

BHIVA Clinical Audit

Management of patients who switch therapy;
re-audit of patients starting therapy from naïve

2004-5 audit projects

Reporting now:

- Survey and case note review of patients switching therapy for the first time
- Re-audit of patients starting therapy from naïve – previous audit autumn 2002.

Reported at spring conference 2005:

- Survey of management of HIV/TB co-infection.

Audit of switching therapy

134 centres responded, with data on 504 patients.

Of these centres:

- 100 (75%) rely on BHIVA guidelines on ART
- 28 (21%) have local guidelines in addition to BHIVA
- 6 (4%) did not answer.

Assessment of adherence

40 (30%) of 134 centres considered that the guidelines they used explicitly addressed support for adherence.

- 109 (81%) assess adherence at every visit for patients on ART
- 22 (16%) assess routinely but not at every visit
- 3 (2%) assess only if difficulties are suspected.

Indicates recognition of importance of assessing adherence. No information as to how this is done in practice.

Management of viral load rebound after previous undetectability

Reported practice when switching ART for VL rebound was:

- 77 (57%) delay until VL > 1000 for resistance test
- 3 (2%) delay for other reasons.
- 17 (13%) switch after second VL > 400
- 11 (8%) switch after second VL > 50
- 26 (19%) not sure, no answer or no preferred practice.

This is reported rather than actual practice.

Often the second VL >400 may be >1000 anyway.

Use of therapeutic drug monitoring in patients with virological failure

- 59 (44%) use TDM only if reduced concentration due to interaction is suspected
- 17 (13%) use TDM routinely if adherence is suspect
- 25 (18%) never or rarely use TDM
- 33 (25%) gave other responses or did not answer

Of the 25 never/rarely using TDM in patients with VL failure, 9 gave lack of availability as the reason and 16 gave other reasons. This may indicate lack of awareness of availability rather than actual lack of access.

Cost of ART drugs

No respondent said cost was a main or major consideration in the choice of ART drugs:

- 72 (54%) said they took cost into account
- 59 (44%) said cost was not a consideration
- 3 (2%) did not answer.

The question may have been interpreted in terms of whether cost was taken into account when prescribing for an individual patient, whereas it may be more likely to be taken into account at the level of setting clinic guidelines and protocols.

Case note review of patients switching therapy

Data was received on 504 patients.

Exclusions:

- Switch less than 12 weeks from starting therapy
- Second or subsequent switch.

67 patients were excluded as ineligible, leaving 437 for analysis.

Exclusions were operationalised as follows:

Less than 12 weeks on treatment or date of switch missing. If date of switch was given but not date of original start, patient was not excluded.

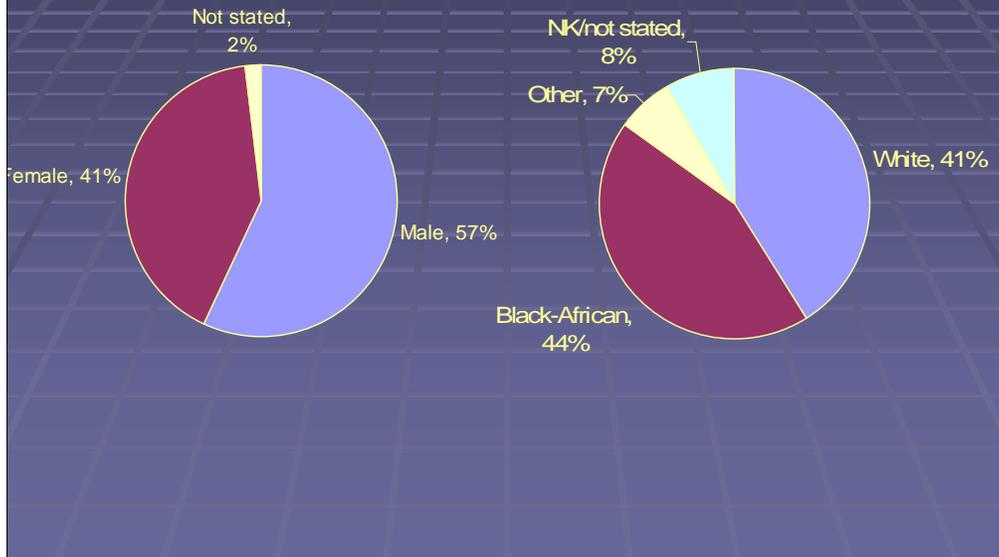
All patients on atazanavir or emtricitabine outside clinical trials prior to switch were excluded.

