DIVISION OF MEDICINE
NELSON R MANDELA SCHOOL OF MEDICINE
UNIVERSITY OF KWAZULU-NATAL

28TH MEDICINE UPDATE SYMPOSIUM

4-5 October 2008
**MEDICINE UPDATE FOR SPECIALIST PHYSICIANS: SATURDAY 4\(^{th}\) OCTOBER**

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<tr>
<td>13h25-13h30</td>
<td>Welcome</td>
<td>Prof R Hift</td>
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<td>Aspects of management in patients with poorly controlled epilepsy</td>
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<td>Gastroenterology</td>
<td>Prof K Newton</td>
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<td>17h15-18h15</td>
<td>Guest Lecturer: “Rational choices in the management of patients with coronary artery disease”</td>
<td>Prof P Commerford</td>
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**MEDICINE UPDATE FOR FAMILY PHYSICIANS: SUNDAY 5\(^{th}\) OCTOBER**

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<tr>
<td>07h30-08h30</td>
<td>Registration</td>
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<tr>
<td>08h25-08h30</td>
<td>Welcome</td>
<td>Prof R Hift</td>
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<tr>
<td>08h30-09h15</td>
<td>Arthur Landau Memorial Lecture:</td>
<td>Prof K Huddle</td>
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<td>“Phaeochromocytoma. Tumour Extraordinaire”</td>
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<tr>
<td>09h15-10h15</td>
<td>What makes the expert clinician expert?</td>
<td>Prof R Hift</td>
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<td>10h15-10h45</td>
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<tr>
<td>10h45-11h45</td>
<td>Vinod Gathiram Memorial Lecture:</td>
<td>Prof P Commerford</td>
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<td>“Practical approach to the management of heart failure”</td>
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<td>11h45-12h30</td>
<td>Early inflammatory arthritis: the importance of early diagnosis and treatment</td>
<td>Dr N Patel</td>
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<tr>
<td>12h30-13h30</td>
<td>Clinical Challenges in HIV</td>
<td>Dr N Magula</td>
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<td>13h30-14h30</td>
<td><strong>LUNCH</strong></td>
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<tr>
<td>14h30-15h15</td>
<td>Non-alcoholic steatohepatitis</td>
<td>Prof R Hift</td>
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<tr>
<td>15h15-16h15</td>
<td>Ethics</td>
<td>Ms M Stobie</td>
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<tr>
<td>16h15-17h00</td>
<td>Dermatology Slide Show</td>
<td>Dr A Mankahla</td>
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On behalf of the Division of Medicine, I have pleasure in thanking you for your support at our annual Medicine Update, and in welcoming you to the symposium.

As a new departure, we have added a half-day meeting to our programme directed specifically at the specialist physician, to complement the traditional Sunday which we share largely, though not exclusively, with our colleagues in family practice. We hope that this will prove successful, and will be continued into the future.

May I express my thanks in particular to: our guest speakers, Prof Pat Commerford and Prof Ken Huddle from Cape Town and Johannesburg respectively, the Academic and Organising Committees, and in particular to Precious Sibiya, Maryann Francis and Sagree Pillay, and to Lullie Pillay, Chandrika Vedalankar and Zonke Goge.

With kind regards
Richard Hift
MEDICINE UPDATE FOR SPECIALIST PHYSICIANS

SATURDAY 4th OCTOBER
Abstract:
The measurement of glycated haemoglobin (HbA\textsubscript{1c}) has become an indispensable aspect of monitoring and management of diabetes mellitus. In the past few years, great strides have been made in standardization of the assay to ensure reproducible results. Furthermore, the International Federation of Clinical Chemists has succeeded in generating a reference method that is highly specific for HbA\textsubscript{1c} and this is the current global reference. With the improved accuracy of HbA\textsubscript{1c} measurement, a multi-centre study has elucidated a means of calculating average glucose from the HbA\textsubscript{1c} – this will assist in patient education and participation in management as HbA\textsubscript{1c} is a concept that has proven difficult for lay persons to understand.

People with type 2 diabetes have an increased incidence of macrovascular disease and this is responsible for substantial morbidity and premature mortality. There has been debate as to the impact of glycaemic control on macrovascular disease, principally since the publication of the UKPDS study in 1998. In this study, intensive glycaemic control failed to significantly reduce the incidence of myocardial infarction, although the p value was close to statistical significance. This has led to a number of studies aimed at answering the question as to whether or not improved glycaemic control is beneficial in terms of reduction of myocardial infarction and other macrovascular complications. In the past year, 3 major studies have provided some clarity on this issue and these include the ACCORD, ADVANCE and UKPDS post trial monitoring studies. These studies show unexpected dangers in aggressive glycaemic management but provide important information regarding glycaemic management.

Since the introduction of incretin-based therapy, the choice of agent employed in step 2 of the glycaemic control algorithm has become more difficult. Each class of agent has its own benefits and adverse effects, but incretin-based therapies have unique properties that may alter the natural history of type 2 diabetes.

Management of type 2 diabetes continues to provide challenges and new demands are made on the clinician as well as the person with type 2 diabetes. Hopefully the current rate of advancement of knowledge and new therapies will ultimately lead to identification of curative therapy.
ADVANCES IN MANAGEMENT OF STROKE

Dr Vinod Patel
Department of Neurology
Division of Medicine
School of Clinical Medicine
Nelson R Mandela School of Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban

ASPECTS OF MANAGEMENT IN PATIENTS POORLY CONTROLLED EPILEPSY

Professor PLA Bill
Department of Neurology
Division of Medicine
School of Clinical Medicine
Nelson R Mandela School of Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban
Congestive Heart Failure (CHF) is one of the leading causes of hospitalisations in patients > 65 years of age. Owing to an ageing population and improved survival of patients with coronary artery disease, the incidence of ischaemic cardiomyopathy (the commonest cause of heart failure) is increasing. In addition, CHF is associated with high rates of re-hospitalisation and a major economic burden.

