New developments in virology & vaccines

Block SA13 MBChB VI
Department of Medical Virology
University of Pretoria/NHLS
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Dr Karin Richter

SA is the country with the most people living with HIV in the world

HIV prevalence in South Africa
– 2008: Estimated 10.6% (5.2 million persons)
– 2012: Estimated 12.2% (6.4 million persons)
  • 1.2 million more than in 2008
    – Combined effect of new infections & a successfully expanded ART programme

HIV sources of information

• Practice guidelines
  – South African National Department of Health
  – Southern African HIV Clinicians’ Society
  – International e.g. WHO, European AIDS Clinical Guidelines, BHIVA, US Department of Health
• Announcements
• Academic journal articles
• Expert opinion/advice
• Other???

HIV – Guidelines

HIV prevalence by province, South Africa 2012

Significantly higher prevalence in urban informal areas vs formal urban/rural areas

[Graph showing HIV prevalence by province]

HIV prevalence by sex and age, South Africa 2012

[Graph showing HIV prevalence by sex and age]

Peak HIV prevalence has shifted: ↑ ART coverage

Practice guidelines
– South African National Department of Health
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• Academic journal articles
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• Other???
SA ART guidelines 2013:
Fixed dose combination (FDC)

- FDC = 1 ARV pill which contains >2 drugs

SA ART guidelines 1st line:
- Tenofovir (TDF)
- Emtricitabine (FTC)
- Efavirenz (EFV)

- One tablet in the evenings:
  - Cheaper (~R90/month)
  - Simpler & more convenient → ↑ adherence → ↑ effective

SA ART guidelines 2013:
Eligible to start ART

- HIV positive adults & children 5-15 years
  - CD4 ≤350 cells/mm³
  - WHO stage 3 or 4, irrespective of CD4 count
  - All types of TB, irrespective of CD4 count
- HIV positive children <5 years of age
- HIV positive pregnant women
  - If CD4 >350 cells/mm³: Give ART for duration of pregnancy & for 1 week after cessation of breastfeeding

RSA NDoH. The South African antiretroviral treatment guidelines 2013

SA ART guidelines 2013:
Fast tracking of certain patients

- Fast track = ART initiation within 7 days of being eligible
  - Pregnant or breastfeeding
  - CD4 count <200 cells/mm³ (or <15% in children)
  - WHO stage 4, irrespective of CD4 count
  - Patients with TB with CD4 count <50 cells/mm³
    - Defers ART for 4-6 weeks if TB meningitis or Cryptococcus meningitis
  - Children with MDR or XDR-TB
  - Children <1 year of age

RSA NDoH. The South African antiretroviral treatment guidelines 2013

SA ART guidelines 2013:
Patients not yet eligible for ART

- Transfer to a wellness programme for regular follow-up and repeat CD4 testing 6-monthly
- Advise on how to avoid HIV transmission to sexual partners and children
- Initiate INH prophylaxis if asymptomatic for TB
- Provide counselling on nutrition, contraception and cervical cancer screening

RSA NDoH. The South African antiretroviral treatment guidelines 2013

SA ART guidelines 2013:
1st line ART regimens

- 1st line regimen for adults
  - Tenofovir (TDF) + Emtricitabine (FTC) + Efavirenz (EFV) => FDC preferred
- 1st line regimen for adolescents (<18 years)
  - Abacavir (ABC) + Lamuvidine (3TC) + EFV

- Alternatives
  - Contra-indications to EFV: Nevirapine (NVP)
  - Contra-indications to TDF: Zidovudine (AZT)
  - Contra-indications to TDF & AZT: Stavudine (d4T)

RSA NDoH. The South African antiretroviral treatment guidelines 2013

SA ART guidelines 2013:
2nd line ART regimens

- Consider switching if the patient has experienced virological failure i.e.
  - HIV VL >1000 copies/ml → check for adherence, compliance, tolerability & drug-interaction & assess psychological issues → repeat HIV VL after 2 months → HIV VL >1000 copies/ml → change to 2nd line regimen
- 2nd line regimen (if on TDF based 1st line)
  - Zidovudine (AZT) + 3TC + boosted liponavir (LPV/r)
- 3rd line
  - Specialist referral

