HBV -- Treatment

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Hepatitis B Virus

- Nucleic Acid: 3.2 kb DNA
- Classification: Hepadnaviridae
- Multiple serotypes and genotypes A-H
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus; hepatocyte and other tissues, human and other primates
Prevalence of HBV: Global Estimates

350 million With Chronic HBV

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAg Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>10-13.8</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>5.7-10</td>
</tr>
<tr>
<td>China</td>
<td>5.3-12</td>
</tr>
<tr>
<td>Africa</td>
<td>5-19</td>
</tr>
<tr>
<td>Philippines</td>
<td>5-16</td>
</tr>
<tr>
<td>Thailand</td>
<td>4.6-8</td>
</tr>
<tr>
<td>Japan</td>
<td>4.4-13</td>
</tr>
<tr>
<td>Indonesia</td>
<td>4.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.6-5.1</td>
</tr>
<tr>
<td>India</td>
<td>2.4-4.7</td>
</tr>
<tr>
<td>Russia</td>
<td>1.4-8</td>
</tr>
<tr>
<td>United States</td>
<td>0.2-0.5</td>
</tr>
</tbody>
</table>

HBsAg Prevalence
- High (>8%)
- Intermediate (2%-7%)
- Low (<2%)


New HBV Infections by Year: United States (1966-2006)

HBV and Hepatocellular cancer (HCC)

- Globally, commonest underlying cause of HCC
- In Asia, up to 40% of HCC in HBV in noncirrhotics
- Western countries show significantly less risk in HBV carriers
- Annual incidence: 0.2% to 2.5%
If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer

Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal:
- Liver cancer is the 2nd highest cause of death by cancer
- Without appropriate treatment or monitoring, 1 in 4 persons with chronic hepatitis B will die of liver cancer or liver disease
Natural History of Chronic HBV Infection

Childhood
- Immune Tolerance (≥95%)

Adulthood
- HBeAg+ CHB
- HBeAg- CHB
- Inactive carrier

<15-30% of HCC associated with HBV occurs in the absence of cirrhosis or advanced fibrosis

HCC
And or cirrhosis

HBV DNA vs. Liver Cirrhosis: REVEAL data

Baseline HBV DNA

No of patients = 3,482

Cumulative rate of liver cirrhosis

* HBeAg negative n=2960

No HBeAg negative

ACG 2015 Nashville Hepatitis School
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Aiming for True Inactive Carrier Status

Milestone 1: Start of decline of HBV DNA
Milestone 2: HBeAg/anti-HBe conversion
Milestone 3: HBV DNA decreased to undetectable
Milestone 4: Clearance of HBsAg
Milestone 5: Clearance of cccDNA

HBsAg+ HBsAg−

ALT level

Immune tolerance Immune clearance Inactive carrier state Functional cure=CURE

This is where we would like our patients to be.

HBV DNA vs. HCC: REVEAL Data

No of patients = 3,653*

Baseline HBV DNA RR

$10^0$ copies/mL 6.6

$10^3$ to $10^5$ 6.1

$10^4$ to $10^5$ 2.3

$300$ to $10^4$ 1.1

$<300$ 1.0

*HBeAg negative n=3085

**Goals of therapy for Hepatitis B**

Liver histology improves

Serum HBV DNA declines

**Prevention of Death, Cirrhosis, and HCC**

Seroconversion (loss of HBeAg, production of anti-Hbe, loss of HBsAg)

ALT normalization

**US FDA dates of Approved Therapies for CHB**

<table>
<thead>
<tr>
<th>Nucleosides/Nucleotides</th>
<th>Drug</th>
<th>Company</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix / Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Entecavir</td>
<td>BARALEASE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPFERA™</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
<tr>
<td><strong>Interferons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2a*</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
</tr>
<tr>
<td>Interferon alfa-2b, recombinant</td>
<td>INTRON® A</td>
<td>Schering / Merck</td>
<td>1992</td>
</tr>
</tbody>
</table>