Increasingly the syndrome of CHF is one of Cardio-Renal Failure, in which cardiac and renal dysfunctions exist simultaneously, with each accelerating the progression of the other: Impaired renal function is the single most important mortality marker in CHF, even above NYHA functional class or Left ventricular performance (Ejection Fraction).

Diuretics are traditionally considered the standard of care in CHF, but, surprisingly, they are one of the few therapies in HF that have not been subjected to randomized controlled trials. Optimal doses in CHF are often controversial. Furthermore, diuretic responses in Acute Decompensated Heart Failure (ADHF), are sub-maximal and are associated with diuretic resistance, which may, in part, contribute to the pathophysiology of progressive Cardio-Renal Failure.

When conventional therapy for ADHF fails, mechanical fluid removal in the form of extra-corporeal Ultrafiltration (UF) may be needed for refractory fluid overload.

UF has been shown to restore diuretic responsiveness and improve cardiac status, with numerous benefits over diuretic therapy, including those beyond fluid volume removal.

Given that the initial costs of UF in CHF might exceed that of conventional therapy, the superior acute and long term benefits (both clinical and financial) of this form of treatment, in the appropriate clinical setting, may prompt more frequent use of this technique, so that it be included in the standard of care of patients with advanced CHF.
Acute Severe Ulcerative Colitis

Professor KA Newton
Head: Department of Gastroenterology
Division of Medicine
Nelson R Mandela School of Medicine
School of Clinical Medicine
College of Health Sciences
University of KwaZulu-Natal

Ulcerative Colitis
- Recurring episodes of inflammation of colonic mucosa
- From rectum, may extend in proximal and continuous fashion to involve other portions of colon
- Typically consists of intermittent exacerbations alternating with asymptomatic periods of remission

Epidemiology
- Rates are highest in northern hemisphere and in high income regions
- Bimodal age distribution 15-40 and 50-80
- Males > Females
- Tends to run in families
- Relationship to cigarette smoking

Diagnosis
- Characteristic history
- Typical endoscopic appearance of mucosa
- Negative microbiology
- Confirmatory histology seen on biopsy

Differential Diagnosis
- Infectious
- Crohn’s Disease
- Radiation Colitis
- Ischaemic Colitis
- Colitis from meds: C. diff. from antibiotics NSAIDS, retinoic acid, gold, OCP’s

Subtypes of UC
- Ulcerative proctitis = disease limited to rectum
• Distal colitis/proctosigmoiditis = process extends into mid-sigmoid
• Left sided colitis = disease extending to but not proximal to the splenic flexure
• Extensive colitis = disease proximal to splenic flexure but not as far as caecum
• Pancolitis = extends to the caecum

Severity
• Mild
• Moderate
• Severe
• Fulminant

Mild Disease
• Intermittent rectal bleeding with mucus
• Mild diarrhea (<4 small stools/day)
• Mild crampy abdominal pain
• Tenesmus and periods of constipation

Moderate Disease
• Frequent loose, bloody stools (4-6/day)
• Mild anemia not requiring transfusions
• Abdominal pain that is not severe
• Low grade fever
• Usually able to maintain adequate nutrition

Treatment – Mild to Mod disease
• Proctitis
• Topical 5-ASA suppositories or steroid foams
• Oral preparations if have anal irritation
• Left-sided Colitis
• 5-ASA or steroids enemas
• Oral preparations if enemas not tolerable or persistent disease
• Pancolitis
• Combination of oral and topical agents

Defining the severe attack
• Severe Colitis
• Diarrhoea with ≥ 6 bloody stools per day

AND
• Pulse >90 /min or
• Temp > 37.8 C or
• Hb < 10.5 g % or
• ESR > 30mm/hr
**Outcome of acute attack**

**UK Experience**

116 patients

- 28% Colectomy
- Mortality <1%
- 41% Remission
- 31% Partial Response

**Hawtorne and Travis, Gut 2002**

**Why identify patients at risk?**
- Discuss “rescue” therapy with patient
- Early introduction of aggressive therapy
- Liaise with surgeon at early stage
- Delayed surgery increases complication and mortality rate
- Introduce stomatherapist

**Predictors of Colectomy**
- Radiological
- Mucosal islands (75%)
- Colon dilatation > 5.5cm (75%)
- Small bowel dilatation (50-73%)
- Clinical markers
- Stool frequency > 12 / day (55%)
- Fever > 38 °C (55%)
- Tachycardia > 100/min (45%)
- Albumin < 30g/l on day 4 (60%)

**Lennard Jones et al, Gut 1975**
**Prognostic Indicators**
- 36 clinical, radiological and laboratory parameters in 51 severe attacks in 49 patients

- **Oxford Index**
  If on day 3 of intensive treatment,
  - Stool frequency > 8 /day
  - CRP > 45 ug/l and stool frequency 3-8 / day
  → Then 85% come to colectomy on that admission

≈ Sweden Index

*Travis et al, Gut 1996*

- 167 patients – 40% colectomy

**Stool frequency**

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Colonic Dilatation</th>
<th>Stool frequency</th>
<th>Independent predictors of colectomy</th>
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<tbody>
<tr>
<td>&lt; 4</td>
<td>0</td>
<td>&lt; 4</td>
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</tr>
<tr>
<td>4-6</td>
<td>1</td>
<td>4-6</td>
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</tr>
<tr>
<td>6-9</td>
<td>2</td>
<td>6-9</td>
<td></td>
</tr>
<tr>
<td>&gt; 9</td>
<td>4</td>
<td>&gt; 9</td>
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</tr>
</tbody>
</table>

