Appendices

Contents

Appendix 1: Summary modified GRADE system

Appendix 2: Literature search
- 2.2: Questions and PICO criteria
- 2.2: Search protocols

Appendix 3: GRADE tables
- 3.1 Choice of NRTI backbone
- 3.2 Choice of third agent
- 3.3 PI monotherapy

Appendix 1

Summary of the modified GRADE system

BHIVA revised and updated the association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

1A Strong recommendation. High-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.
1B Strong recommendation. Moderate-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa Evidence from randomised, controlled trials with important limitations (inconsistent

results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk. Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C Strong recommendation. Low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain. Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
1D Strong recommendation. Very low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence limited to case studies. Strong recommendation based mainly on case studies and expert judgment.

2A Weak recommendation. High-quality evidence. Benefits closely balanced with risks and burdens Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Weak recommendation, best action may differ depending on circumstances or patients‟ or societal values.
2B Weak recommendation. Moderate-quality evidence. Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. Evidence from randomised, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk. Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.

2C Weak recommendation. Low-quality evidence. Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain. Weak recommendation; other alternatives may be reasonable.
2D Weak recommendation. Very low-quality evidence. Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. Evidence limited to case studies and expert judgment. Very weak recommendation; other alternatives may be equally reasonable.

References

1. BHIVA Guideline Development Manual, 13th September 2011. www.bhiva.org
2. Guyatt GH, Oxman AD, Kunz R et al. Going from evidence to recommendations. BMJ 2008; 336: 1049–1051.
3. The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group. www.gradeworkinggroup.org

Appendix 2

Systematic literature search

2.1 Questions and PICO criteria

Data bases: Medline, Embase, Cochrane Library,

Conference Abstracts:

- IAS Conference on HIV pathogenesis and treatment
- International AIDS conference
- Conference on retroviruses and opportunistic infections
- European conference on clinical aspects and treatment of HIV infection
- Interscience conference on antimicrobial agents and chemotherapy

- International congress on drug therapy in HIV infection
- British HIV Association annual conference

Date parameters:
- data bases: 2008 –September 2011
- conference abstracts: 2009-September 2011

When to start:

Study design: Systematic reviews (SRs), randomised control trials (RCTs), Observational, risk, economic

Chronic HIV Infection:
Population: HIV infected naïve to Antiretroviral(ART) therapy
Intervention: starting ART early: i) at CD4 count >350 cells/µL, ii) at CD4 count >500 cells/µL, iii) immediate at time of diagnosis
Comparator: Starting ART CD4 count <350 cells/µL
Outcomes: Death, AIDS, non-AIDS co-morbidities, drug adverse events, drug resistance, HIV transmission/incidence

Questions:
1. Is there improved or greater long term clinical benefit starting patients with chronic HIV infection earlier at CD4 counts >350 cells/µL compared to starting when CD4 count is 350 cells/µL or lower?

2. Does early ART prevent Non AIDS co-morbidities (cirrhosis, end stage renal failure, myocardial infarction, cardiovascular disease, cancer, all cause mortality)?

3. What is the cost (financial, toxicity, resistance) vs. benefit (decreased AIDS, death, non-AIDS endpoints and transmission) of early vs. later ART?

Primary HIV infection:
Population: Acute/primary HIV infection
Intervention: immediate ART therapy (short course or continued)
Comparator: no therapy, starting ART as per chronic infection
Outcomes: time to CD4 count <350cells/µL, death, AIDS, HIV transmission/incidence

Question
4. Is there benefit in starting patients diagnosed with primary/acute HIV infection immediately on ART compared to waiting till CD4 count <350 or <500 cells/µL? What is the magnitude of this benefit?

Advanced HIV disease
Population: HIV infection, advanced disease,
Intervention: immediate ART
Comparator: deferred ART
Outcomes: Death, new AIDS diagnosis, immune reconstitution disorders.

Question
5.Should patients presenting with severe AIDS defining opportunistic infections start ART immediately, or defer until after treatment of OI?

.
ART to prevent transmission
Population: HIV infected with HIV negative partner, sero-discordance
Intervention: Immediate ART
Comparator: starting ART at CD4 count <350 cells/µL
Outcome: HIV transmission to negative partner

Question
6. What is the cost (financial, toxicity, resistance) vs. benefit (reduced AIDS, death, non-AIDS endpoints and reduced transmission) of starting treatment earlier [similar question to 3 above]

What to start with

Study design: SRs, RCTs,

Preferred regimen/ choice of third agent
Population: HIV infected naïve to ART and i) VL >100,000, ii) VL <100,000 copies/ml
Intervention: Darunavir or Atazanavir or Raltegravir, Maraviroc, Etravirine or Rilpivirine containing combination ART
Comparator: Efavirenz containing combination ART
Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question
7.How does each third drug compare to efavirenz in terms of efficacy and safety?