**Preferred therapies – AASLD Guidelines**
Candidates for HBV Treatment

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>20,000</td>
<td>2000</td>
<td>20,000</td>
<td>20,000</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>2000</td>
<td>2000</td>
<td>2000</td>
<td>2000-20,000</td>
</tr>
<tr>
<td>ALT: Normal range</td>
<td>-</td>
<td>-</td>
<td>Use revised, lower range (M: 30 U/L; F: 19 U/L)</td>
<td>Use revised, lower range (M: 30 U/L; F: 19 U/L)</td>
</tr>
<tr>
<td>When to treat: key factors</td>
<td>HBV DNA and ALT</td>
<td>HBV DNA and ALT</td>
<td>HBV DNA and ALT</td>
<td>HBV DNA and ALT</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
</tr>
</tbody>
</table>


Treatment Guidelines: Recommendations for First-Line Therapy in Patients Without Cirrhosis

**HBeAg Positive or Negative Chronic HBV**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Adefovir</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Telbivudine*</td>
<td></td>
</tr>
<tr>
<td>Peg-IFN alfa-2a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HBV DNA must be undetectable at 24 weeks to continue (Keeffe).
AASLD guidelines: lamivudine and telbivudine not preferred due to relatively high rate of resistance. Adefovir not preferred due to weak antiviral activity and relatively high rate of resistance in HBeAg-negative studies.

Treatment Guidelines: Recommendations for Patients With Cirrhosis

Compensated Cirrhosis

Preferred | Potential | Not Preferred
--- | --- | ---
Tenofovir DF | Peg-IFN alfa-2a* | Lamivudine
Entecavir | Adefovir | Telbivudine

Decompensated Cirrhosis

Preferred | Not Preferred
--- | ---
Tenofovir DF plus lamivudine | Peg-IFN alfa-2a and alfa-2b†
Tenofovir DF | Entecavir

Note: therapies are approved for monotherapy only.
*Early cirrhosis only.
†Contraindicated.


ETV 3-year Clinical Trial HBV DNA Suppression HBeAg-negative Patients

<table>
<thead>
<tr>
<th></th>
<th>ETV-027</th>
<th>HBeAg(-) ETV Long-term Cohort (ETV-027→ETV-901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/57†</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>4%</td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>End of Dosing</td>
<td>93/99</td>
<td>84/90</td>
</tr>
<tr>
<td>Baseline</td>
<td>4/99</td>
<td>79/95</td>
</tr>
<tr>
<td>Wk 144</td>
<td>56/95</td>
<td>84/90</td>
</tr>
<tr>
<td>Wk 12</td>
<td>59%</td>
<td>91%</td>
</tr>
<tr>
<td>Wk 24</td>
<td>72/77</td>
<td>91%</td>
</tr>
<tr>
<td>Wk 48</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Wk 72</td>
<td>67/74</td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†In the randomised controlled study (ETV-027), patients received 0.5mg ETV. In the 901 rollover study, patients received 1mg ETV
‡10 patients who remained on treatment at Week 144 of ETV-901 visit had missing PCR samples

Shouval D, et al. AASLD 2008; poster 927.
**Studies 102/103:**

**Virologic Suppression With Tenfovir at Year 6**

<table>
<thead>
<tr>
<th>Response</th>
<th>HBeAg- Patients (Study 102)</th>
<th>HBeAg+ Patients (Study 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 5</td>
<td>Year 6</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL Intent-to-treat*, % (n/N)</td>
<td>83 (291/350)</td>
<td>81 (281/345)</td>
</tr>
<tr>
<td></td>
<td>Year 5</td>
<td>Year 6</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL On treatment†, % (n/N)</td>
<td>99 (292/295)</td>
<td>99.6 (283/284)</td>
</tr>
</tbody>
</table>

* LTE-TDF (missing = failure/addition of FTC = failure)   † Observed (missing = excluded/addition of FTC = included)

- 80% of 585 patients entering the open-label phase remained on study at Year 6; 73% of enrolled patients remained on study
- HBeAg loss/seroconversion rates of 50% and 37%, respectively, through 6 years
- 11% of HBeAg+ patients had confirmed HBsAg loss (8% with seroconversion)
- No resistance to TDF was detected through 6 years