- All patients with score > 6 need colectomy
- Score ≥ 4
- 85% sensitivity
- 75% specificity

*Ho et al, Aliment Pharm Therap 2004*

**Endoscopic features**
- Extensive deep ulceration
- Mucosal detachment at edge of ulcer
- “Well-like” ulcers
- Large mucosal abrasions

> 80% sensitivity and specificity for colectomy

*Carbonnel et al, Aliment Pharm Therap 2004*
Summary of outcome of severe attack
- Only 70% respond to intensive therapy
- Clinical predictors of poor response are available
- Trigger appropriate action
- ? Rescue therapy
- ? Colectomy
- Early surgery has reduced mortality from 24% to < 1%
- PROBLEM: No uniform “activity index”

Indications for urgent and emergency colectomy in acute severe colitis
- Urgent colectomy
- Severe colitis (after 5-7 days ineffective treatment)
- Toxic megacolon (after 48-72 hrs of ineffective treatment)
- Growth retardation primarily in children and adolescents
- Emergency colectomy
- Fulminant colitis unresponsive to intravenous steroids
- Toxic megacolon with impending perforation
- Massive unrelenting haemorrhage
- Colonic perforation
- Total obstruction from stricture
- Acute intractable colitis
- Multiple organ dysfunction syndrome

ACG Criteria for diagnosis of severe and fulminant colitis

Severe colitis
- > 6 bloody stools per day
- Fever > 37.8
- Tachycardia > 90/min
- Anaemia (Hb <75% normal)
- ESR >30mm/hr

Fulminant colitis
- >10 bloody stools per day
- Fever > 37.8
- Tachycardia >90 /min
- Anaemia requiring transfusion
- ESR >30 mm/hr
- Colonic dilatation >6cm on radiography
- Abdominal distension with tenderness

Kombluth & Sachar, Am J Gastroent. 2004

Acute severe attack
Management guidelines
- Physical exam at least once daily
- Vital signs 4X daily
- FBC /ESR /CRP /U+E / LFT(incl alb) daily +- 
- Daily AXR if colon initially dilated
- IVI electrolyte solution /BTF : HB > 10g/dL
- Subcut heparin
- Hydrocortizone 400mg/daily IVI
- Antibiotics if infection not ruled out.
Carter et al Gut 2004

When to consider rescue therapy
- Fulminant Colitis: 3-4 days after initiating treatment if not responding.
- Severe Colitis: 6-7 days after initiating treatment if poor response.

Infliximab vs Cyclosporine
- Comparable efficacy: 65-80% early favourable
  Campbell et al, Eur J Gastroenterol Hepatol 2005
- Both toxic to similar degrees
- Both expensive

Cyclosporine
- Never really “caught on”
- Toxicity
- Unfamiliarity
- Not a long-term solution
- However short t½ → ?
  Preferred agent as rescue in fulminant colitis because of high risk of surgery
- Low dose 2mg/kg vs 4mg/kg equal efficacy
  Van Aasche et al, Gastroenterology 2003
- If CSA response continue oral CSA X 3months then gradually wean to azathiaprine/6MP

Infliximab
- Prior proven utility in Crohns Disease
- 70% response in acute colitis
- Long-term treatment feasible
  Jarnerot et al, Gastroenterology 2005
- Risk of infection esp. TB
- ? Best TB prevention strategy in TB endemic regions
- Long t1/2 may make subsequent emergency surgery more hazardous
Outcomes following CyA vs placebo in 20 pts with severe UC

20 pts
- 11 CyA
  - 9 response
    - 1 = elective colectomy
    - 8: oral CyA
  - 2 = no response: surgery
  - 4 = no response: surgery
- 9 placebo
  - 5 = no response: Open-label CyA (crossover)
  - 5: response

Conclusion
- Rescue therapy here to stay
- Infliximab favoured except for early in fulminant attack where cyclosporin may be better
- The challenge is to not adversely affect mortality by delaying colectomy.
RATIONAL CHOICES IN THE MANAGEMENT OF PATIENTS WITH CORONARY DISEASE
MEDICINE, STENTS, SURGERY

Prof PJ Commerford
Head: Department Of Cardiology
University of Cape Town and
Groote Schuur Hospital

Few topics engender as much heat and controversy as this one and I believe it is fair to say that there is no single absolutely correct answer or opinion for some clinical situations. It is clear however that each individual patient requires careful formulation of a lifelong strategy. This needs to be based on an understanding of the prognosis of each of the coronary syndromes and an appreciation of the benefits of intensive, evidence-based pharmacological interventions which need to be maintained in the long-term. This needs to be combined with an understanding of the risks and benefits of coronary revascularization. All too often it seems that patients receive advice and are encouraged to undergo revascularisation procedures at extremely short notice. In reality this is seldom driven by true clinical urgency. Patients also seem to perceive revascularization as a “cure” which of course it is not. This may lead to the abandonment of treatments of proven efficacy.

Primary percutaneous intervention (PPCI) is the best form of treatment for patients with ST-elevation acute myocardial infarction provided it can be performed timeously by experienced operators in high-volume centres. If those criteria are not met then fibrinolysis offers a better option and prognosis. All too often delays, dithering and inter-hospital transfer for PPCI interfere with optimal management. Arguably better systems of care which ensure that simple, readily available and cheap therapies are implemented appropriately will have a bigger impact than any single new therapy.