Note: Refer to guidelines for alternative options and full details:
RSA NDoH. The South African antiretroviral treatment guidelines 2013
SA ART guidelines 2013: 3rd line drugs available

- For the 1st time, 3rd line ARVs available for the public sector, including
  - Efavirenz
  - Atazanavir
  - Darunavir
  - Raltegravir

For the 1st time, 3rd line ARVs available for the public sector, including:
- Etravirine
- Atazanavir
- Darunavir
- Raltegravir

http://www.nspreview.org/2013/06/11/upping-the-competition/

SA ART guidelines 2013: ART regimens in children

- 1st line ART regimens
  - <3 years (or <10kg)
    - Abacavir (ABC) + lamuvidine (3TC) + boosted liponavir (LPV/r)
  - ≥ 3 years (and ≥ 10kg)*
    - Abacavir (ABC) + lamuvidine (3TC) + efavirenz (EFV)
    - Children ≥ 3 years and exposed to NVP for ≥6 weeks (PMTCT) should be initiated on ABC + 3TC + LPV/r

- 2nd line ART regimens: Expert advice

Note: Refer to guidelines for alternative options and full details: RSA NDoH. The South African antiretroviral treatment guidelines 2013

HIV Post-exposure prophylaxis

Preferred ARV regimens for PEP

**Preferred**

- Once a day
  - Tenofovir (TDF) + emtricitabine (FTC) (Truvada®)

**Alternatives**

- Twice a day
  - Stavudine 30mg (d4T) + lamuvidine (3TC)
  - Zoduvudine (AZT) + lamuvidine (3TC) (Combivir®)

**Preferred**

- Twice a day
  - Raltegravir 400mg (Insentress®)

**Alternatives**

- Once a day
  - Atazanavir (Reyataz®)/ritonavir
  - Darunavir (Prezista®)/ritonavir
  - Efavirenz 600mg (part of FDC)

**Twice a day**

- Lopinavir/ritonavir (400/100) (Aluvia® 2 tabs)

**Current 1st line “recommendation”**

- Truvada®
  - 1 tablet once a day
  - Fixed-dose combination of 300mg tenofovir DF (TDF) & 200mg emtricitabine (FTC)

- Raltegravir
  - 1 tablet (400mg) twice a day
**Raltegravir**

**Advantages**
- Site of action
- Safe
- Efficacious
- Excellent tolerability
- Not affected by food
- For nPEP: ↑ concentrations in the female genital tract than PIs & NNRTIs
- Not current 1st line ART

**Disadvantages**
- Twice a day dosing
- Cost

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**Zoonotic diseases**

1. Rabies
   - Dead-end transmission to humans through bites of infected animals

2. Ebola/Marburgvirus
   - Transmission to humans through contact of hunters with infected gorillas/chimpanzees followed by several cycles of human-to-human transmission

3. Yellow fever
   - Mosquito-borne transmission from monkeys to humans that can be maintained for many cycles

4. HIV
   - Several transmission events of related viruses from apes/monkeys to humans followed by sustained transmission

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**Emerging & re-emerging infections**

