SUMMARY OF KEY POINTS OF THE WORKSHOP

A. Tuberculosis and OIs -Richard Murphy

1.Early inpatient ART initiation after OI

Henry Sunpath of McCord Hospital provided a review of inpatient initiation of ART in HIV-infected patients with opportunistic infection (OI). Hospitalized patients with advanced HIV disease and TB/OI have been shown under routine conditions to have low ART uptake and poor outcomes when discharged for outpatient ART. Inpatient ART may offer a new opportunity to engage very ill patients. What is the evidence base? (1) For TB, several studies show lower mortality if ART started within 2 weeks of TB diagnosis, particularly for patients with CD4 cell count <50 cells/mm3. (2) For other OIs, early ART initiated in hospital within 14 days of OI diagnosis reduced progression of disease or death (ACTG 5164), (3) Local studies show that this can be operationalized in SA using an Early ART Care Team[1]

References

1. Sunpath H *et al.* Int J Tuberc Lung Dis. 2012 Jul;16(7):917-23.

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2. Update on smear-negative TB in HIV-infected patients

Yunus Moosa of UKZN provided an update that on smear-negative tuberculosis in HIV-infected patients. For such patients who have danger signs (RR>30, pulse>120, unable to walk), rapid referral to a higher level of care is critical. For these patients, early empirical TB therapy – if no response to broad spectrum antibiotics by 3-4 days – can be lifesaving. Moosa recommends avoiding fluoroquinolones in TB suspects. For the diagnosis of TB generally, the cardinal symptoms remain relevant in HIV-infected: >2 weeks of cough, nightsweats, or fever. Weight loss in HIV-infected patients is still TB until proven otherwise. An HIV test is essential in all TB suspects. Chest x-ray is of limited use, many abnormal findings are consistent with TB. It is best considered a tool to rule-in TB in the presence of many types of abnormalities in the HIV-infected patient including lymphadenopathy, infiltrate, innumerable "military" nodules or pleural disease. It is less useful in ruling-out TB. He urged clinicians: Don't be afraid to overtreat TB, at least initially. But if TB treatment is started empirically (without AFB, molecular evidence such as GeneXpert or culture), careful patient follow-up is key: (1) At 8 weeks check for improvement: Weight gain, improved hemoglobin, 50% symptom improvement and – if available – reduction in CRP. If not, possible causes include IRIS TB, drug-resistant TB (especially if adherence has been good), alternative infectious disease (e.g. disseminated histoplasmosis), malignancy (e.g. pulmonary KS) or, less commonly, a connective tissue disease.

3. Update on TB transmission

A Willum Sturm of the Department of Health noted that our current efforts to reduce TB transmission are not working well. None of facilities in KZN recently audited did well. In his opinion, an overcrowed OPD is the most dangerous place for TB transmission. Moreover, a considerable amount of TB is also transmitted in hard to control places like taxis, markets. Unfortunately drug-resistant TB strains in KZN are fit strains, not impaired strains. What new strategies might reduce transmission? Sturm recommends active early TB case finding and earlier ARV treatment are potentially key strategies. But Sturm believes the use of isoniazid preventative therapy (IPT) in KZN is ill-advised because of the potential effect of IPT on drug resistance. The baseline prevalence of INH resistance in KZN is 26%. If IPT is roll-out in KZN, he predicts this rate will rise to 40%.

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4. TB control

Jacques Grosset of K-RITH noted that standard 1st line TB therapy is 95% effective but it has long been observed that patients who do not complete therapy will have a high failure rate and some will develop drug resistance. He notes that what we see today is that – in the absence of real directly observed therapy (DOT) with observed pill-taking – in countries such as SA, 1st-line TB therapy performs poorly and results in a growing pool of drug-resistant cases. He estimates that SA current treatment success rates 63-79% and SA defaulter rate 10-20%. MDR-TB is even harder to treat effectively. He commented that if we are unable to cure 'easy to cure' cases, we won't be able to cure difficult to cure cases. Therefore he urges that we focus most of our resources on assuring treatment success in drug-sensitive cases to improve the current crisis.