Patients with non-ST-elevation acute coronary syndromes benefit from conventional medical therapy with heparins, anti-platelet agents and anti-ischaemics. Routine early angiography followed by revascularization is fashionable and often advised. This strategy reduces repeat infarction, angina and repeat rehospitalisation but carries a higher early mortality hazard and a trend to reduced mortality in the long-term. These niceties are difficult to explain to patients and families and require careful and detailed discussion before coronary angiography.

Patients with stable angina or asymptomatic and minimally symptomatic coronary disease have a surprisingly good prognosis. Revascularization whether by coronary bypass surgery (CABG) or percutaneous intervention (PCI) provides excellent relief of symptoms and is preferred whenever
symptoms interfere with desired lifestyle. CABG offers improved prognosis to selected subsets of patients whereas PCI does not offer any prognostic benefit at all. There is excellent evidence that indicates that optimal medical therapy and vigorous risk factor intervention provides a good long-term outcome and revascularization can often be safely deferred until warranted for symptomatic relief. Even after revascularisation all patients require continued optimal medical therapy and life-style modification if the benefits of revascularization are to be sustained.

Attempts to characterise management strategies or their practitioners as “conservative” or “invasive” are out-dated and should be discarded. The prudent physician will embrace all necessary strategies to provide patients with optimal prognostic and symptomatic benefit. No single strategy can stand alone. Optimal integration remains the key to successful patient management.
MEDICINE UPDATE FOR FAMILY PHYSICIANS

SUNDAY 5th OCTOBER
ARTHUR LANDAU MEMORIAL LECTURE:

"PHAEOMOCYTOMA. TUMOUR EXTRAORDINAIRE"

Professor Ken Huddle
Head of the Department of Medicine
Chris Hani Baragwanath Hospital and
University of Witwatersrand
WHAT MAKES THE EXPERT CLINICIAN EXPERT?

Professor R Hift
Head: Division of Medicine
Acting Head: School of Clinical Medicine
School of Clinical Medicine
Nelson R Mandela School of Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban

The diagnostic process
Is it a deductive process? This would imply a linear process, In other words: one advances a hypothesis, then seeks to confirm or refute it by a process of enquiry and elimination.

Is it a process of scheme induction? This implies an algorithmic approach, with the “branching points” firmly fixed in the clinician’s mind, such that all he or she needs to do is ask the right questions and get the right answers to navigate down the decision tree.

Finally, is it all a process of pattern recognition, of having seen it all before? For expert clinicians, the evidence suggests that they frequently make use of an intuitive, automatic and non-analytic process probably based strongly on pattern recognition. However there is evidence that all three mechanisms come into play depending on the clinician’s familiarity with the type of problem with which he or she is faced; further more, pattern recognition is both faster and more accurate than an inductive process, whereas a logical, scientific-style process of deductive reasoning is the least accurate, slowest and therefore least effective method of them all.

There are strong parallels to be drawn between expertise in diagnostic reasoning and expertise in other fields, such as chess. Current evidence strongly supports the contention that expertise is not dependent on an ever-more polished “skill”, but rather on the committing to memory of an ever-increasing repertoire of standard templates and exemplars, with which the immediate problem to be solved is compared and, if a match exists, is rapidly retrieved for further analysis.

This has important implications for medical expertise and medical education. It raises interesting questions about the true value of a knowledge of the basic sciences, it stresses the tyranny of “content specificity”, which indicates that diagnostic expertise in one field fails utterly to translate into expertise in another. It also implies that expertise in diagnosis cannot be learnt as a free-standing skill, but is completely dependent on the laying down of a huge store
of patterns and exemplars for future reference. Chunking theories of memory suggest how the human mind may deal with the resultant quantities of information which require storage and retrieval without being overwhelmed by the sheer quantity of such information.

Finally, all evidence suggests that expertise in any field is a direct function of the time spent on personal, "effortful practice"; the process cannot be accelerated by the provision of "packaged" information or experience.
VINODH GATHIRAM MEMORIAL LECTURE

“PRACTICAL APPROACH TO THE MANAGEMENT OF HEART FAILURE”
Prof P Commerford (UCT)
“PRACTICAL APPROACH TO THE MANAGEMENT OF HEART FAILURE”

Prof PJ Commerford
Head: Department Of Cardiology
University of Cape Town and
Groote Schuur Hospital
The recognition of early inflammatory arthritis is crucial as there is increasing evidence that early intervention may confer a long-lasting benefit on the patient. The concept of a ‘window of opportunity’ implies that early intervention will result in a significant and disproportionate benefit to patients treated early and aggressively. The challenge therefore is at the level of primary health care to recognize these patients and refer them appropriately.

The presentation will cover the following aspects of early inflammatory arthritis:

- History: diagnostic clues with regards to the pattern of arthritis, stiffness, swelling etc
- Examination: Recognition of clinical disease patterns, taking into account atypical presentations
- Red flags: when to consider septic arthritis
- Investigations: new serological markers and their value, radiology and newer techniques useful in early arthritis
- Screening tools
- When to refer a patient with early inflammatory arthritis
Introduction

- Goals of Antiretroviral Therapy
- Treatment Failure
- Case Scenarios
- Newer Drugs

Goals of HIV Therapy

- Maximal and durable suppression of viral replication
- Restoration and/or preservation of immune function
- Reduction of HIV-related morbidity and mortality
- Improvement of quality of life - conversion of HIV to a “chronic disease”
- Reduction of HIV transmission
Treatment Failure: 
Mechanisms for Development of Resistance 
Selective Pressure or Transmission 