<table>
<thead>
<tr>
<th>Year</th>
<th>Virus</th>
<th>Disease</th>
<th>Where</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Avian influenza H5N1</td>
<td>Severe respiratory disease</td>
<td>Hong Kong → other countries</td>
</tr>
<tr>
<td>1997</td>
<td>Nipah virus</td>
<td>Encephalitis (from pig &amp; bats)</td>
<td>Malaysia &amp; Bangladesh</td>
</tr>
<tr>
<td>1998</td>
<td>Avian influenza H9</td>
<td>Influenza-like illness</td>
<td>Hong Kong &amp; China</td>
</tr>
<tr>
<td>2001</td>
<td>Human metapneumovirus</td>
<td>Respiratory disease, esp. &lt;5 years old</td>
<td>Worldwide</td>
</tr>
<tr>
<td>2002</td>
<td>SARS Coronavirus</td>
<td>Severe respiratory disease</td>
<td>China → other</td>
</tr>
<tr>
<td>2003</td>
<td>Avian influenza H7</td>
<td>Conjunctivitis</td>
<td>Netherlands</td>
</tr>
<tr>
<td>2004</td>
<td>New coronavirus NL63 &amp; HKU1</td>
<td>Respiratory disease</td>
<td>Worldwide</td>
</tr>
<tr>
<td>2005</td>
<td>Human bocavirus</td>
<td>Respiratory disease</td>
<td>Worldwide</td>
</tr>
<tr>
<td>2008</td>
<td>Lujo ( Arenaviridae)</td>
<td>Viral haemorrhagic fever</td>
<td>Zambia → SA</td>
</tr>
<tr>
<td>2009</td>
<td>Influenza A H1N1 pdm</td>
<td>Influenza</td>
<td>Mexico → worldwide</td>
</tr>
<tr>
<td>2010</td>
<td>Huaiyangshan (Bunyaviridae)</td>
<td>Severe fever with thrombocytopaenia syndrome (SFTS)</td>
<td>China</td>
</tr>
<tr>
<td>2012</td>
<td>MERS Coronavirus</td>
<td>Severe respiratory illness</td>
<td>UK (via Pakistan &amp; Saudi-Arabia)</td>
</tr>
<tr>
<td>2013</td>
<td>Influenza A H7N9</td>
<td>Severe respiratory illness</td>
<td>China</td>
</tr>
</tbody>
</table>

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**Vaccine preventable diseases – what’s new?**

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**HEALTHCARE WORKERS HANDBOOK**

**ON**

**INFLUENZA**

Last updated: April 2013
http://www.nicd.ac.za

Developed by:
The National Institute for Communicable Diseases (NICD), a division of the National Health Laboratory Service (NHLS), in collaboration with:
The South African National Department of Health and World Health Organization (WHO)
Average onset of the flu season over the past 8 years has been the last week of May (week 21-22); however, transmission has been detected as early as the 2nd week of April (week 15).

Influenza A & B vaccine
WHO recommended vaccination for 2014 Southern Hemisphere
- A/California/7/2009 (H1N1)-like virus
- A/Texas/50/2012 (H3N2)-like virus
- B/Massachusetts/2/2012-like virus

Pandemic influenza (‘swine flu’) strain
*Future: Quadrivalent Influenza vaccine with 2 influenza B strains (2 distinct lineages)

2014 Influenza SA vaccination guidelines
1. Persons who are at high risk for influenza and its complications because of underlying medical conditions, including
   - chronic pulmonary, cardiac & renal diseases
   - diabetes mellitus & similar metabolic conditions
   - immunosuppressed (incl. HIV-infected with CD4 >100 cells/µl)
   - individuals who are morbidly obese (BMI ≥40)
2. Pregnant women – irrespective of stage of pregnancy
3. Residents of old-age homes, chronic care & rehabilitation institutions
4. Children on long-term aspirin therapy
5. Medical & nursing staff responsible for the care of high-risk cases
6. Adults & children who are family contacts of high-risk cases
7. All persons >65 years of age
8. Any persons wishing to protect themselves from the risk of contracting influenza, esp. in industrial settings, where large-scale absenteeism could cause significant economic losses.

2014 Influenza SA vaccination guidelines
- Dosage
  - Adults
    - Whole or split-product or subunit vaccine – 1 dose IM
  - Children (3 - 12 years)
    - Split-product or subunit vaccine – 1 dose IM
  - Children <9 years who have never been vaccinated
    - 2 doses 1 month apart
  - Children <3 years of age
    - ½ the adult dose on 2 occasions separated 1 month apart
- Influenza vaccine is not recommended for infants less than 6 months of age

Influenza chemotherapy
- At present influenza A (H1N1) pdm09, H3N2, & influenza B viruses remain largely sensitive to oseltamivir & zanamivir
- Oseltamivir treatment in adults
  - Standard dose & duration: 75mg bd p.o. for 5 days
  - Most effective when administered as early as possible, i.e. <2 days after onset of illness
  - Use Zanamivir if oseltamivir resistance suspected (rare)
- Indications
  - Severe, complicated or progressive influenza
  - Patients with uncomplicated illness who are in a risk group (refer to vaccination guidelines)

