014, in press

HBV/HIV coinfections in Africa



- Cross-sectional study in Khartoum, Sudan with 358 (100%) treatment-naive HIV-positive adults.
 - 62 % showed evidence of current or past HBV infection
 - 96 patients (26.8%) were HBV-DNA positive, of those
 - 42 patients (11.7%) HBsAg positive
 - **54 patients (15.1%) HBsAg negative** → indicating occult HBV infection

Yousif et al., IJID 2014, in press; Mudawi et al., IJID 2014, in press

Occult hepatitis B virus infection (OBI)



- OBI: absence of HBsAg and low viral replication of HBV (< 200 IU/ml HBV DNA).
- Usually referred to "anti-HBc-only" or "isolated anti-HBc"
- OBI can reactivate during immunosuppression (e.g. caused by HIV/AIDS)
 - Can cause serious (fulminant) liver disease
- **HIV treatment in case of HIV/HBV coinfection should include Tenofovir.**

Yousif et al., IJID 2014, in press; Mudawi et al., IJID 2014, in press

Conclusions



- HBV has been classified phylogenetically into at least 9 genotypes and over 35 (sub)-genotypes
- (Sub)-genotypes show distinct geographical distributions
- In Africa, genotypes A, D and E prevail, in Khartoum D>E>>A
- Differences in clinical manifestation and response to antiviral therapy
- Genotyping can predict risk for development of severe liver disease and response to antiviral therapy
- HBV/HIV coinfections should be carefully monitored
- In Khartoum, 26% of HIV-infected adults are HBV coinfecting.
- 15% of HIV-infected adults have an OBI !
- Support and funding of African research labs is urgently needed

International Meeting on Molecular Biology of HBV 2015



Organizers:

Dieter Glebe, PhD

Justus Liebig University Gießen

Haitao Guo, PhD

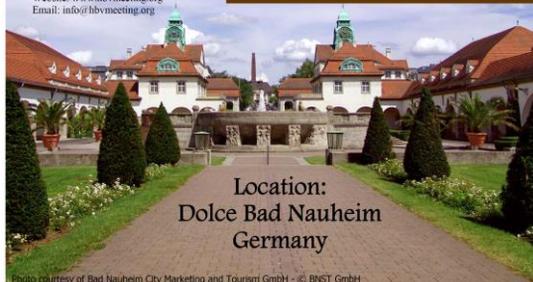
Indiana University School of Medicine

Website: www.hbvmeeting.org

Email: info@hbvmeeting.org

Save the Date!

**2015 International Meeting
Molecular Biology of Hepatitis B Viruses**
OCTOBER 4 – 8, 2015



**Location:
Dolce Bad Nauheim
Germany**

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