- Social/Personal Issues 
- Regimen Issues 
- Toxocities 

- host genetics 
- Poor Absorption 
- Rapid Clearance 
- Poor Potency 
- Wrong Dose 

Insufficient Drug Level 

Viral Replication in the Presence of Drug 

Resistant Virus 

Transmission 

WHO Definitions for Clinical, Immunologic and Virologic Failure 

<table>
<thead>
<tr>
<th>Failure Type</th>
<th>Description</th>
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<tr>
<td>Clinical Failure</td>
<td>New or recurrent WHO stage 4 condition* (some WHO stage 3 conditions may indicate treatment failure, some WHO stage 4 conditions may not indicate treatment failure)</td>
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<tr>
<td>CD4 Cell Failure</td>
<td>Fall of CD4 count to pre-therapy baseline (or below); or 50% fall from the on-treatment peak value (if known); or persistent CD4 levels below 100 cells/mm³</td>
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<tr>
<td>Virological Failure</td>
<td>Plasma viral load above 10,000 copies/ml</td>
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*Some Stage 3 conditions may indicate treatment failure. Some Stage 4 conditions may not indicate treatment failure.

Definitions from 2008 DHHS Adult and Adolescent Guidelines

VIROLOGIC FAILURE:
- Incomplete virologic response in treatment naïve patients initiating therapy
  - Two consecutive VL > 400 copies/ml after 24 weeks
  - VL > 50 copies/ml after 48 weeks
- Virologic rebound: detectable VL (e.g. >50 copies/ml) after suppression
- Decision to switch:
  - Aggressive approach: Switch if repeated VL detectable (e.g. two consecutive >50 copies/ml after suppression) and not a “blip”
  - Less aggressive: Switch if VL reaches a certain threshold (e.g. 1000-5000 copies/ml), but risk of accumulating drug resistant mutations
- Immunologic failure
  - Failure to achieve and maintain CD4 above a certain threshold (despite virologic suppression)
  - e.g., CD4>350 or 500 cells
  - Or increase in CD4 of less than 50 or 100 above baseline
- Do not wait for clinical failure

Resistance is Irreversible
- Once selected by drug pressure, resistance mutations remain in the viral population
- Resistance assays commonly detect mutations only if present in >20% of viral population
- When drug pressure is discontinued, mutations may drop below 20% and not be detected by standard assays
- Attempts to recycle the drug (or cross-resistant drugs) may result in rapid reappearance (>20%)

Some Key Mutations for Some Antiretroviral Drugs with a Genetic Barrier of 1

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>CONFERS COMPLETE RESISTANCE TO:</th>
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<tbody>
<tr>
<td>NNRTI</td>
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</tr>
<tr>
<td>K103N</td>
<td>EFV, NVP, DLV</td>
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<tr>
<td>NRTI</td>
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<tr>
<td>M184V</td>
<td>3TC</td>
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<td>K65R</td>
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<tr>
<td>D30N</td>
<td>NFV</td>
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http://www.hivfrenchresistance.org/2006/tab2.html

Which Regimen to Switch to for Second-line ART?

[WHO Second-line regimen if standard first-line used]

NRTIs

- DDI or TDF and
- ABC or 3TC with or without AZT and
- PI/r

[Second-line regimen if triple NTRI used]

NRTIs

- DDI and
- PI/r and
- EFV or NVP

Gilks CF et al, Lancet 2006; 368: 505-10
WHO HIV Treatment Guidelines, Adults and Adolescents, 2006:
http://www.who.int/hiv/pub/guidelines/en
Newer Drugs
New drug in an Old Class: NNRTI

- HIV-1 reverse transcriptase has a crucial role in viral replication it transcribes the viral RNA into DNA, which is then integrated into the host cell genome
- Etravirine approved by the FDA in January 2008
  - for the treatment of HIV-1 infection in combination with other antiretroviral agents
  - for treatment-experienced patients who have HIV-1 strains that are resistant to other drugs in this class (nevirapine and efavirenz)
  - potentially becoming the first NNRTI for use in second-line therapy after failure of efavirenz or nevirapine
- Developing resistance to one NNRTI leads to resistance to all drugs in the class
  - can arise after the development of only one mutation in the reverse transcriptase gene
- Etravirine was specifically designed to be less susceptible than other NNRTIs to resistance mutations
- Interactions with protease inhibitors make combinations involving etravirine complicated.
  - an especially important issue for a second-line NNRTI that may be used in salvage regimens with protease inhibitors.

DUET-1 and -2: Phase III Trials of ETR Plus DRV/RTV-Containing OBR

HIV-infected patients with VF on current HAART regimen, history of ≥ 1 NNRTI resistance mutations, ≥ 3 primary PI mutations, HIV-1 RNA > 5000 copies/mL

(DUET-1: N = 612; DUET-2: N = 591)

ETR 200 mg BID + DRV/RTV-containing OBR* (n = 599)

Placebo + DRV/RTV-containing OBR* (n = 604)

*Investigator-selected OBR consisting of DRV/RTV (600/100 mg/mL BID) + ≥ 2 NRTIs ≥ ENF.