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**HCC Risk in Caucasian, Chronic HBV Patients Treated With Entecavir or Tenofovir DF**

- Multi-country cohort (Greece, Italy, Turkey, Spain, The Netherlands) (n=1231)
  - Chronic HBV with no co-infection, liver transplantation, or HCC
  - Initiated either entecavir (43%) or tenofovir DF (55%)
- HCC 5-year incidence
  - 4.2% at median of 17 months
  - 13.5 new HCC cases/1000 person-years
- Strongest HCC risk factors
  - Decompensated liver disease (HR: 2.78; P=0.019), lower platelet count (HR: 0.97; P=0.002), older age (HR: 1.05; P=0.12)
- Asian-based HCC risk scores may not be applicable to Caucasians with chronic HBV

Interferon

- Short fixed duration therapy (16-48 weeks)
- No Renal toxicity
- Ideal for patients with high ALT and medium to low DNA
- Has stopping rules and “continuation” rules
- Chance of DNA suppression long-term is less than 20%
- HBsAg loss is 10%
  - Same as with Nuc therapy
- HBsAg quant is best stopping (test) rule, but not available in the US

HBsAg Reduction at Week 24 of PEG INF can Predict of Future HBsAg Clearance

Among HBeAg-negative patients who achieved HBsAg decline ≥10% from baseline at Week 24 of treatment*

45% of those achieved HBsAg clearance at 5 years post-treatment (N=13/29)

43%

achieved HBV DNA ≤ 10,000 copies/mL SUSTAINED IMMUNE CONTROL (N=29/67)

*56% of patients achieved HBsAg decline ≥10% at week 24

NIDDKD Cohort: HBsAg Loss by Mode of HBeAg Clearance

- Treatment-induced HBeAg clearance (n=51)
  - Interferon related: 86%
- Cumulative incidence of HBeAg loss per year (P=0.02)
  - Spontaneous: 1.6%
  - Nucleoside analog induced: 4.4%
  - Interferon induced: 6.3%
- Most significant predictors of HBsAg loss
  - Mode of HBeAg loss
  - Race

Probability of HBsAg Loss by Mode of HBeAg Clearance

- Interferon-Related HBeAg Loss (n=19)
- Nucleoside Analog-Related HBeAg Loss (n=2)
- Spontaneous Loss of HBeAg (n=8)


HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients


When can treatment be stopped?

IFN defined duration, 12 months for both HBeAg+ and HBeAg- patients

Nucleos(t)ide analogues until treatment endpoint

• HBeAg+ patients HBeAg seroconversion + >6 mos consolidation Rx, ~50% after 5 yr Rx

• HBeAg- patients endpoint not defined, HBsAg loss ~5% after 5 yr Rx

• Cirrhotics life-long Rx?

Cirrhosis Reversal Following Lamivudine Rx in HBV

Courtesy of Ian Wanless, MD.
Types of Virological Response

On Continuous Treatment

- Primary non-response
- Breakthrough

LLOD LLOD

V DNA (Log10 IU/ml)

Relapse

On Treatment

Sustained Response

Months

- Months

Maintained Response

HBV DNA

Antiviral Resistance: Nomenclature

<table>
<thead>
<tr>
<th>Genotypic resistance</th>
<th>Detection of HBV polymerase mutation(s) associated with resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypic resistance</td>
<td>Decreased \textit{in vitro} susceptibility to an antiviral agent</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in HBV DNA by &gt;1 log_{10} over nadir on treatment</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT on treatment</td>
</tr>
</tbody>
</table>

Differences in Development of Resistance with Long-term Treatment in Nuc-naïve Patients

Different patient populations and trial designs

Lamivudine\(^1\) Adefovir\(^2\) Entecavir\(^3\)–\(^6\) Telbivudine\(^7\),\(^8\) Tenofovir\(^9\),\(^10\)