Patients who were on lopinavir/r prior to switch and had started therapy during or before 1999 were excluded. CHANGED TO BEFORE 1999

Patients who were on tenofovir prior to switch and had started therapy during or before 2000 were excluded. CHANGED TO BEFORE 2000

Male patients on boosted saquinavir were NOT excluded.

Demographic data



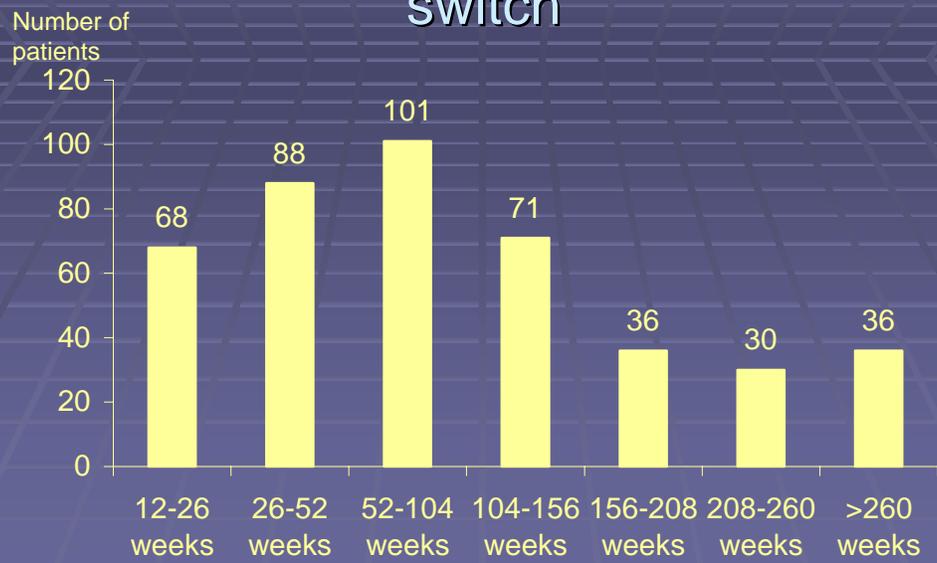
62% of those who had been on ART for more than 4 years were white.

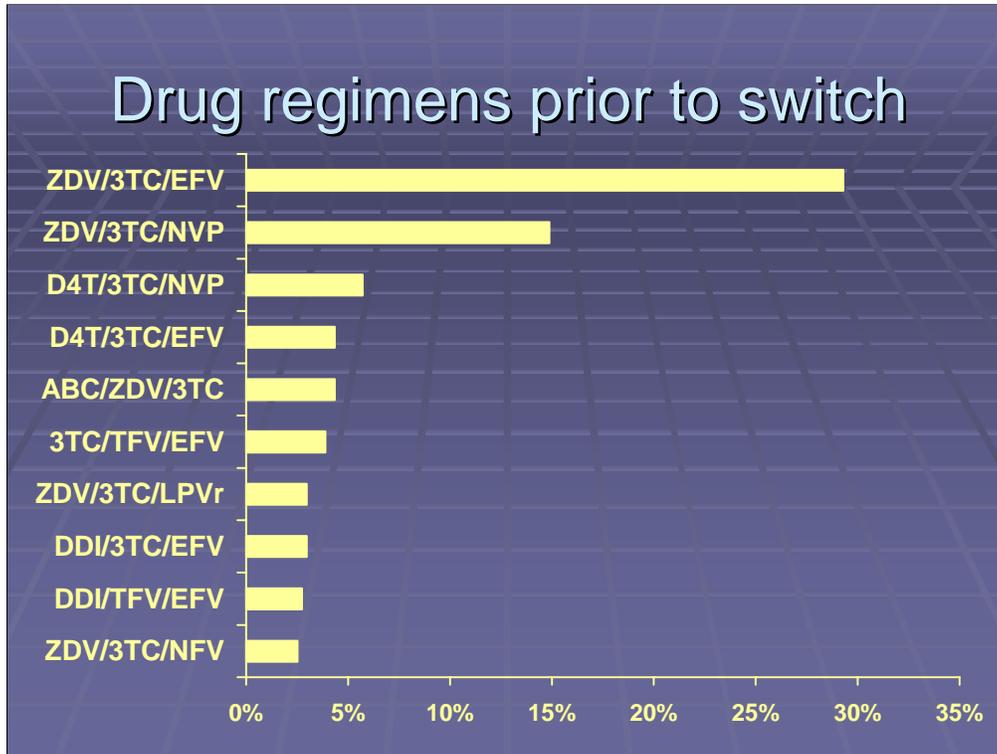
Trial participation

18 (4%) of the 437 analysed patients were reported to be in clinical trials related to ART.