DUET-1 and -2: VL < 50 c/mL at Wk 48, Overall and by Active Agents in OBR
Mean changes in CD4+ cell count response at Week 48 significantly greater in etravirine arm: +98 cells/mm³ vs +73 cells/mm³ in placebo\(^{[1,2]}\)

VircoType assay clinical cutoffs for ETR susceptibility defined: lower clinical cutoff (1.6), upper clinical cutoff (27.6)\(^{[3]}\)

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**NNRTI: etravirine**
- most of the data available for etravirine is in experienced patients who have failed multiple regimens,
  - the drug is expected to be used in this population
  - probably in combination with a boosted PI and NRTIs with or without other newer agents (raltegravir, maraviroc or enfuvirtide)
  - use of etravirine as a second NNRTI regimen (with 2 NRTI) after failure of a first NNRTI + 2 NRTI regimen is currently not recommended

**New Class of ARV agents**

**HIV Entry Inhibitors**
- HIV enters the CD4 cell by first binding to the CD4 receptor
  - In order to enter the cell it has to bind to one or two receptors
    - CCR5 or CXCR4
- Two types of viruses
  - R5 viruses
    - Utilize only the CCR5 co-receptor
    - most frequently transmitted type found in 99% of newly infected patients
  - X4 viruses
    - Utilize the CXCR4 co-receptor
    - Emerge later in disease in up to 50% of patients
- CCR5 inhibitors

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Maraviroc
The first of the new class of ARV drugs approved by the FDA in August 2007
Inhibits interaction between chemokine receptor CCR5 and HIV-1 gp120
Approved for patients already experiencing virologic failure because of resistance to other ARV drugs

Vicriviroc
Still in development for treatment-experienced patients

Aplaviroc
Development stopped after significant hepatotoxicity became evident in animal studies

Maraviroc
- Activity against HIV-1 that is exclusively CCR5 tropic
  - Determination of tropism is necessary before initiation of therapy
  - Trofile assay is the most widely used assay for determination of tropism
- No cross-resistance with drugs from other classes
- Efficacy established in two concurrently run clinical trials
  - MOTIVATE 1 and MOTIVATE 2

MOTIVATE 1 and 2: MVC in Treatment-Experienced Patients With R5 Virus
Randomized, double-blind, placebo-controlled, phase IIb/III study

Patients infected with R5; HIV-1 RNA ≥ 5000 copies/mL; stable ART or no ART for ≥ 4 weeks; previous ART experience with ≥ 1 agent (≥ 2 for PIs) from 3 of the 4 antiretroviral drug classes for ≥ 6 months or documented resistance to members of 3 of 4 classes
(N = 1049)

2:2:1 randomization; stratified by ENF use and HIV-1 RNA < or ≥ 100,000 c/mL
Week 24 planned endpoint analysis

<table>
<thead>
<tr>
<th>Arm</th>
<th>MVC* 150 mg or 300 mg BID + OBR</th>
<th>Placebo + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n = 426)</td>
<td>(n = 209)</td>
</tr>
<tr>
<td>2</td>
<td>MVC* 150 mg or 300 mg QD + OBR</td>
<td></td>
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<tr>
<td>3</td>
<td>(n = 414)</td>
<td></td>
</tr>
</tbody>
</table>

*Patients receiving PI (except TPV) or delavirdine received 150 mg; all others received 300 mg.

### Combined Virologic Efficacy at Week 48

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Placebo + OBR (n = 209)</th>
<th>MVC QD + OBR (n = 414)</th>
<th>MVC BID + OBR (n = 426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.7%</td>
<td>45.5%*</td>
<td>43.2%*</td>
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<tr>
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<tr>
<td>48</td>
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</tbody>
</table>

*P < .0001 vs placebo

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**MOTIVATE 1 and 2: Maraviroc Safe and Well Tolerated at Week 48**

- No unexpected adverse events through Week 48
- Similar frequency of serious all-grade adverse events, toxicity-driven discontinuations, laboratory abnormalities, AIDS-defining infections, and AIDS- or non–AIDS-defining malignancies among MVC vs placebo arms at Week 48
- Most common adverse events across study arms: diarrhea, nausea, fatigue, headache
- Analysis of MVC resistance
  - gp120 V3 loop mutations important in conferring genotypic resistance to MVC in some patients who fail with R5 virus
    - Amino acid substitutions detected in stem and tip of V3 loop in MVC-treated pts
    - Clinical implications of mutations not fully understood

**Background on Enfuvirtide**

- First and only inhibitor of HIV-1 entry to be approved for clinical use
  - Member of subclass of fusion inhibitors
  - Active in treatment-experienced patients
- Synthetic peptide consisting of 36 amino acids
  - Administered twice daily by subcutaneous self-injection

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This is a common condition. Patients develop a fatty liver which may be indistinguishable from alcoholic fatty liver clinically and on biopsy. Problems in classification can obviously arise where people take alcohol as well. Patients are often middle aged and female; there is an association with diabetes, pre-diabetes, obesity and steroid therapy. Currently we understand NAFLD as being part of the spectrum of insulin resistance associated with the metabolic syndrome.

NAFLD covers the spectrum for steatosis alone (no inflammation on biopsy) to non-alcoholic steatohepatitis (NASH), where inflammation present on biopsy. NAFLD—and particularly NASH—may progress over many years to cirrhosis. Current treatment is directed at improving insulin resistance, with weight loss, exercise and control of diabetes, particularly with drugs such as metformin and the thiazolidinediones (e.g. pioglitazone) which improve insulin sensitivity. Other, secondary causes of fatty liver include steroid therapy, bariatric (weight-reduction) surgery, fasting, starvation and rapid weight loss. So-called microvesicular steatosis is a feature of the acute and potentially fatal conditions acute fatty liver of pregnancy, tetracycline toxicity, valproate toxicity and Reye’s syndrome.
ETHICAL ISSUES RAISED BY HIV / AIDS

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Introduction
- HIV presents a plethora of ethical challenges.
- This presentation will only focus on a select few.
- Chosen challenges represent various “levels” of concern: macro (e.g., global justice), meso (e.g., national policies) and micro.
- We will focus on the micro level.