Summary: Guidelines for Management of Antiviral-Resistant HBV

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rescue Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Add adefovir or tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Stop lamivudine, switch to emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Add lamivudine</td>
</tr>
<tr>
<td></td>
<td>Stop adefovir, switch to:</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Switch to or add entecavir (If no prior lamivudine resistance)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Switch to tenofovir DF or emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Add adefovir or tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Stop telbivudine, switch to emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Adefovir/</td>
<td>Consider tenofovir emtricitabine DF, or tenofovir+ entecavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
</tr>
<tr>
<td>Lamivudine Entecavir</td>
<td>Consider tenofovir DF/entecavir</td>
</tr>
</tbody>
</table>

Tenofovir + Entecavir for Multidrug resistant HBV infection

- 51/57 (90%) of patients achieving HBV-DNA undetectability (LLoD 80IU/ml)

Indications for HBV vaccination

- HBIG and HB vaccine to infants of HBsAg+ mothers
- Routine vaccination of infants and adolescents
- Catch-up vaccination of children
- Vaccination of adults at risk of infection
HBV DNA Level and Perinatal Transmission of HBV

Perinatal Transmission

No cases of transmission from mothers with HBV DNA <8 log_{10} copies/mL.
One case of escape mutation identified.


Treatment during pregnancy

- **Xu et al**

<table>
<thead>
<tr>
<th>Maternal HBV DNA (copies/mL)</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infants of HBV DNA-Positive Mothers</td>
<td>2.9%</td>
</tr>
<tr>
<td>HBeAg-Positive Mothers</td>
<td>6.6%</td>
</tr>
<tr>
<td>&lt;10^6</td>
<td>0%</td>
</tr>
<tr>
<td>10^6-10^8</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;10^8</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

- Primary endpoint HBsAg + infant at 1 yr
- Secondary endpoint HBsAb+, HBV DNA+

Treatment during pregnancy

- Xu et al: Improved outcomes for the infants

<table>
<thead>
<tr>
<th>Infant Status at 52 weeks</th>
<th>LAM (n = 56)</th>
<th>Placebo (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg(+), %</td>
<td>18</td>
<td>39</td>
<td>.014</td>
</tr>
<tr>
<td>HBV DNA(+), %</td>
<td>20</td>
<td>46</td>
<td>.003</td>
</tr>
</tbody>
</table>

HBsAb positive 84% vs. 61% (p=0.008)

Treatment of HBV: Special Cases

- Prophylactic treatment during chemotherapy to prevent reactivation (Rx from 1 wk before to 3-12 mo after)¹
  - % with hepatitis: 53% untreated vs. 14% lamivudine-treated
- Treatment of women during the third trimester of pregnancy to reduce rate of vertical transmission²
  - Studies limited; use in women with HBV DNA >10⁸ c/mL
- HBV/HIV coinfection³
  - If HAART needed, then tenofovir + emtricitabine or lamivudine
- Prophylactic treatment after liver transplantation to prevent reinfection³

HBV Reactivation Following Rituximab-Containing Chemotherapy

- Single-center cohort with a variety of hematologic diagnoses (n=62) (2011-2013)
  - HBsAg negative, anti-HBc positive
  - HBV DNA <10 IU/mL
  - No concomitant liver disease or prior HBV treatment
  - Reactivation: HBV DNA >10 IU/mL regardless of HBsAg status
  - Follow-up: 36.6 months
- High rate of reactivation
  - Majority occurred within the first 6 months (86.7%)
  - Presence of low anti-HBs levels was not protective against HBV reactivation

Cumulative Rate of HBV Reactivation

- 9-Month Cumulative Rate: 29.3%
- Majority occurred within the first 6 months (86.7%)
- Presence of low anti-HBs levels was not protective against HBV reactivation

Hepatitis B reactivation recommendations High-Risk Patients (Anticipated Incidence of HBV Reactivation, > 10% of Cases)

- Tenofovir/Entecavir preferred agents
- Continue antiviral therapy for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B-cell–depleting agents).
  - Hepatitis B surface antigen (HBsAg)-positive/anti-hepatitis B core antibody (HBC)-positive patients treated with B-cell–depleting agents (eg, rituximab, ofatumumab)
  - HBsAg-positive/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin)
  - HBsAg-positive/anti-HBc–positive patients treated with moderate-dose (10-20 mg prednisone daily or equivalent) or high-dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥ 4 weeks.