3 CORRS, 3 NOCTE, 1 PgP, 1 SONHIA, 1 ALCAR, 1 Gilead, 1 Pharmacogenetics of HIV therapy, 1 B1 Switch, 1 Zodiac, 1 FORTE, 1 APV 3002, 1 Tetra, 2 not stated.

Duration on treatment before switch





25% of patients were on combinations not shown in this chart – a very wide variety.

Overall, 74% were on an NNRTI, 18% on a PI, 7% on neither and 1% on both.

CAUTION: There is no denominator shown, ie regimens used by patients who did NOT switch therapy. The committee suggested comparing this switch audit data with the 2002 audit of starting therapy – this has been done but is not shown on slide because interpretation is confusing and confounded by differing dates of starting therapy. Briefly, the 2002 start audit data included a higher proportion of patients on ABC/ZDV/3TC, a lower proportion on D4T, and a lower proportion on TFV. Possible explanations:

Patients started on ABC/ZDV/3TC had largely already been switched to new regimens before the time of this switch audit.

Patients started on D4T are more likely to switch.

TFV was not in widespread use as a first-line agent in 2002.

Reasons for switching therapy

- 223 (51%) toxicity, including 71 (16%) metabolic problems
- 132 (30%) virological failure
- 63 (14%) adherence difficulties
- 43 (10%) patient choice
- 42 (10%) treatment simplification
- 21(5%) poor CD4 response

NB: more than one reason could be given for each patient.

For 148 (35%) patients, toxicity was the ONLY reason given for switching therapy.

44% of those for whom adherence difficulties were cited as a reason switched to once daily therapy

4 of those who switched for simplification also had virological failure. Of the 38 who switched for simplification, 7 switched to ZDV/3TC/EFV and 6 to ABC/ZDV/3TC. 17 switched to once daily therapy including 6 each on boosted ATZ and FTC.

Reasons for switching therapy (continued)

- 22 (5%) co-morbidity (3%) +/- or potential for drug interactions (3%)
- 15 (3%) therapy not meeting current recommendations
- 14 (3%) planning pregnancy
- 5 (1%) pregnant
- 3 (<1%) trial end-point.

NB: more than one reason could be given for each patient.

Of co-morbidity/interaction patients:

2 switched on *completion* of anti-TB therapy.

TB was mentioned for a further 4 patients, and gabapentin and anti-epileptic medication for one each.

Two patients switched to 3TC/TFV regimens because of hepatitis B co-morbidity.

Of those who switched because of therapy not meeting current recommendations, 12 were on D4T, 2 on ABC/3TC/ZDV and 1 on 3TC/ZDV before switching.

Of those planning pregnancy, 11 were on EFV, 2 on ABC/3TC/ZDV and one on D4T before switching.

Of those pregnant, 4 were on EFV, one on ABC/3TC/ZDV before switching.

Other reasons included NVP to NFV switch prior to stopping (2 patients).

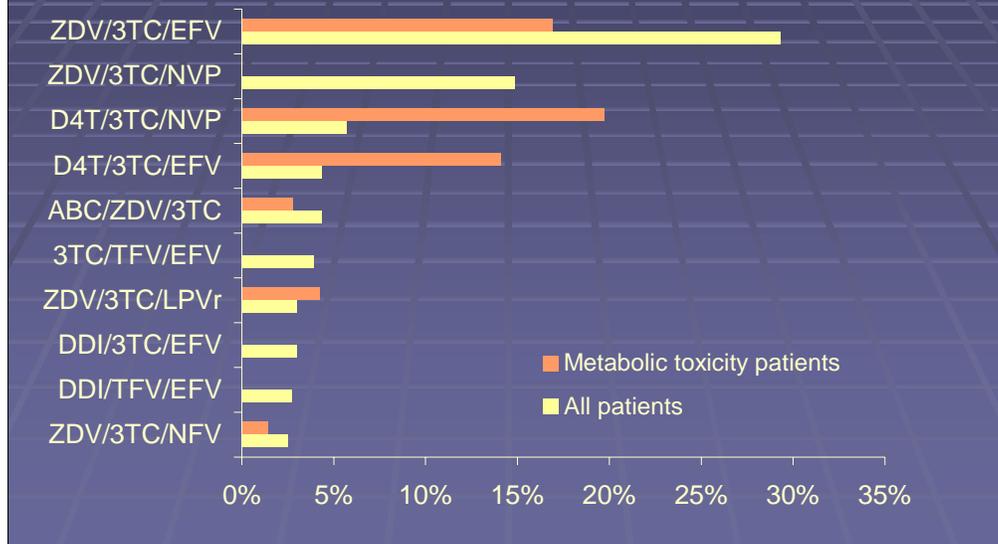
Metabolic toxicity

Metabolic problems were the most common toxicities cited as a reason for switching therapy, affecting 71 (16%) of patients, including:

- 44 lipoatrophy
- 26 hypercholesterolaemia
- 17 hypertriglyceridaemia
- 12 central obesity
- 1 hyperglycaemia.

NB: some patients had more than one condition.

Drugs taken before switch in patients with metabolic toxicity



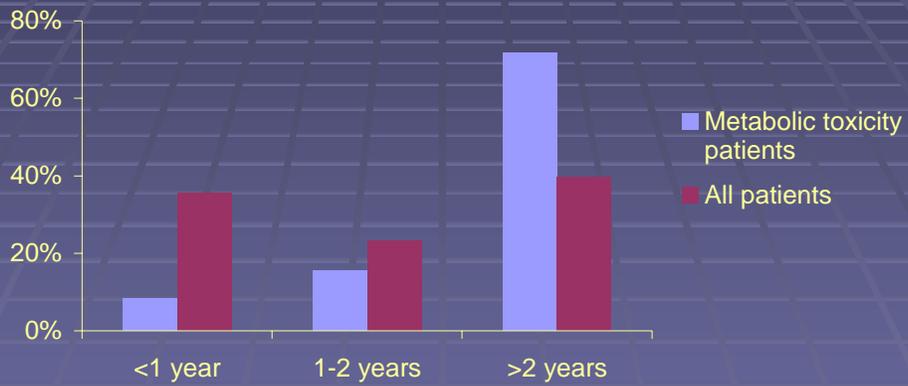
Of those with metabolic toxicity, 28% were on a PI before switch (compared with 18% of all patients), 66% were on an NNRTI (74%), 1% were on both (1%) and 4% were on neither (7%).

41% of metabolic toxicity patients were on combinations not shown here, including 7 (10%) on indinavir, 4 (6%) on saquinavir (3 boosted).

In total 38 (54%) metabolic toxicity patients were on stavudine.

Caution: differences in pre-switch drug use patterns between metabolic toxicity and other patients may be partly a reflection of longer duration on therapy.

Duration on treatment before switch in relation to metabolic toxicity



Other reported toxicities

- 41 CNS or similar
- 25 GI tract
- 18 peripheral neuropathy
- 16 anaemia
- 9 hepatitis/liver related
- 5 drug hypersensitivity
- 6 nail +/-or skin discolouration
- 3 hyperlactataemia/lactic acidosis
- 3 renal

40 of those with CNS-related toxicities were on EFV prior to switch

13 of those with GI toxicity were on a PI before switch.

Of the peripheral neuropathy patients, 14 were on 3TC before switch, 8 were on D4T, 5 were on DDI – all were on at least one of these drugs.

Of drug hypersensitivity patients, 4 switched away from NVP, 1 from EFV

All 3 patients with hyperlactataemia/lactic acidosis were on DDI before switch.

Virological failure

Virological failure (rebound, not reaching undetectability, and/or increase in VL) was cited as a reason for switching therapy in 132 (30%) of patients.

Time to switch in VL rebound

Of the 70 patients who had ever had undetectable VL, the time from the first consistently detectable VL to the change of therapy was:

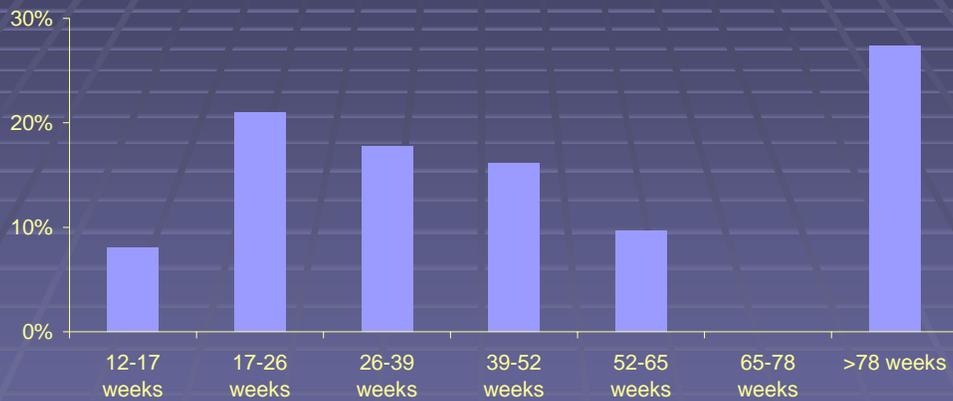
- 24 (34%) more than 6 months
- 14 (20%) 4-6 months
- 30 (43%) less than 4 months.