Informed Consent
- Entrenched in National Health Act (Chapter 2, sections 7-9) and all ethics guidelines, including GCP and HPCSA guidelines.
- National Health Care Act: S7.2: “A health care provider must take all reasonable steps to obtain the user’s informed consent”
- Standards of disclosure are set by the test of reasonableness.
- Requirements of Informed Consent are:
  - Information
  - Understanding
  - Consent
  - Authorisation
- Proxy consent should be sought for HIV testing for incompetent patients. Such consent is typically presumed to best come from physicians (who know the clinical best interests of the patient) and/or family members (who know the values the patient adheres to).
- Involving family members in such discussions is desirable but may be fraught, and there are multiple reasons why their vested interests may mean their proxy consent is not in fact based on the patient’s values, but instead their own. It is impossible to determine their motivation.

Needlestick Injuries
- Needlestick injuries: globally, rate of HIV transmission is 0.3% per injury (Gerberding 1994; Ippolito et al. 1999). HBV transmission risk is 6-30% while HBC transmission is 0-7% (CDC).
- These risks sound low, but health care staff in SA face higher risks.
- One has to regard the context when making ethical decisions. If KZN, or SA’s risk is much higher, there is a justifiable beneficence-based reason for testing for this purpose.

Children and HIV
- Consent issues complex with children
- Testing infants is implicit testing of mother
• Children can independently consent to HIV tests from age of 14
• But there’s a statutory requirement for HCW to report underage sexual activity (<16yo)!
• HIV status may negatively affect treatment protocol for children (Fransman et al)

Confidentiality
• Confidentiality is a prima facie ethical principle for doctors.
• But, as a prima facie principle, it can be overridden!
• The Tarasoff case
• Careful balancing of costs and benefits, including concern around negligence.
• In negligence, the defendant is “held liable for a careless action or omission where that defendant had a duty toward the plaintiff and an injury was caused by negligence.” (EAE)

Micro-Allocation of Resources
• Similar to techniques used in economics, where costs and benefits are calculated (e.g., DALYs)
• Other contextual factors, e.g.: Aside from clinical criteria, ART roll-out requirements could be:
  ▪ Disclosing status to partner
  ▪ Having access to adequate nutrition
  ▪ History of keeping clinic appointments and finishing courses of medication
• Public health versus care for individual patient.

Reporting on Death Certificates
• In the interests of public health to accurately record cause of death on certificate.
• But may negatively affect surviving family (e.g. insurance).
• Improvements in the death certificate form should mean that there is not excuse for the ultimate cause of death to be recorded as HIV infection.

Cultural Ethics
• In Africa, cultural notions have an important impact on the following aspect of HIV:
  ▪ Illness
  ▪ Gender
  ▪ Children
  ▪ Consent
  ▪ Confidentiality
  ▪ Non-compliance
  ▪ Treatment sharing

Conclusion
• We have briefly examined some key “micro” concerns around HIV.
• While laws and ethics guidelines provide assistance in thinking these through, dilemmas can remain: when one has to choose between a number of unpalatable options.
• In the era of HIV, doctors require not just sound clinical knowledge, but the wisdom of Solomon.
Abstract:

Skin diseases in pigmented races pose serious diagnostic challenges because the descriptions of the skin rashes in most dermatological texts are based on Caucasian skins for example erythema which is defined as redness of the skin may not be so in a person of colour. This will be reviewed. Dermatosis and dyschromias that are of concern to the ethnic patient will be discussed.

Ethnic skin diseases
- Ethnic skin: non-Caucasian darker skin
- South African rainbow nation excluding Caucasians


Top Hair and Skin Concerns for Blacks
1. Uneven skin tone
2. Dry skin
3. Acne/ oily skin
4. Razor bumps
5. Dry hair
6. Dry scalp
7. Hair breakage
8. Unwanted hairs

The Twelve Most Common Dermatoses in Blacks
1. Acne vulgaris 27.7%
2. Eczema 20.3%
3. Pigmentary disorders 9.0%
4. Seborrhoeic dermatitis 6.5%
5. Alopeica 5.3%
6. Fungal infections 4.3%
7. Contact dermatitis 3.1%
8. Warts 2.4%
9. Pityriasis vesicolar 2.2%
10. Keloids 2.1%
11. Pityriasis rosea 2.0%
12. Urticaria 2.0%

**Spectrum of Asian Skin Diseases**
- Eczematous conditions
- Psoriasis
- Pigmentary changes
- Photodermatosis
- Skin cancers
- Macular and lichen Amyloidosis

**Common Skin Diseases in Blacks**
- Acne
- Eczema

**Acne in Black Skin**
- Most common disorder
- Clinical disease is mild
- Nodulocystic type is unusual
- Post inflammatory hyperpigmentation is a common sequela

**Acne in Blacks**
- Summary
  - Clinically non-inflamed lesions are very inflamed histologically and hyper reactive
  - Mild to moderate acne very easily results in scarring
  - Aggressive early treatment is necessary

**Eczema in Blacks**
- Follicular presentation
- Lichenification
- Hyperpigmentation
Common Skin Diseases in Blacks
- Pseudofolliculitis barbae
- Pigmentary disorders

Pseudofolliculitis Barbae
- Responsible for racial tensions in military and civilian life
- Clinical features
  - Papules
  - Pustules
  - Hyperpigmented macules

Pseudofolliculitis Barbae
- Therapeutic recommendations
  - Cessation of shaving
  - Trimming of the beard
  - Benzoyl peroxide washes
  - Topical antibiotics
  - Tretinoin with a topical steroid
  - Topical glycolic acid peel
  - Laser hair removal