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5. Cryptococcal meningitis

Tariro Amakadzange of Zimbabwe described the current landscape of cryptococcal meningitis (CM) diagnosis and treatment. In terms of diagnosis CSF cryptococcal latex-agglutination test remains the most critical took but that the introduction of the lateral flow assay may allow for a cheap and effective point-of-care diagnostic. For treatment, preference is for amphotericin-based regimens. In settings where amphotericin plus flucytosine is not available, amphotericin plus fluconazole is a reasonable alternative. During amphotericin-based treatment, electrolyte monitoring is recommended. It is critical that maintenance fluconazole is continued at least until CD4 count > 200 cells/mm3 and viral load is undetectable. Unlike other OIs, early ART initiation for CM is associated with early mortality. Dr Amakadzange thinks it is reasonable to initiate ART at 3 - 4 weeks after initiation of antifungal therapy. Prevention is important. Screening of patients with CD4<100 cells/mm3 for presence of positive serum cryptococcal latex-agglutination test is recommended and can predict those who will go on to meningitis. Fluconazole monotherapy may be used in patients with positive CSF cryptococcal antigen who do not have CNS symptoms. Those with CNS symptoms need LP +/- amphotericin-based treatment as LP dictates.

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6. Palliative care

Liz Gwyther from Cape Town notes that palliative care has been too long ignored in HIV-infected patients in SA. Why is palliative care essential in HIV medicine? There is a very high symptom burden including fatigue, diarrhea, pain, anxiety, depression. Palliative care is not inconsistent with ongoing antiretroviral treatment but recognizes that the needs in HIV-infected patients are broader than ARVs. A patient appropriate for palliative care evaluation include one whom the clinician "would not be surprised" to see die in 6-12 months as well as patients who make gestures suggesting that no longer are seeking curative treatment. Gwyther notes that we apply ourselves to improving ARV coverage but fail to apply same energy to address the disabling symptoms of HIV. She notes that addressing palliative care may help with the Achilles heal of our ARV programs: loss to follow-up and treatment fatigue. For Gwyther, palliative care advocacy means speaking on behalf of patients who have limited voice to advocate for themselves to other providers, to hospitals and to government.

7. Isoniazid preventative therapy in HIV-infected patients

Nesri Padayatchi of CAPRISA noteed that isoniazid preventative therapy (IPT) is one of the few potential preventative tools that exist in South Africa, where TB mortality remains extremely high. She notes that compared with no IPT and no ART, a package of IPT plus ART provides 80% protection against TB. IPT must be targeted at patients with positive tuberculin skin testing (TST) testing and accompanied by initial and monthly screening for active TB. In a large Botswana study, IPT provided benefit for TST (+) patients but less so for TST (-) patients. The longer the IPT provided, the longer the protection. She notes that there is no consistent association between IPT and increased population isoniazid resistance.

B . ART outcomes –Vince Marconi

1. Issues in Second Line ART (Murphy)

Dr. Richard Murphy discussed issues related to use of second-line antiretroviral therapy (ART) in resource-limited settings. This regimen consists of two nucleosides plus lopinavir/ritonavir (LPV/r). Several studies have shown that LPV/r was effective after virologic failure (VF) of first-line ART containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) with or without HIV drug resistance. The choice of NRTI did not appear to affect second-line virologic response when LPV/r was used. According to a report from Durban, adherence on LPV/r improves over time after a switch to LPV/r for VF and is predicted by first-line ART adherence. For individuals experiencing VF on LPV/r, several studies have shown that the emergence of protease inhibitor (PI) mutations are relatively rare and triple-class drug resistance is uncommon. When LPV/r is prescribed concomitant with tuberculosis therapy containing rifampicin, the LPV/r dose should be increased to ultimately four tabs twice daily. Raltegravir may be a potential future option as studies to date have not found significant changes in drug concentrations. Boosted atazanavir is the most lipid and glucose friendly PI, followed by boosted darunavir and then LPV/r. Finally, Dr. Murphy reviewed the efficacy of statins in this setting commenting that rosuvastatin had the greatest impact in LDL, followed by atorvastatin and pravastatin at a distant third. Data are still emerging regarding drug-drug interactions between rosuvastatin and ART.