Duration on therapy before rebound

Duration on therapy before switch of 70 patients who had achieved undetectability before rebound:

- 10 (14%) less than one year
- 19 (27%) one to two years
- 41 (59%) more than two years

Time to switch for patients who did not achieve undetectability



Duration on therapy before switch of 62 patients who were not reported to have achieved VL undetectability.

Resistance testing in patients with virological failure

Among 132 patients switching for virological failure:

- 95 (72%) switched after a resistance test result had been obtained
- 12 (9%) switched while resistance testing was being done but before results were available
- 4 (3%) had a sample stored for future resistance testing
- 14 (11%) were neither tested for resistance nor had a sample stored
- 7 (5%) information was unclear.

5 of those for whom test was not done had last VL over 1000 copies/ml (including one who switched after only 3 months on treatment with toxicity as well as VL failure, and one who switched after 5 months with VL failure and poor CD4 response). 8 had last VL below 1000 copies/ml. Data were unclear for one.

Virological failure, cont

Of 132 patients with virological failure:

- 64 (48%) switched to 3 or more new drugs*
- 42 (32%) switched to 2 new drugs
- 26 (20%) switched to one new drug

88% of those on an NNRTI regimen switched to a PI.

67 % of patients on a PI regimen remained on a PI and 33% switched to an NNRTI.

*RTV at booster dose was not counted. FTC was not counted as a new drug in patients previously taking 3TC.

Nine patients remained on an NNRTI regimen after failing virologically:

3 switched after less than 6 months on treatment and 2 after 6-10 months for failure to reach undetectability – of this subgroup 4 also had other reasons for switching therapy (toxicity, adherence etc)

3 had been on therapy very long term (>240 weeks) – it is possible these were not all first switches

1 had been on therapy for 127 weeks and had rebounded more than nine months before switching, but changed only one drug (ZDV/3TC/NVP to ZDV/TFV/NVP) on the basis of resistance test results.

3 patients switched from an NNRTI to triple NRTI regimens after reportedly failing virologically. One switched after 54 weeks on therapy, without achieving undetectability, on the basis of a resistance test result. One had been on therapy for 126 weeks apparently without achieving undetectability, and switched without a resistance result (sample stored only). For the third, dates and VL data were unclear but the switch may have been for low level rebound and adherence problems after 128 weeks on therapy.

Of 12 patients who remained on a PI regimen after failing virologically:

11 were on RTV-boosted PI regimens (including one on DDI/ATZ/r only)

1 was on full-dose RTV.

Again, it is possible these were not all first switches.

Conclusions of switch audit

Some patients remained on therapy with detectable VL for long periods before switching for virological failure.

In over a quarter of patients with reported virological failure a resistance test result was not obtained before switching therapy.

Conclusions of switch audit, cont.

Toxicity was the main reason for switching therapy.

Few patients were reported to be in clinical trials.

Caveat: a substantial number of patients were excluded from analysis, and some of those remaining in the data-set may not have been switching therapy for the *first* time.

Re toxicity, reminder that patients who switched after less than 12 weeks on therapy were excluded.

Key messages

Clinical centres should reassess their practice so as to:

- Minimise delay before changing therapy in patients with virological failure.
- Ensure appropriate use of resistance testing.

Re-audit of patients starting therapy from naive

Key conclusions of 2002 audit:

- Significant delays can occur between diagnosis and starting ART even for patients with extremely low CD4.
- BP, glucose +/- or lipids were not measured before starting ART in a substantial proportion of patients.

We re-audited up to 5 patients per centre who started therapy between 1 April and 30 September 2004.

Demographics

Of 495 patients submitted for the re-audit:

- 52% were male and 48% female
- 50% were Black-African, 34% white, 7% other and 9% unstated.

13 patients were reported to be taking part in clinical trials of ART.

Reasons for starting ART

- 423 (86%) advanced disease eg low CD4 and/or symptoms
- 64 (13%) prevention of vertical transmission
- 6 (1%) recent seroconversion
- 18 (4%) other reasons.