Pigmentary disorders in ethnic skin patients
- Rank third in frequency of visits to the dermatologist
  - Post inflammatory hyper and hypopigmentation
  - Melasma
  - Vitiligo
Causes of post inflammatory hyperpigmentation

- Acne
- Eczema (atopic dermatitis)
- Allergic contact dermatitis
- Bullous diseases
- Drug eruptions

Fixed drug eruption

Lichen planus

Contact dermatitis
Psoriasis

Causes of post inflammatory hypopigmentation
- Eczema (atopic dermatitis)
- Seborrhoeic dermatitis
- Psoriasis

Melasma
- Aetiology
  - Genetic factors
  - UV and visible light
  - Pregnancy
  - Oral contraception

Treatment of Melasma
- Sunscreen
- Discontinuation of OCP’s
- Hydroquinone
- Tretinoin
- Azelaic acid
- Kojic acid
- Salicylic acid
- Trichloroacetic acid
- Licorice extract
- Kligmans' formula
Exogenous Ochronosis

Macular amyloidosis

Vitiligo in ethnic skin
- More obvious contrast
- Depigmentation is an alternative

Pityriasis alba
Pityriasis vesicolor

Discoid lupus erythematosus
- Form of chronic cutaneous lupus erythematosus
- Small percentage meet criteria for SLE
- Sunprotection, steroids and antimalarias first line of treatment

Discoid Lupus Erythematosus

Keloidal scarring

Treatment of Keloids
- Intraleisonal glucocorticoids
- Combined Cyrotherapy and intraleisonal triamcinolone
- Intraleisonal bleomycin
- Silicone cream and silicone gel sheet
- Onion oil extract
• Radiotherapy
• Laser surgery
• Surgical excision
  ▪ Local anaesthetic Must be mixed with triamcinolone
  ▪ Meticulous scar management
  ▪ Onion oil extract to be applied to scar after surgical wound has healed
  ▪ Intrallesional glucocorticoids post surgery
• Recurrence possible post surgery

Unusual Skin disease Occurring More Commonly in Blacks
• Sarcoidosis

Sarcoidosis
• Black skin
  ▪ The other great ‘mimicker’
  ▪ More severe than in whites
  ▪ Extensive
  ▪ Recalcitrant to treatment

Ethnic hair and scalp disorders
• Black hair: tightly coiled, helical or spiraled and elliptical/ flattened in X-section

Ethnic Hairstyles and Hair Grooming Practices
• Thermal straightening
• Chemical straightening
• Natural styles- afro braids, twists and locks
• Hair weaving and extensions
• Permanent waving
• Hair maintenance products

Ethnic hair and scalp disorders
• Seborrhoeic dermatitis
• Psoriasis
• Irritant and allergic contact dermatitis
• Acne keloidalis
• Dissecting cellulitis
• Folliculitis decalvans
• Traction alopecia
• Scarring alopecia
• Tinea capitis
• Cutaneous sarcoidosis
• Discoid lupus

Folliculitis decalvans

Dissecting cellulitis/ Acne keloidalis

Acne keloidalis: Treatment
• Topical antibiotics
• Oral antibiotics: tetracyclines
• Rifampicin
• Topical corticosteroids (high potency)
• Intralesional corticosteroids
• Cryotherapy

Traction alopecia
Treatment of Traction Alopecia

- Discontinue hair styles that put tension on the hair
- Avoid hair irritating chemicals
- Oral and topical antibiotics
- Topical and intralesional corticosteroids
- Topical minoxidil
- Camouflouge techniques

Tinea capitis

Dermatophyte infections of the nail: Tinea unguium

Skin cancer in Blacks

- Lower frequency than whites
- Higher mortality than whites
• Squamous cell carcinoma
• Cutaneous T Cell lymphomas
• Malignant melanoma

Skin Cancer in Blacks in the HIV Era
Kaposis sarcoma

Approach to AIDS associated Kaposi’s Sarcoma
• Evaluate for involvement of other systems particularly the GIT and respiratory tract
• Skin biopsy
• CD4 count
• ART irrespective of CD4 count levels
• Refer to oncologist

Lasers in ethnic skin

THE BIG ISSUE WITH LASERS IN ETHNIC SKIN

• Post inflammatory pigmentary changes which may be permanent and cosmetic disfiguring

Conditions in ethnic skin amenable to laser surgery
• Dyshcromias
  ▪ Post inflammatory hyperpigmentation
  ▪ Melasma
    ▪ 694 ruby laser
    ▪ 511-nm copper vapor laser
    ▪ 514-nm argon laser
    ▪ 755-nm alexandrite laser

Acne scarring
• Demabrasion less risky than laser resurfacing in ethnic skin patients
• Ablative lasers ie CO2 laser increased risk of complications
• Nonablative lasers ie Nd YAG1320-nm less complications, but clinical results are subtle and serial treatments are required
Hirsutism and hypertrichosis

- Long pulsed alexandrite laser safer in darker skin; able to destroy the hair follicle while protecting the epidermal melanin unit
- Selective photothermolysis

Lasers in ethnic skin

- Balance of effective treatment with minimal risk to the patient
- Conservative treatment parameters minimise untoward risk
- Expanded basic and clinical research and development of laser technologies to protect the epidermal melanin unit from damage will provide us with data and tools to improve outcomes

Dermatosis caused by cultural practices

- **BLACKS**
  - Pomade acne
  - Scarring from traditional marks
- **ASIANS**
  - Coin rubbing
  - Cupping
  - Moxibustion
  - Henna

- Eighty percent of the world population consists of individuals with pigmented skins
- Significant work remains to be performed in the area of ethnic skin disorders to properly manage dermatosis in the non-Caucasian population.