2. HIV Prevention (Abdool Karim)

The latest information on various prevention strategies were reviewed by Dr. Quarraisha Abdool-Karim, the principal investigator of the CAPRISA study. The field has experienced a resurgence in approaches to prevention since July 2010. Prior to this period, the main options consisted of male circumcision, condoms, sexually transmitted infection treatment, counselling and testing along with other behavioural interventions. Since that time, multiple studies have shown the efficacy of biomedical approaches including oral pre-exposure prophylaxis (followed by the recent U.S. FDA-approval of TDF/FTC for PrEP), microbicides, treatment as prevention (TasP) which was highly efficacious (demonstrating a 96% reduction in transmission), and a modestly efficacious vaccine. The current challenges in PrEP and TasP are improving adherence and safety, minimizing resistance and the concern for condom displacement and finally identifying ways to reduce the cost and added burden onto the healthcare system. Moving forward, the remaining questions surround determining the most efficacious and safe combinations, dosing frequency, impact of resistance and rollout feasibility. Dr. Abdool-Karim made an appeal to the delegates for support of programs that prevent transmission in men who have sex with men, adolescents, injection drug users and mitigate the impact of stigma and discrimination.

3. PMTCT (Reddy)

Dr. Jennifer Reddy from the CDC brought the audience up to date on efforts to prevent mother to child transmission (PMTCT) of HIV. Tremendous progress has been made on this front in KZN thanks to the Department of Health leadership, evidence-based guidelines, partnership and coordination (especially with community involvement) and health system strengthening. However, there are key implementation issues that remain in terms of improving access for patients and programmatic delivery. Currently there is a gap between the trial efficacy evidence and any demonstrable studies examining implementation effectiveness (knowledge versus action as she described). The current needs for PMTCT are structural (building infrastructure, equipment, medications), technical (training and enhancing the knowledge base), functional systems and aiming for greater patient-centered care. She pointed to the importance of utilizing quality and process improvement methodologies to assess your program's current success and provided several key dashboard indicators to assist in this process.

4. Evaluating Adverse Reactions in RLS (Manickum)

Dr. Viloshni Manickum provided a summary of the Pharmacovigilence data on adverse drug reactions reporting. Spontaneous reporting which is unsolicited communication by health care professionals has had several limitations including suboptimal awareness of the process, inadequate training, time consuming, the causality is often unknown, there is poor reporting of death/pregnancy, the form is not conducive to complete reporting, and the denominators are not known. Solicited reporting, which is mandatory reporting required to be completed whenever a provider needs to change an ART regimen has been more highly accessed. Peripheral neuropathy and gynecomastia were reported more frequently in males whereas lactic acidosis, lipodystrophy and multiple drug reactions were more commonly reported in females. Interestingly, young patients (ages 0-19.99 years old) were more likely to have lipodystrophy reported. EFV was more often associated with dermatological or CNS events, ZDV with

hematological events, d4T with pancreatitis, steatosis, lipodystrophy, lactic acidosis, peripheral neuropathy, and multiple reactions. Nearly 857% of reported patients were on d4T+3TC+NNRTI and 93% were on d4T. Comorbidities, concomitant meds, laboratory and outcome fields were frequently not completed.

5. Adherence and Retention in Care (del Rio)

Dr. Carlos del Rio from Atlanta gave the day 2 plenary talk on adherence and retention in care. He emphasized that "It is not enough to test and treat, we need to link and retain patients in care" The term "clinic adherence" was used to describe this indicator. Some of the major manifestations of poor clinic adherence were delays in testing, delays in care, and early drop out. The major consequences of starting late include more frequent hospitalization, higher rates of VF, mortality, and drug-drug interactions, more common reports of IRIS, and a greater cost of treatment and care. Dr. del Rio provided some caution to be cognizant of vulnerable groups in your setting, the complexity of a patient's life, and your system capacity to manage the patients in your clinic. Empowerment, self-efficacy and stigma were primary drivers of the individual's ability to remain in care. Key structural barriers that can be intervened upon included food, transportation, and housing. It is also crucial to integrate ART provision with substance abuse and psychiatric treatment. At an institutional level, programs should seek to improve trust, communication, and wait times. He mentioned several ways to improve adherence especially long term such as pill boxes, social capital and regular monitoring with at least self-report measures.

6. ART Resistance Workshop (Marconi)

Dr. Marconi discussed a case of VF on a first-line regimen and reviewed the fundamental aspects of ARV drug resistance. This included the clinical and molecular factors that drive drug resistance. There was also a review of surveillance data on transmitted (TDR) and acquired drug resistance (ADR) within resource limited settings. This data showed that TDR is low (<5%) but growing in many parts of sub-Saharan Africa. ADR is between 60 and 90% after VF. Although ADR requires a change in regimen, most patients do well on second-line therapy containing LPV/r. Patients experiencing VF without resistance have worse outcomes in part related to their poor retention in care and adherence to ART. Single NRTI switches for toxicity are appropriate for patients who are virologically suppressed but if failing at least two active ARVs should be used in the new regimen. Use of a holding regimen can be employed while waiting for third line agents as ART is better than no ART. Early warning indicators are key to evaluating the probability of seeing unacceptable rates of VF and drug resistance in your program and Interventions to improve adherence and retention are paramount to ensuring high rates of virologic suppression. VF should be treated as an emergency in your clinic.