Preferred regimen/Choice of NRTI backbone
Population: HIV infected naïve to ART
Intervention: Abacavir/lamivudine containing combination ART
Comparator: Tenofovir/Emtricitabine containing combination ART

Outcomes: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question
8. What are the advantages and disadvantages of using tenofovir/emtricitabine (Truvada) vs. abacavir/lamivudine (Kivexa)?

Novel treatment strategies
Population: HIV infected naïve to ART
Intervention: i) PI mono-therapy ii) NRTI sparing and PI based dual regimens (Raltegravir + either Darunavir/r or Atazanavir/r or Kaletra; Maraviroc + either Draunavir/r or Atazanavir/r)
Comparator: standard triple combination ART
Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question
9. What are the advantages and disadvantages of each of these strategies compared to standard triple combination ART?

Supporting patients on ART

Switching Therapy (simplification)

Study design: SRs, RCTs
Population: Antiretroviral therapy experienced, treatment experienced, virologicaly suppressed, viral load <50 copies/ml
Intervention: protease inhibitor monotherapy, switch third agent, switch NRTI backbone
Comparator; continuing current therapy
Outcome; virological suppression, virological failure, discontinuing regimen, grade3/4 AEs, HIV drug resistance

Questions
10. What are the benefits and disadvantages of simplifying from conventional ART to protease inhibitor monotherapy?

11. In patients on conventional ART (2 NRTIs + EFV or boosted PI), what are the relative advantages and disadvantages of switching to alternative third agents or NRTI backbone (e.g PI/r→ NNRTI, Integrase inhibitor, ; NNRTI → PI/r)?

Stopping therapy

Study design: SRs, RCTs, observational

Population: Antiretroviral therapy experienced, treatment experienced
Intervention: Stopping ART, treatment/ART interruption
Comparator: continuing ART
Outcome: HIV drug resistance, PK parametres

Question
12. Which is the least harmful (risk of resistance and/or failure to re-suppress on re-starting ART) way to stop treatment containing an NNRTI (simultaneous/staggered or switched stopping)?

Managing Virological failure

Low level viraemia and recurrent viral load blips

Virological failure with treatment options

Virological failure with limited treatment options

Study designs: SRs, RCTs, observational
Population: ART experienced, virological failure, dual and triple class HIV drug resistance, viral load blips
Intervention: switching ART, continuing lamivudine(3TC) or Emtricitabine (FTC), salvage therapy, etravirine, Raltegravir, maraviroc, tipranavir, Darunavir
Outcomes: virological suppression, virological failure, discontinuing regimen secondary to AEs, Grade3/4 AEs, CD4 count, HIV drug resistance

Questions
13. What is the risk of virological failure with resistance in patients with recurrent (2 or more) viral load blips above different thresholds?

14. Should FTC/3TC be included in second-line regimens in patients who had developed M184V at time of virological failure of first-line therapy?

15. What is the best management of patients with virological resistance to 2/3 drug classes – how many fully/partially active drugs are necessary for full efficacy of the optimal treatment regimen?

ART in special populations

Study design: SRs, RCTs, observational

HIV associated neurocognitive disorders
Population: HIV associated neurocognitive impairment/disorders, HIV associated dementia
Intervention: Antiretroviral therapy (list all ART drugs)
Outcomes: progressive HIV neurocognitive disorders.

Question
16: Does the choice of specific drugs or regimens with high CSF penetration lead to improved neurocognitive outcomes in any specific circumstances?

Non-AIDS co-morbidities: chronic kidney disease, cardiovascular disease
Population: chronic kidney disease, estimated Glomerular filtration rate <60 mls/min/1.73sqm, cardiovascular disease, myocardial infection
Intervention: ART, Tenofovir, Abacavir, protease inhibitors (Lopinavir/r, Darunavir/r, Atazanavir/r)
Outcomes: progressive CKD, Kidney disease clinical events, CVD clinical events

Question
17. Are there patients with evidence of renal or cardiovascular disease in whom treatment with tenofovir, abacavir or PI/rs respectively should be avoided?