NB: More than one reason could be cited for each patient.

Time from diagnosis to starting ART

- 299 (60%) within 3 months of diagnosis
- 55 (11%) 3-6 months after diagnosis
- 135 (27%) more than 6 months after diagnosis
- 6 (1%) information missing.

CD4 just before starting treatment

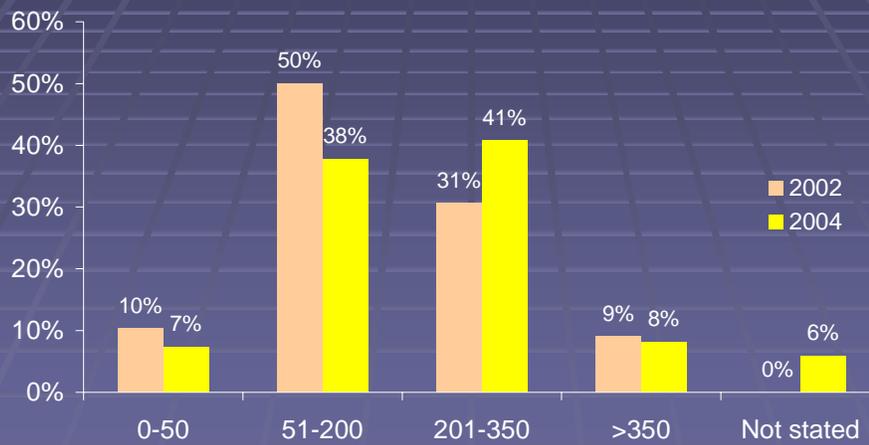
Overall, 306 (62%) patients started ART at CD4 <200, including 110 (22%) at <50.

Starting ART at low CD4 was associated with recent diagnosis.

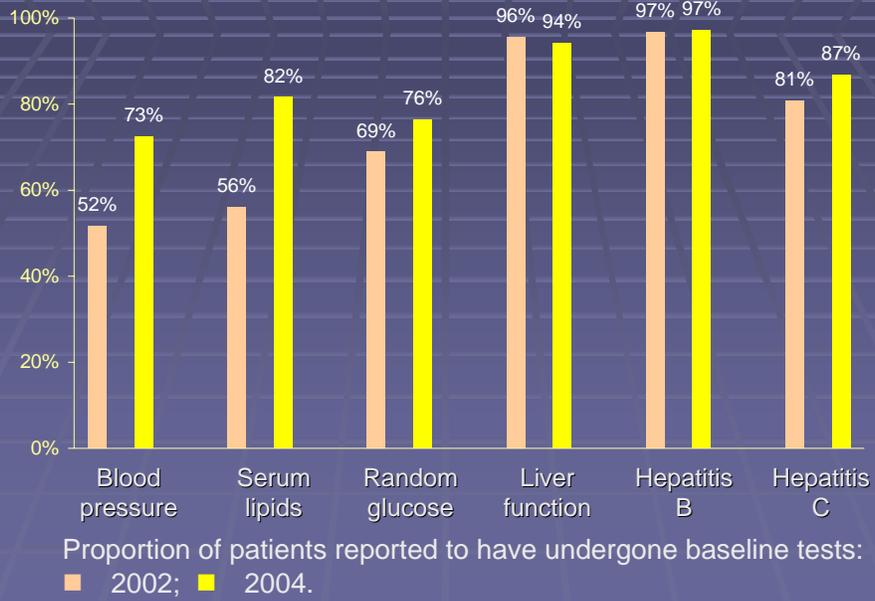
Pre-treatment CD4 in patients diagnosed less than 3 months before starting treatment



Pre-treatment CD4 in patients diagnosed more than 6 months before starting treatment



Baseline tests performed



Baseline resistance testing

In 2002 only 10% of patients were tested for HIV resistance before starting ART.

2004 data were:

- 142 (29%) tested before starting ART
- 16 (3%) previously tested.
- 84 (17%) sample stored
- 228 (46%) resistance test not done
- 25 (5%) information missing.

Conclusions from audit of starting ART from naïve

Patients continue to start ART later than guidelines recommend. This is partly but not solely attributable to late diagnosis.

Baseline testing rates have improved since 2002, but key tests were not recorded for a significant minority of patients.

The majority of patients did not have a resistance test result before starting ART.

The low rate of trial participation in both audits remains unexplained.

Welcome feedback on barriers to resistance testing and to trial participation.