7. NIMART (Fredlund/Mfeka)

Dr Victor Fredlund and Gloria Mfeka provided an overview of nurse initiated and monitored ART (NIMART). It is clear that universal access to ART has not yet been reached. It was expressed that while serving many

individuals, we have failed the community at large. Doctors must consider the tremendous personnel shortage an emergency. Therefore, Task Shifting (or Sharing) with Nurses could be effectively accomplished by stratifying patients based upon CD4 count and opportunistic infections. The rationale being that there are more nurses available every day and that these nurses stay longer during the day. They also have institutional knowledge and continuity over longer periods of time in the clinic. Some of the challenges include a large training investment, a shortage of primary health clinic nurses, and the concern of diverting nurses away from other important duties. There are also risks involved to this approach such as doctors abandoning all ART to nurses, developing more vertical (not integrated) care, and a potential for declining standards of care.

8. HIV in the Aging Population (Venter)

Dr. Francois Venter gave a very entertaining lecture on the implications of an aging HIV population. He described the impact of HIV on the aging process whereby inflammation associated with HIV disease can accelerate organ and cellular degeneration. This includes bone density, lungs, the cardiovascular and immune system, kidneys, and the brain. Older patients are also at increased risk of cancer coupled with an independent cancer risk from HIV makes screening more complicated and challenging. Similarly, older patients have more complex drug metabolism due to changes in liver enzymes and body fat, natural declines in the immune system and challenges associated with mobility (vision and hearing loss, frailty, and a decline in cardiovascular endurance) and finances. He said that it is important to use medical common sense. His final key messages were to emphasize with patients to stay active, eat better, maintain social contact, reduce stress, stop smoking, and control their blood pressure and glucose.

C. Specialist care and public health- Nigel Garrett

1. Management of abnormal liver function tests in HIV positive patients

Managing HIV-positive patients with abnormal liver function tests can be a real clinical challenge, especially in a setting with high TB prevalence. **Raj Gandhi** from Harvard University and Co-Chair of the Conference reminded the audience that 4% of patients prior to starting ART and up to 20% on ART will experience abnormal liver function tests. He used three interactive case studies to dispel some of the anxieties doctors and nurses may have when managing these patients by presenting a stepwise approach from taking a medication and alcohol history to ordering further investigations including an ultrasound scan and liver biopsy. He suggested considering three areas in the differential diagnosis: i) drug-induced hepatitis especially in the context of co-infection with Tuberculosis or hepatitis B infection; ii) viral or bacterial super-infection such as herpes simplex virus and syphilis, and iii) immune reconstitution inflammatory syndrome. He quoted **Hy's Law**: *drug-induced hepatic injury accompanied by jaundice has a high mortality'* to detect patients at particular risk and stressed the importance of clinical vigilance by referring to his own case series of Atazanavir-induced gallstones. www.livertox.nih.gov is a useful reference tool to check for drug-interactions.

2. Breakout Session: Paediatrics and Adolescent Care

The latest UNICEF report states that significant improvements have been made in reducing under-5 mortality rates across the world, but that an additional effort is required to achieve further reductions, especially in infant mortality.

Dr Mo Archary re-examined the CHER study, which showed a large reduction in infant mortality if ART was started within the first year of life compared to after year 1. He argued that this effect was already apparent when comparing 7 versus 16 week data and that therefore HIV PCR at 6 weeks should be mandatory. New guidance released recently supports introducing a PCR at birth in all infants with symptoms suggestive of HIV. However, the KZN experience illustrates that testing alone is not sufficient when only half of infants who tested positive (1518/ 3007) actually received treatment last year. Better linkage to care is vital and health professionals and laboratory staff have to realize that a positive PCR should be considered as a medical emergency and should trigger immediate case finding.