2.2 Search protocols (main databases search)

Search 1: When to Initiate ART

Questions 1-6

Component	Description
Review area	**Timing of ART initiation**
Objectives	To assess the benefits and risks of earlier rather than later initiation of ART
Populations	Chronic HIV Infection, Primary HIV infection, Advanced HIV disease, HIV infected with HIV negative partner
Interventions	Antiretroviral therapy (all drugs)
Comparisons/ aspects covered by search	Initiation : at diagnosis: at CD4 count >350 cells/µL: at CD4 count >500 cells/µL
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational studies, risk, economic
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + early/later starting See attached Medline strategy document for details: searched 15/9/11
Search results	Medline= 529 Embase= 595 Cochrane = 108 Total deduplicated/sifted = 525
Key papers	SMART study J Infect Dis 2008,197:1133-1144; Sterne JA et al Lancet 2009,373:1352-1363; HIVCAUSAL Collab Annals of internal medicine 2011, 154(8:)509-151; Fidler, S (conf Ab); Grant PM Plosone 2010 Jul1, 5(7) e11416 ; Cohen M S New Engl Jnl 2011, 365(6): 493-505

Search 2: ART first line regimens

Questions 7-9

Component	**Description**
Review area	**Preferred initial ART regimens**
Objectives	Safety and efficacy of various different first line regimens in ART naïve patients
Populations	HIV infected, naïve to ART Adults – all questions
Interventions	Q7: third agents rilpivirine darunavir, atazanavir, raltegravir, maraviroc, etravirine, nevrapine, lopinavir/r Q8: Kivexa (abacavir/ lamivudine) Q9: PI monotherapy or NRTI sparing regimens (raltegravir, darunavir, atazanavir ,lopinavir/r, maraviroc)
Comparisons/ aspects covered by search	Q7: third agent efavirenz Q8: Truvada (tenofovir/ emtricitabine) Q9: conventional triple combination HAART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs,
Exclusions	Animal studies, letters, editorials, comments, case reports Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS (selected terms) + naïve/ first line See attached strategy document for details: searched 15/9/2011
Search results	Medline=460 Embase= 510 Cochrane = 259 Total deduplicated/sifted = 556
Key papers	McComsey et al Clin Infect Dis 2011; 53 (2):185-96, Daar,ES Ann Inter med 2011;154(7):445-56, Lennox, JL JAIDS 2010; 55(1): 39-48, Taiwo,B AIDS epub Aug 2011 (not yet on Medline or Embase), Ghosn, J HIV Med 2010; 11(2:) 137-42

Search 3 : Switching/ simplification of ART regimens and /or stopping therapy

Questions 10-12

Component	**Description**
Review area	**ART simplification/ switching/ stopping options**
Objectives	Safety and efficacy of switching drug therapy, simplifying drug regimens or stopping ART therapy
Populations	HIV infected on ART Adults – all questions
Interventions	Q10: PI monotherapy Q11: alternative third agents, NRTI backbone Q12: treatment cessation
Comparisons/ aspects covered by search	Standard combination triple ART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + switching/ simplification/ treatment cessation See attached strategy document for details : searched 16/9/11
Search results	Medline= 375 Embase= 465 Cochrane = 168 Total deduplicated/sifted = 489
Key papers	MONET trial J Antimicrob Therap; 2011 66(8) :1878-85, Katlama C AIDS 2010 24(15:) 2365-74 , Waters L AIDS2011 25(1): 65-71, Squires KE AIDS 2010 24(13:) 2019-27, Martinez E JAIDS 2009 51 (3) :290-7

Search 4: Virological failure

Questions 13-15

Component	Description
Review area	**Managing Virological failure/drug resistance**
Objectives	Risk of and management of patient with virological failure/ resistance
Populations	HIV infected on ART with or at risk of virological failure/ resistance Adults – all questions
Interventions	resistance or virological risk stratification Alternative ARVs/ strategies
Comparisons/ aspects covered by search	Standard combination triple ART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + resistance/ virological (treatment) failure See attached strategy document for details: searched 16/9/11
Search results	Medline= 831 Embase= 855 Cochrane = 206 Total deduplicated/sifted = 1104
Key papers	OPTIMA PlosOne2011 6(3):e14764 , Katlama C Antivir Ther 2010 15(7): 1045-52, Garcia-Gasco P J antmicrob Chemo 2008 61 (3): 699-704

Search 6 : ART in HIV patients with CKD and / or CVD

Questions 17

Component	**Description**
Review area	**ART use in HIV patients with CKD and / or CVD**
Objectives	To establish whether PIs, tenofovir and abacavir should be avoided in patients with CKD/CVD
Populations	HIV infected on ART Adults – all questions
Interventions	Tenofovir, abacavir, lopinavir/r, darunavir/r, atazanavir/r, NNRTIs, maraviroc
Comparisons/ aspects covered by search	Risk of each/ all drugs
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + CVD/Renal See attached strategy document for details: date searched 16/9/11
Search results	Medline= 188 Embase= 397 Cochrane = 26 Total deduplicated/sifted = 432
Key papers	Cruciani M AIDS 2011 epub (not yet on databases), Choi AI AIDS 2011 25 (10) :1289-98, Lang S Arch inter med 2010 170(14):1228-38, Worm SW J infect Dis 2010 201(3:) 318-30, Mocroft A AIDS 2010 24(11) :1667-78