Influenza chemoprophylaxis (WHO)

- Chemoprophylaxis for contacts of persons with influenza is **not recommended**
- Advise **presumptive treatment for high-risk** (severely immuno-compromised) **individuals** exposed to influenza
  - Oseltamivir or zanamivir - dose & duration as per treatment recommendations
- Non high-risk individuals exposed to influenza
  - Monitor exposed, high-risk patients for early signs and symptoms of acute respiratory infection influenza like illness → start antiviral treatment promptly if symptoms

Vaccination to prevent human papillomavirus (HPV) & cervical cancer

- >275 000 deaths due to cervical cancer/year
  - >85% in developing countries
- HPV = etiologic agent in cervical cancer
  - High risk HPV (hrHPV) types cause cervical cancer
    - 70% caused by HPV types 16 & 18
  - Low risk HPV (lrHPV) types cause genital warts
    - 90% caused by HPV types 6 & 11
- HPV is mainly sexually transmitted
  - Ideal age: 9-15 years old (before sexual debut)

HPV vaccines

- **Gardasil®** (Merck)
  - quadrivalent
  - types 6,11,16 & 18
- **Cervarix®** (GSK)
  - bivalent
  - types 16 & 18

**HPV 16 & 18** → 70% of cervical cancers
**HPV 6 & 11** → 90% of genital warts

HPV vaccines: Virus like particles (VLPs)

- Gene coding for L1 capsid protein are transferred into a yeast or insect virus expression system
- L1 capsid protein of HPV can self-assemble into VLPs which closely mimic the structure of natural HPV virions
- Do not contain any genetic material
  - Not infectious or toxic = SAFE
  - Well tolerated
  - No oncogenic potential
  - No disease causing potential
  - No serious vaccine-related adverse events reported

HPV vaccines

- 2 vs 3 dose regimens
  - Initially marketed as: 0, 1 or 2 & 6-months
  - Government schedule: 0 & 6 months
    - New data
    - More girls will complete the course
    - Limited resources
- Efficacy if HPV naïve at baseline: 100%
  - NOT a therapeutic vaccine
- Cervical cancer screening will still be necessary
  - For types of HPV that are not included in the vaccine
  - For unvaccinated women
  - For women vaccinated after their sexual debut

A vaccine to prevent zoster

**Varicella/Chickenpox** ➔ **Latency** ➔ **Zoster/shingles**

Aerosol spread via respiratory droplets & via vesicle fluid

Vesicle fluid infectious – can cause chickenpox in a susceptible individual
A vaccine to prevent zoster

**ZOSTAVAX** (Live, attenuated VZV vaccine)
- Minimum of 19 400 PFU per dose
- 14 times the minimum potency of the varicella vaccine
- Single subcutaneous dose
- Indicated for immunisation of individuals ≥50 years of age
  - Prevention of herpes zoster (shingles)
  - Prevention of post-herpetic neuralgia (PHN)
  - Reduction of acute and chronic zoster-associated pain
- Contra-indicated in
  - Immunocompromised individuals
  - Individuals with hypersensitivity to vaccine components e.g. gelatin
  - Persons with active untreated tuberculosis

A vaccine to prevent zoster

**ZOSTAVAX** (Live, attenuated VZV vaccine)
- Vaccine efficacy to prevent zoster
  - 50-59 years of age: 70%
  - 60-69 years of age: 64%
  - 70-79 years of age: 41%
  - ≥ 80 years of age: 18%
- Vaccine efficacy to prevent PHN: 67%
- Vaccine efficacy to prevent burden of illness: 61.1%
- **Cannot** be used to treat existing shingles or the pain associated with existing shingles

A vaccine to prevent zoster

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After primary VZV infection or zoster VZV-specific memory T cells is induced

Memory immunity to VZV may be boosted periodically by exposure to VZV or silent reactivation from latency

The decline of VZV-specific memory T cells below a threshold correlates with an increased risk of zoster

**ZOSTAVAX** vaccine may prevent VZV-specific T cells from dropping below the threshold for zoster occurrence