Hepatitis B reactivation recommendations
Moderate-Risk Patients (HBV Reactivation, 1%-10% of Cases)

- Tenfovir/Entecavir preferred, continue treatment for 6 months after discontinuation of immunosuppressive therapy
- HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tumor necrosis factor alpha inhibitors (eg, etanercept, adalimumab, certolizumab, infliximab)
- HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with other cytokine or integrin inhibitors (eg, abatacept, ustekinumab, natalizumab, vedolizumab)
- HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tyrosine kinase inhibitors (eg, imatinib, nilotinib)
- HBsAg-positive/anti-HBc–positive patients treated with low-dose (< 10 mg prednisone daily or equivalent) corticosteroids for ≥ 4 weeks
- HBsAg-negative/anti-HBc–positive patients treated with moderate-dose (10-20 mg prednisone daily or equivalent) or high-dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥ 4 weeks
- HBsAg-negative/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin).

How do we screen for HCC in HBV

- No studies define unequivocally the best modality for diagnosing HCC
- Ultrasonography (US) every 6 months with alpha-fetoprotein (AFP) every six months is current standard of care for screening high risk patients
  - US has technical limitations (operator dependence, reduced efficacy in those with elevated BMI)
  - US if subject has normal BMI
- AFP alone is not sufficient unless imaging modalities are not available
- Our practice at IU: MRI every 9 months or Dual Phase Spiral CT, or US every 6 months if normal BMI
  - MRI or US preferred due to radiation risk with CT scan
AASLD Guidelines: HBV

- Surveillance recommended in at-risk groups
  - Specific hepatitis B carriers
    - Asian males >40 years
    - Asian females >50 years
    - Africans >20 years
    - All HBV cirrhotic pts
  - Family history of hepatoma
- Patients should be screened at 6-month intervals
  - US and AFP level

Other Clinical Pearls

- Avoid entecavir use in HBV/HIV
  - leads to HIV resistance
  - Check HIV serology prior to initiating entecavir
- Telbivudine /Tenofovir are pregnancy category B
  - Useful in young females trying to conceive
  - Acute HBV in pregnancy
  - Low rate of resistance if HBV undetected by week 24 but must monitor for resistance
Indications for treatment of chronic hepatitis B
Who Should be Treated?

- Chronic HBV infection: HBsAg+ > 6 months
- Evidence of virus replication: serum HBV DNA >10^4-5 copies/ml (2000-20,000 IU/ml)
- Evidence of liver damage: elevated ALT and/or chronic hepatitis on biopsy

Summary

Prevention
- Avoid unnecessary treatment
- Initiate treatment with potent antiviral that has low rate of drug resistance (tenfovir or entecavir) or with combination therapy
- Switch to alternative therapy in patients with primary non-response

Monitoring
- Test for serum HBV DNA (PCR assay) every 3-6 months during treatment
- Check for medication compliance in patients with virologic breakthrough
- Confirm antiviral resistance with genotype testing
Summary of Guidelines

Treatment of Hepatitis B

When to start therapy

- Elevated HBV DNA (>20,000 IU/mL for HBeAg(+)) and 2,000 IU/mL for HBeAg(-)) plus elevated ALT, and/or significant disease on liver biopsy

When to stop or alter therapy

- HBeAg(+): HBeAg seroconversion and (-) HBV DNA
- HBeAg(-): ?long-term therapy
- Inadequate VR (≥2,000 IU/mL) at week 24
- Development of antiviral drug resistance

Summary

Treatment

- Guided by genotypic assays
- Add on therapy or switch therapy per guidelines
- Rescue therapies for multi-drug resistance
  - tenofovir+entecavir
  - tenofovir DF/emtricitabine