Ms Alice Armstrong and **Dr Brian Zanoni** provided a passionate argument for the introduction of specialist clinics for adolescents living with HIV. An estimated two million adolescents are currently infected with HIV and treatment programmes have shown particularly poor outcomes in this age group. The speakers stressed the importance of holistic care to improve adherence and retention in care. Good communication requires the clinician to respect and engage in conversation with the teenager, to guarantee confidentiality and to address disclosure at an early stage of care. Furthermore, the HEADSSS screening tool can be used to identify barriers for good adherence. The speakers Specialist Teen Clinic achieved commendable outcomes with 94% of adolescents on first-line therapy and 95% virologically suppressed after a median of 3 years of follow-up.

3. Challenges of expanding ART access in SA

The response to the HIV epidemic in South Africa faces further challenges. With more than 5 million individuals infected in the country, but only 1 million on treatment so far, much more has to be done. In KZN, in particular, the HIV incidence remains at 2.3%, the highest in the country. **Professor Umesh Lalloo** reminded everyone that expanding ART access was imperative and that this task could only be achieved by addressing key areas. Firstly, South Africa could learn from the successful model of Malawi where task-'sharing' empowered nurses and lay counsellors to initiate ART. A spontaneous applause from the audience erupted when Prof Lalloo urged the educational system to ensure that every SA nursing or medical graduate should be able to initiate ART and that red-tape should be cut by authorities to allow all clinics to provide ART. Secondly, one would have to combat the chronic health care worker shortage and focus on retaining an effective workforce especially in rural settings. This workforce could be supported by establishing academic learning centres at rural sites which could link in and benefit from expertise in urban centres. Priorities to expand access to ART should also include prevention of drug stock-outs, addressing causes of non-adherence, preparing a budget plan to include consideration of increased costs of second and third line ART and preparation for the next challenges, especially the increased burden of non-communicable diseases.

4. Rheumatology and chronic inflammation in HIV

Dr. Ajesh Maharaj gave a fascinating overview of rheumatological disease in the context of HIV infection. HIV with ART has become a chronic condition and rheumatological conditions can present at all stages of the disease.

He highlighted the paradox of seeing an increase in autoimmune, inflammatory conditions in immune-compromised individuals. The main reason for this is an increase in cytokine release and loss of protection from autoimmunity by CD4 cells. The list of rheumatological conditions is long and most present more commonly in HIV infected patients. Specifically, Prof Maharaj reported on an increased prevalence of spondyloarthropathies despite a low prevalence of HLA B27 in the population, psoriatic arthritis and reactive arthritis. This finding gives supporting evidence that HIV itself is driving the pathogenesis. Moreover, some conditions can worsen during immune reconstitution including rheumatoid arthritis, SLE and sarcoidosis, and often there is muscle involvement, predominantly affecting the proximal muscles. He also reminded the audience of the increased incidence of lymphoma in this population. Managing HIV positive patients with rheumatological conditions can be a challenge, but a simple assessment including a detailed history and basic investigations can prompt the need for specialist referral. It is important to note that most patients do well on ART alone. In general, indomethacin and short term prednisolone are safe options, while immunosuppressive therapy should not be started without ART and disease-modifying agents should ideally be commenced at higher CD4 counts.

5. Starting and Sequencing ART in resource limited settings

When to start ART has been a much debated topic. **Dr N Kumaraswamy** gave an overview of the evidence for starting therapy at CD4 counts higher than 350. The HPTN 052 study reported a 96% reduction in transmission in serodiscordant couples. Additionally, the study found a 50% reduction in TB cases which contributed to the cost-effectiveness of the strategy. While the NA ACCORD study has shown a reduction of non-AIDS complications in the US, further evidence is expected soon from the START study which randomized participants into early (CD4 >500) versus a delayed (CD4 <350) therapy start . Dr Kumaraswamy then summarized the evidence for the current WHO guidelines of starting first-line ART with two NRTIs and a NNRTI. There is also good evidence that a protease inhibitor or an integrase inhibitor can be used in conjunction with the NRTI backbone. He specifically highlighted the PEARLS study which showed that ACT/3TC/EFV and TDF/FTC/EVF had similar viral load outcomes, but that they differed in safety endpoints especially among women. AZT use as first-line was also associated with an increase of resistance including K65R mutations in up to 26% of participants in Malawi, therefore potentially affecting the effectiveness of second-line therapy. According to Dr Kumaraswamy boosted Atazanavir and Darunavir will be available as generic drugs in the near future. Darunavir in particular should be reserved for early intervention during second-line failure. Studies like SELECT and EARNEST will provide further evidence on choices for second-line therapy including NRTI sparing options.